Appendix A: Search Strategy

Search run on August 24, 2011:

Database(s): **Ovid MEDLINE(R)** 1948 to August Week 2 2011**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** August 23, 2011**, EBM Reviews - Cochrane Central Register of Controlled Trials** 3rd Quarter 2011

#	Searches	Results
1	((acute and coronary and syndrome$) or ACS or myocardial infarction or ST elevation or non-ST elevation or percutaneous coronary intervention or (percutaneous and coronary and intervention) or PCI or stent$ or implant$ or CABG or (coronary and artery and bypass and graft$) or coronary artery bypass graft$ or stroke or TIA or (transient and isch?emic and attack) or (peripheral and arter$ and disease$) or (atrial and fibrillation) or (coronary and artery and disease) or (unstable and angina) or (angina and (ischemic or pectoris)) or ((cardiac or heart) and catheterization) or respond$ or non-respon$).af. or exp acute coronary syndrome/ or exp myocardial infarction/ or exp peripheral arterial disease/ or exp stent/ or exp atrial fibrillation/ or exp coronary artery bypass graft/ or exp stroke/ or exp transient ischemic attack/ or exp coronary artery disease/ or exp unstable angina/ or exp patient selection/ or exp coronary angiography/	1,283,614
2	(clopidogrel or plavix or prasugrel or effient or ticlopidine or ticlid or aggrenox or dipyridamole or ticagrelor or dipyridamole or persantine or (p2y12 and inhibitor) or antiplatelet$ or anti-platelet$ or "thienopyridine" or platelet inhibition).af. or (90055-48-4 or 55142-85-3 or 150322-43-3or 58-32-2 or 274693-27-5).rn.	32,231
3	(cytochrome p450 or pharmacogenetics or cyp450 or cyp-450 or polymorph$ or genetic$ or cyp2c19 or 2c19 or genotype or p-450 or rs4244285 or rs28399504 or rs56337013 or rs12248560 or pharmacogenomics or allele$ or varia$ or ((platelet and activ$) or (platelet and aggregation) or platelet reacti$ or "platelet aggregation" or (platelet and function) or "thrombelastography" or "thromboelastography" or "pfa 100" or ((optical or (light and transmission) or (light and transmittance) or (whole and blood)) and aggregometry) or (turbidimetric and optical and detection) or aggregometer or ("platelet" and "aggregation" and "inhibitors") or vasp or verifynow or p2y12 or ultegra or rpfa)).af.	3,752,737
4	1 and 2 and 3	9351

Appendix B. Excluded Studies

Studies are listed in alphabetical order by first author under each main reason for exclusion (bold headings): foreign language (not English), not population of interest (usually healthy volunteers, not patients), measurements not used as a predictive test or for decisionmaking, insufficient sample size, no primary data, not study design of interest, not test of interest, not treatment of interest, and not outcome of interest. PMIDs are given, when available, at the end of each reference.

Foreign Language

Ainetdinova DK, Udovichenko AE, Sulimov VA. [Resistance to antiplatelet drugs in patients with non ST elevation acute coronary syndrome]. Kardiologiia 2008;48(6):35-39.
PMID: 18729834.

Barbou F, Frere C, Hovasse T, et al. [Platelet function after a high dose bolus of tirofiban immediately after coronary angioplasty]. Arch Mal Coeur Vaiss 2006 Oct;99(10):894-99.
PMID: 17100140.

Bochenek T, Wilczynski M, Wita K, et al. [Evaluation of platelet response to antiplatelet drugs. An important clue for cardiologists and cardiosurgeons]. Kardiol Pol 2007 Oct;65(10):1266-69.
PMID: 17979060.

Bode C. [Therapy of acute mayocardial infarction: COMMIT (Clopidogrel and Metoprolol Infarction Trial)]. Internist (Berl) 2006 Jul;47(7):764-66.
PMID: 16794823.

Buriachkovskaia LI, Uchitel' IA, Sumarokov AV, et al. [Difficulties in evaluating the efficacy of antiplatelet therapy in clinical practice]. Ter Arkh 2009;81(5):41-47.
PMID: 19537585.

Cai J, Wu Q, Fan L, et al. [Impact of different proton pump inhibitors on the antiplatelet activity of clopidogrel in combination with aspirin for patients undergoing coronary stent implantation]. Zhongguo Ying Yong Sheng Li Xue Za Zhi 2010 Aug;26(3):266-69.
PMID: 21038666.

Chen H, Yan W, Wu XY. [Relationships of blood stasis syndrome, CYP2C19 gene polymorphism with clopidogrel resistance and post-PCI prognosis]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2010 Dec;30(12):1245-49.
PMID: 21302482.

Cuisset T, Frere C, Quilici J, et al. [Beneficial effect of a loading dose of 600 mg of clopidogrel on platelet parameters in patients admitted for acute coronary syndrome]. Arch Mal Coeur Vaiss 2006 Oct;99(10):889-93.
PMID: 17100139.

De SS, Lettino M. [The TRITON-TIMI 38 trial]. G Ital Cardiol (Rome) 2008 Mar;9(3):149-54.
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Frolova NS, Shakhnovich RM, Sirotkina OV, et al. [Clopidogrel resistance in patients with acute coronary syndrome]. Ter Arkh 2010;82(8):14-20.
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Han YL, Li CY, Li Y, et al. [The antiplatelet effect of clopidogrel is not attenuated by statin treatment in patients with acute coronary syndromes undergone coronary stenting]. Zhonghua Xin Xue Guan Bing Za Zhi 2007 Sep;35(9):788-92.
PMID: 18070466.

Han YL, Su QF, Li Y, et al. [The effects of post coronary stenting triple antiplatelet therapies on platelet functions]. Zhonghua Nei Ke Za Zhi 2006 Aug;45(8):635-38.
PMID: 17074146.

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PMID: 11534098.

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Li Z, Liu F, Cui W, et al. [Impact of application time of aspirin and clopidogrel on platelet aggregation in patients with acute coronary syndrome]. Zhonghua Xin Xue Guan Bing Za Zhi 2010 Apr;38(4):311-14.
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PMID: 19595223.

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PMID: 17343035.

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PMID: 20659030.

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Yun KH, Rhee SJ, Park HY, et al. Effects of omeprazole on the antiplatelet activity of clopidogrel. Int Heart J 2010 Jan;51(1):13-16.
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Measurements Not Used as a Predictive Test or for Decisionmaking

Abuzahra M, Pillai M, Caldera A, et al. Comparison of higher clopidogrel loading and maintenance dose to standard dose on platelet function and outcomes after percutaneous coronary intervention using drug-eluting stents. Am J Cardiol 2008 Aug 15;102(4):401-03.
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Appendix C. U.S. Food and Drug Administration Documents Reviewed

The following documents from the U.S. Food and Drug administration were reviewed for this report. They were identified though a search of the database of the 510(k) Database[1] (1996–current) using the following stem or key words: aggreg*, PFA*, Ultegra*, Impact*, VerifyNow*, platelet*, plateletwork*, CY2C19, *2C19*, CYP2*, VASP*.

Document	Test name	Comments
Genetic testing		
K101683	INFINITI CYP2C19 Assay	Population not described so document not included; however, indirect data given on limits of detection, sequencing concordance, and interlaboratory reproducibility.
K042259	Roche AmpliChip CYP450 Test	Gene not of interest (CYPCD6).
K043576	Amplichip CYP450 Test for CYP2C19	Population not described so document not included; however, indirect data given on limits of detection, sensitivity and specificity, sequencing concordance, interassay agreement, comparison with a reference standard, cross-contamination, and reproducibility.
K012966	COBAS TaqMan Analyzer	Population not described so document not included; however, indirect data given on the dynamic range, limits of detection, sensitivity, and specificity.
Phenotypic testing		
K992531	Accumetrics Ultegra System Rapid Platelet Function Assay-TRAP	Population is of interest (patients undergoing PCI [also treated with abciximab]) and reports interassay correlation. However, antiplatelet agents other than abciximab were not reported.
K011337	Accumetrics Ultegra System Rapid Platelet Function Assay-TRAP	Population is of interest (patients undergoing PCI [also treated with abciximab]) and reports interassay correlation. However, antiplatelet agents other than abciximab were not reported.
K012701	Accumetrics Ultegra System Rapid Platelet Function Assay-ASA	Test not of interest (measuring response to aspirin)
K013596	Accumetrics Ultegra System Rapid Platelet Function Assay	Population is of interest (patients undergoing PCI [also treated with abciximab or eptifibatide]) and reports interassay correlation. However, antiplatelet agents other than abciximab or eptifibatide were not reported..
K060489	Dade PFA-100 Platelet Function Analyzer Dade PFA-100 Reagents	Populations not of interest (data summarized from studies in children and in patients with bleeding disorders)
K970505	Dade PFA-100 Platelet Function Analyzer Dade PFA Collagen/Epinephrine Test Cartridge Dade PFA Collagen/ADP Test Cartridge Dade PFA Trigger Solution	Collagen/epinephrine test not of interest. For collagen/ADP test, populations not of interest (data summarized from a study of subjects with normal platelet function or paitients with von Willebrand disease, aspirin-induced dysfunction, or Glanzmann's thromasthenia)
K002885	Dade PFA-100 Platelet Function Analyzer Dade PFA Collagen/Epinephrine Test Cartridge Dade PFA Collagen/ADP Test Cartridge Dade PFA Trigger Solution	Collagen/epinephrine test not of interest. For collagen/ADP test, populations not of interest (data summarized from studies of healthy children, healthy adults, and children with von Willebrand disease))
K042423	Accumetrics VerifyNow-Aspirin Assay	Test not of interest (measuring response to aspirin)
K051231	Accumetrics VerifyNow P2Y12 Assay	Population is of interest (patients treated with clopidogrel with a history of vascular disease or risk factors) but n=10 only.
K093626	INNOVANCE D-Dimer Assay	Population not of interest (patients presenting to emergency department with suspected deep-vein thrombosis)
K990398	Plateletworks Platelet Aggregation Assay	Population not of interest (includes healthy volunteers)
K012723	Collagen for Plateletworks	No data available (only approval statement is in database)
K023761	Plateletworks	No data available (only approval statement is in database)

[1] Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm; last accessed: April 25, 2012. ASA=acetylsalicylic acid (aspirin), RPFA=rapid platelet function assay, TRAP=thrombin receptor activating peptide.

K061991	Plateletworks Arachidonic Acid	Test not of interest (measuring response to arachidonic acid)
K032951	Chrono-log Whole Blood Aggregometer, Model 591A/592A	Population not of interest ("normal, healthy, drug free subjects" or "normal donors and patients known to have von Willebrands Disease")
K050265	Model 700 Chrono-log Whole Blood Lumi-Aggregometer	Population not of interest ("normal, healthy, drug free subjects")
K830749	Chrono-log Model 560 Whole Blood Lumi-Aggregometer	No data available (no downloadable information in database)
K851025	AGGRO/LINK Interface	No data available (no downloadable information in database)
K962426	Chrono-log Whole Blood Aggregometer, Model 591/592	No data available (only one-page summary is in database)
K954997	Centocor Aggrestat, Collagen Reagent, Control Reagent	No data available (no downloadable information in database)

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Appendix D. Appendix Figures and Tables for Key Question 1

Key Question 1a - Figure

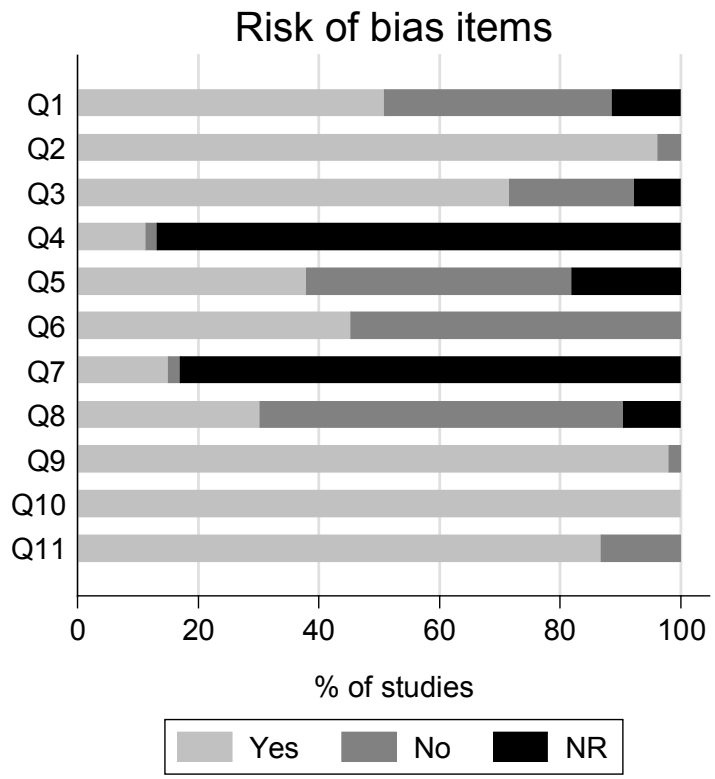
Appendix Figure D1: Study Quality and Completeness of Reporting for Studies on the Analytic Validity of Genetic Tests for CYP2C19 Variants

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Shuldiner, 2009 [19706858]	YES	NR	NA	NR	NR	NR	NO	NO	YES	NO	NO
Sibbing, 2009 [19193675]	YES	NR	NA	NR	NR	NR	NO	NO	YES	NO	NO
Sibbing, 2011 [21527445]	YES	NR	NA	NR	NR	NR	NO	NO	YES	NO	NO
Sibbing, 2011 [20083681]	YES	NR	NA	NR	NR	NR	NO	NO	YES	NO	NO
Trenk, 2011 [21685174]	YES	NR	NA	NR	NR	NR	NO	NO	YES	NO	NO

Each row corresponds to a study (listed with first author surname, publication year [PMID]). Each column refers to a question (Q) about quality and reporting (see list below for the complete questions). “YES,” “NO,” and “NR”/“NA” (green, red, and yellow circles, respectively) refer to whether the question was addressed and the salient information reported in the study.
Q1=Was the execution of the assay described in sufficient detail to permit replication?
Q2=Were both positive and negative control samples tested?
Q3=Were negative control materials from the same type of tissue, and collected, stored, and processed in the same way that sample materials used clinically for testing will be?
Q4=Were the tests performed with positive or negative control samples being blinded to the testers?
Q5=Were the testing results interpreted with positive or negative control samples being blinded to the interpreters?
Q6=Were criteria for determining a testing result as positive, negative, indeterminate, or uninterpretable set a priori?
Q7=Was the limit of detection of the test reported?
Q8=Was the assay linearity range reported?
Q9=Was the reproducibility of the test when performed multiple times on a single specimen established?
Q10=Was the reproducibility of the test adequately established (across operators, instruments, reagent lots, different days of the week, different laboratories)?
Q11=Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?

Key Question 1b - Figure

Appendix Figure D2: Risk of Bias Assessment for Studies Contributing Data to Key Question 1b



Item definitions as for Appendix Figure D1.

Key Question 1a - Tables

Appendix Table D1: Descriptive characteristics of studies reporting analytic validity information

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Study design for the assessment of analytic validity	Sample size	Results
Shuldiner 2009{Shuldiner, 2009 116 /id} USA 19706858	Patients undergoing nonemergent PCI; those with MI within 48 h were excluded.	TaqMan SNP assay (rs4244285, rs4986893, rs56337013, rs12248560, corresponding to *2, *3, *5, *17, respectively) [Applied Biosystems, Foster City, CA]	Not clear	Repeat genotyping of samples	Not reported (for the subset of duplicate samples)	Genotype concordance rate >98%
Sibbing 2009{Sibbing, 2009 133 /id} Germany 19193675	Patients undergoing PCI in a single center; patients included in the study were selected among those participating in a set of randomized trials of abciximab	TaqMan assay (rs4244285, corresponding to *2) [ABI Prism Sequence Detector 7000, Applied Biosystems]	Blood was obtained after diagnostic angiography and before PCI; timing of genetic analysis was not clear	Repeat genotyping of samples (20% of all genotyped samples; selection NR)	20% of 2485 = 497	"All repeated experiments revealed identical results when compared with the initial genotype"
Sibbing 2011{Sibbing, 2011 2 /id} Germany 21527445	Patients undergoing PCI in a single center; patients included in the study were selected among those participating in a prospective trial (blood for genotyping was available for 95% of the study participants)	TaqMan assay (rs4244285, corresponding to *2) [ABI Prism Sequence Detector 7000, Applied Biosystems]	Blood was obtained after diagnostic angiography and before PCI; timing of genetic analysis was not clear	Repeat genotyping of samples (20% of all genotyped samples; selection NR)	20% of 1524 = 305	"Repeat genotyping revealed identical results", the call rate was 100%
Trenk 2011{Trenk, 2011 226 /id} Germany 21685174	Patients undergoing elective coronary stent placement after pre-treatment with 600 mg of clopidogrel and aspirin (≥100 mg per day for at least 5 days) in a single center; patients were participants in the EXCELSIOR study	For CYP2C19 *2 (rs4244285): PCR using the Drug Metabolism Genotyping Assay (Applied Biosystems, Frankfurt, Germany)[2] For CYP2C19 *17 (rs12248560): TaqMan assay [Applied Biosystems, Foster City, CA]	Not clear	Repeat genotyping of samples	Not reported (for the subset of duplicate samples)	Concordance rate = 100%
Sibbing 2010{Sibbing, 2010 95 /id} Germany 20083681	Patients with CAD undergoing PCI in a single center; patients included in the study were selected among those participating in a prospective study (blood for genotyping was available for 95% of the study participants)	TaqMan assay (rs12248560, corresponding to *7) [ABI Prism Sequence Detector 7000, Applied Biosystems, Foster City, CA]	Blood was obtained directly before PCI; timing of genetic analysis was not clear	Repeat genotyping of samples (20% of all genotyped samples; selection NR)	20% of 1524 = 305	"Repeat genotyping revealed identical results"

h = hour; MI = myocardial infarction; PCI = percutaneous coronary intervention; PMID = PubMed identification number.

[2] Information on the genotyping assay was extracted from Trenk et al. 2008 (PMID = 18482659)

Appendix Table D2: Reporting characteristics and methodological quality of studies of analytic validity

Author Year Country PMID	Was the execution of the assay described in sufficient detail to permit replication?	Were both positive and negative control samples tested?	Were negative control materials from the same type of tissue, and collected, stored, and processed in the same way that sample materials used clinically for testing will be?	Were the tests performed with positive or negative control samples blinded to the testers?	Were the testing results interpreted with positive or negative control samples being blinded to the interpreters?	Were criteria for determining a testing result as positive, negative, indeterminate, or uninterpretable set *a priori*?	Was the limit of detection of the test reported?	Was the assay linearity range reported?	Was the reproducibility of the test when performed multiple times on a single specimen established?	Was the reproducibility of the test adequately established(across operators/ instruments/reagent lots/ different days of the week/ different laboratories)?	Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?
Shuldiner 2009{Shuldiner, 2009 116 /id} USA 19706858	YES	NR	NA	NR	NR	NR	NO	NO	YES (concordance on repeat genotyping)	NO	NO
Sibbing 2009{Sibbing, 2009 133 /id} Germany 19193675	YES	NR	NA	NR	NR	NR	NO	NO	YES (concordance on repeat genotyping)	NO	NO
Sibbing 2011{Sibbing, 2011 2 /id} Germany 21527445	YES	NR	NA	NR	NR	NR	NO	NO	YES (concordance on repeat genotyping)	NO	NO
Trenk 2011 {Trenk, 2011 226 /id} Germany 21685174	YES	NR	NA	NR	NR	NR	NO	NO	YES (concordance on repeat genotyping)	NO	NO
Sibbing 2010{Sibbing, 2010 95 /id} Germany 20083681	YES	NR	NA	NR	NR	NR	NO	NO	YES (concordance on repeat genotyping)	NO	NO

NA = not applicable; NR = not reported; PMID = PubMed identification number.

Key Question 1b – Tables

Appendix Table D3: Patient characteristics for studies reporting analytic validity information

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
Collet, 2009{Collet, 2009 140 /id} 19108880 France AFIJI (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) registry	259 78% White European 16.6% North African 3.1% Black 2.3% Asian 92.3% 40.1 (± 5.1)	NR NR NR 73% PCI ; 8% CABG NR NR NR NR 78.8% STEMI; 21.2% NSTEMI	54% 56% 20.1% HTN 10.4%	3.1% Clopidogrel: 83.4% initiated at first event; 19.9% not on clopidogrel NR NR	86% 32% DES 54% BMS	Survivors of AMI enrolled in a multicenter registry; followup was on an outpatient basis	Clopidogrel MD = 75 mg for at least 1 mo	Low dose aspirin (dose NR)
Fontana, 2008{Fontana, 2008 182 /id} 17681590 Switzerland NR	81 100% Caucasian 79% 65.9± 12.2	NR NR NR NR NR NR NR 50.6% ACS NR	71.6% Hyperlipidemia 30.9% 59.3% HTN 18.5%	NR NR 98.8% 13.6%	100% NR NR	PCI with stent placement	Clopidogrel LD=300 mg MD = 75 mg	99% Aspirin maintenance (dose NR)
Giusti, 2007{Giusti, 2007 190 /id} 18004210 Italy NR	1419 NR 73% Median= 69 (range: 27-94)	NR NR NR NR NR NR NR NR NR	56.1% Dyslipidemia 40.9% "Smoking habit" 65% HTN 21.1%	NR NR NR NR	NR NR NR	PCI for ACS	LD: clopidogrel 600 mg (orally) + 500 mg ASA (IV); MD: clopidogrel 75 mg and ASA 100 mg (both daily)	None
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	804 (of whom 772 consented to participation in the genetics substudy) NR 74.6% NR	NR LVEF = 47% ±12% NR 20.9% PCI 7.5% CABG 33.9% 40.2% NR 25.5% NR	59.7% Dyslipidemia; 89.4% on statins 34.4% 65.4% HTN 22.2%	NR NR NR 94.8%	100% 100% DES (sirolimus or paclitaxel) 439 (56.8%) had multi-vessel disease; NR if all received multiple stents	PCI	All patients received aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance). Loading dose was administered before the procedure	UFH was used during the procedure as the anticoagulant.
Gladding, 2009{Gladding, 2009 248 /id} 19926050 New Zealand NR	40 88% Caucasian 78%	18% 5% NR 88% NR NR	43% 10% NR	NR 100% NR	NR NR NR	PCI>2 wk previously	All patients had a 600-mg clopidogrel loading dose, followed by clopidogrel 150 mg once daily for 7 days	NR

[3] Mean (standard deviation), unless otherwise stated.

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
	67±11	NR NR	50% 20%	33%				
Jinnai, 2009{Jinnai, 2009 120 /id} 19531897 Japan Partly industry funded	30 100% East Asian 73.3% 70 ± 8.3	NR NR NR NR NR NR NR 12% NR	64% Hyperlipidemia; 72% on statin 16% Current smokers 68% HTN 16%	NR NR NR 20%	NR NR NR	Elective PCI, for symptoms or based on stress testing	Patients were on low-dose Aspirin (81-100 mg/day) at study enrollment; They received clopidogrel 300 mg loading dose on the first day and then 75 mg daily maintenance.	None
Mega, 2009{Mega, 2009 141 /id} 19106084 Multinational Genetics substudy of TRITON-TIMI 38 [Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction]	1477 Caucasian, 1442 (97.6%); Hispanic, 18 (1.2%); African, 10 (0.7%); Asian, 5 (0.3%) Other, 2 (0.1%) 1044 (70.7%) 60.1 ± 11.1	NR NR 51 (3.5%) NR NR NR NR 240 (16.2%) NR	725 (49.1) 562 (38.1%) HTN=972 (65.8%) 322 (21.8%)	NR NR NR NR	1389 (1389 of the 1459 subjects with analyzable data = 95% of all included in analyses) NR NR	ACS with planned PCI	Clopidogrel 300 mg loading dose, followed by a 75 mg daily maintenance dose.	All decisions regarding concomitant medications were left to the treating physician. It was recommended that long-term aspirin therapy be 75 to 162 mg. Patients may receive unfractionated heparin, low–molecular-weight heparin, any approved direct thrombin inhibitor, and/or GPIIb/IIIa receptor antagonist. Because of a lack of information regarding the safety of thienopyridines in combination with warfarin, blinded study drug is discontinued in patients requiring anticoagulation with warfarin, and open-label thienopyridine use is left to the discretion of the treating physician. (source: Wiviott et al., American Heart Journal, Volume 152, Issue 4, Pages 627-635, PMID = 16996826)
Shuldiner, 2009{Shuldiner, 2009 116 /id} 19706858 USA Sinai Hospital of Baltimore Study	227 White=140 (61.7%); African-American=83 (36.6%); other=4 (1.8%) 139 (59.9%) 64.3 ± 11.5	100% (all undergoing non-emergent PCI) NR NR NR NR NR NR NR All patients underwent non-emergent PCI	183 (80.6%) 58 (25.6%) [current smoker] SBP = 140.7 ± 20.2;DBP = 72.3± 14.1; HTN=174 (76.7%) 83 (36.6%)	NR 90 (39.6%) at the time of study entry 227(100%) NR	NR NR NR	Non-emergent PCI	On the day of PCI patients received clopidogrel 600 mg (n=112) or 300 mg (n=25) loading dose; 90 subjects already on clopidogrel maintenance therapy with 75 mg daily at the time of PCI were not	Patients were also treated with bivalirudin or heparin, with (n=107) or without (n=120) eptifibatide. Anticoagulant therapy was discontinued at the completion of the procedure.

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
							reloaded. All patients received 81-325 mg aspirin daily for ≥1 week prior to PCI and 325 mg on the day of the procedure. Aspirin 325 mg per day and clopidogrel 75 mg per day was prescribed to all patients at discharge.	
Sibbing, 2009{Sibbing, 2009 133 /id} 19193675 Germany NR	2661 fulfilled the study inclusion criteria; of those 2485 had DNA available for genotyping NR 539 (78.3%) 66.5 ± 10.2	NR NR NR Previous CABG 325 (13%) NR UA = NR; Total ACS = 846 (34%) NR 801 (32%) NR	Hypercholesterolemia = 1204 (48%) 402 (16%) HTN = 1563 (63%) 881 (35%)	NR NR NR NR	100% DES = 623 (25%); BMS = 1862 (75%) 2006 (81%)	Patients undergoing planned PCI	Clopidogrel LD= 600 mg before stent placement.	None
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	1608 patients were included in a study of platelet function; 1524 (95%) of those had samples available for inclusion in the genetic study. NR 1180 (77.4%) 67.4 ± 10.5	All patients had known CAD NR [ejection fraction = 54.7± 11.1] NR CABG = 223 (14.6%) NR NR NR 483 (31.7%) NSTE MI = 169 (11.1%) of all included patients	Hypercholesterolemia = 1068 (70.1%) Active smokers = 207 (13.6%) Arterial HTN = 1392 (91.3%) 430 (28.2%)	164 (10.8%) On any thienopyridine = 644 (42.3%) 1155 (75.8%) 270 (18.1%)	100% DES = 100% (planned) 1292 (84.8%)	CAD and planned DES placement	All patients received a loading dose of clopidogrel 600 mg; After PCI patients received clopidogrel 75 mg (1/d) and aspirin 100 mg (2/d) maintenance	UFH was used as the anticoagulant ("in the majority of patients") and bivalirudin was used for "only some of the patients". <5% of patients received abciximab
Varenhorst, 2009{Varenhorst, 2009 122 /id} 19429918 Sweden Genetic sub-study	110 patients in parent study; 98 consented to inclusion in the genetics sub-study; of these 47 were on the clopidogrel group White = 47 (100%) 96% 65 ± 5.7	NR NR NR NR NR NR NR NR NR	NR "Yes" = 4 (9%);"No" = 43 (91%) NR Yes = 8 (17%)	NR NR All patients were aspirin treated 9 (19%)	NR NR NR	Stable CAD	Patients were aspirin treated. The group relevant to this KQ received clopidogrel LD= 600 mg, followed by MD= 75 mg	None
Frere, 2008{Frere, 2008 176 /id} 18394438 France NONE	603 NR 456 (75.7%) 64.7± 12.2	NR Excluded NYHA IV heart failure NR NR NR NR NR	NR [56.4% on statin treatment] 266 (44.1%) Hypertensive = 339 (56.3%) 169 (28%)	NR NR NR NR	NR NR NR	NSTE-ACS undergoing angiography	clopidogrel LD= 600 mg Aspirin LD= 250 mg ≥12 hours before coronary angiography	None; patients receiving IIb/IIIa inhibitors before the procedure were excluded.

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
		NR 100% NSTE-ACS						
Frere, 2009{Frere, 2009 117 /id} 19496924 France Part of larger observational study	598 NR 453 (76%) 64.7±12 (NR if SD or SE)	NR NR NR NR NR NR NR NR 100% NSTE-ACS	Dyslipidemic = 321 (54%); On statin = 336 (45%) Current smokers=263 (44%) HTN = 332 (56%) 169 (28%)	NR NR NR NR	NR NR NR	NSTE-ACS	clopidogrel LD= 600 mg; no additional details reported	NR
Bonello-Palot{Bonello-Palot, 2009 107 /id} 2009 19932784 France NR	73 NR 59 (80.8%) 62.8 ± 12.4	ACS: 40% NR (Left ventricular ejection fraction in %: 54.6 ± 9.8) NR NR NR NR NR Previous MI: 40.1% NR	Hypercholesterolemia(tot chol >250 mg/dL): 61.1% 38.4% HTN (>140/90 mm Hg at rest): 58.9% 31.5%	NR NR (Though all patients received clopidogrel during the study) NR Omeprazole: 5%	NR NR NR	PCI for ACS	Clopidogrel LD=600 mg; for pts with high on treatment platelet reactivity :up to 3 additional LDs of 600 mg were prescribed 24 hours after the previous dose till a VASP index <50% was obtained.	None
Harmsze 2010{Harmsze, 2010 102 /id} 19934793 Netherlands NR	428 NR 335 (78.2%) 62.9	65.2% NR NR NR NR NR NR 47.2% NR	82% 12% 79.4% 19%	NR 69.4% 100% 23%	NR NR NR	PCI for ACS	Chronic clopidogrel maintenance: 75 mg/day for more than 5 days before the coronary stent implantation Clopidogrel loading dose (LD): Loading dose of 300 mg clopidogrel 24 h to 5 days before the coronary stent implantation followed by 75mg/day. All patients received aspirin (80–100mg daily) for >5 days before the coronary stent implantation.	None

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
Trenk 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	802 NR 627 (78%) 66.4 ± 9.1	NR NR [LVEF<55%: 35.8% NR Previous balloon angioplasty:34.2%; previous CABG: 14% CANADIAN Cardiovascular Society angina class III or IV: 24.8% NR NR 22.9% NR	NR Active smokers: 10.8% arterial hypertension (definition NR): 82.3% 24.8%	NR NR 100% NR	36.4% 100% DES multivessel PCI: 22.2%	CAD, elective PCI with stent implantation	Pretreatment: with pre-treatment with 600 mg of clopidogrel & aspirin (100 mg per day for at least 5 days); After PCI: All patients received aspirin (≥100 mg per day) lifelong & clopidogrel (75 mg per day) for 30 days after placement of bare-metal stents or for 6 months after placement of at least 1 drug-eluting stent.	During procedure: All patients received an intra-arterial dose of 100 to 140 U/kg heparin;
Tantry 2010{Tantry, 2010 39 /id} 21079055 Multicountry - North America and Europe Genetic substudy of ONSET/OFFSET and RESPOND	82 (clopidogrel group, from RESPOND and ONSET/OFFSET) White 74 (90%) Black 6 (7%) 62 (76%) 65± 8	NR NR NR CABG 32 (39%) NR NR NR 41 (50%) NR	Dyslipidemia including hypercholesterolemia 79 (96%) 8 (10%) HTN 60 (73%) 17 (21%)	NR NR 100% 17 (21%)	NR NA NA	Stable CAD receiving aspirin who consented to genotyping	All patients received 75 to 100 mg/d aspirin clopidogrel (600-mg load, 75 mg/d thereafter)	None
Wallentin, 2010{Wallentin, 2010 56 /id} 20801498 Multiple countries (43 countries in North America, South America, Europe, Asia, Australia) PLATO	5148 (clopidogrel group) White 5058 (98%) 3571 (69%) 62.5 ±11.04	NR NR NR NR NR NR NR NR NR	NR Non-smoker 2049 (40%) Ex-smoker 1270 (25%) Habitual smoker 829 (36%) NR 1189 (23%)	NR 2486 (48%) 4946 (96%) 2083 (40%)	NR NR NR	Hospitalization for ACS, with or without ST-segment elevation	75 mg once daily (300–600 mg loading dose)	None
Hochholzer, 2010{Hochholzer, 2010 76 /id} 20510210 Germany EXCELSIOR	802 NR 72% 66	NR NR NR NR NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR	37% NR NR	Elective coronary stent placement	Pre-intervention: All patients received a LD of 600 mg of clopidogrel. After PCI: All patients received clopidogrel (75 mg/day) for 30 days after placement of bare-metal stents or for 6 months after placement of at least 1 drug-eluting stent. After PCI: All patients received aspirin (≥100 mg/day), lifelong,	None
Jeong 2010{Jeong, 2010 70 /id} 20650435 Korea	126 Whites: 0%	NR NR 6 (4.8) 1 (0.8)	46 (36.5) 35 (27.8)	NR 100	122 (96.8) 4 (3.2)	treated with PCI for symptomatic coronary artery disease.	One-hundred and six patients were collected from a registry of the ACCEL (Adjunctive	None

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
NR	85 (67.5) 61.6±11	28 (22.2) 34 (27) NR 70 (55.6) 36 (28.6)/ 28(22.2)	67(53.2) 31 (24.6)	NR 1 (0.8)	35 (27.8)		Cilostazol Versus High-MD Clopidogrel) studies , which were performed to compare the degree of platelet inhibition by adjunctive cilostazol versus high-MD clopidogrel in patients within a specific subset: HPPR, diabetes, drug-eluting stent implantation for complex lesions, and acute myocardial infarction. The high-MD group received a high-MD clopidogrel of 150 mg/day for 1 month. A minority (n = 20, 15.9%) of patients received high-MD clopidogrel for over 1 month after PCI at the attending physician's discretion.	
Barker, 2010{Barker, 2010 52 /id} 20965456 USA NR	41 NR 35 (85.3) 66.6±10.6	NR NR NR (>80%) NR NR NR 13 (31.7) NR	36 (87.8) NR 36 (87.8) 16 (39)	NR NR NR 10 (24.3)	NR NR NR	CAD patients if they: 1) had received maintenance clopidogrel or a loading dose of clopidogrel ≥300 mg and 2) had high OTR, defined as Verifynow P2Y12 reaction units (PRU) ≥235.	Patients were administered clopidogrel 150 mg/day for 7 days, after which platelet reactivity was reassessed.	None
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	411 NR 321 (78.1) 62.9±12.2	NR NR NR NR NR NR NR NR NR	218 (53) 154 (37.5) 243 (59.1) 143 (34.8)	NR 100% 100% 65 (15.8)	NR NR NR	undergoing PCI for non–ST-segment elevation acute coronary syndrome	All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement. Dose adjustment was performed before PCI in all patients.	None
Gurbel 2011{Gurbel, 2011 24 /id} 21392617 USA NR	118 94(63%) 52 (35%) 63± 11	NR NR NR 29 (21%) NR NR NR 37 (31%) NR	85(72%) History 23 (19%) Current 18 (15%) Systolic 135±18 Diastolic 72±15 HTN 93(79%) 46 (39%)	NR 100% 100% 22(29%)	NR NR NR	Established CAD	Maintenance clopidogrel for at least 2 weeks (Dose NR)	None
Hwang 2011{Hwang, 2011 35 /id}	190 Asian 100%	NR NR	22.6	NR	97.9	Elective coronary stent implantation	All patients received a 300-mg loading dose	None

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
21075428 South Korea NR	71.6 62.6 ±11	1.6 PCI 8.9, CABG 2.6; NR 40.5 NR 8.4 NR	41.1 HTN 57.9 30	NR NR 2.1	DES 24.7		(LD) of clopidogrel and aspirin at least 12 hours before PCI, followed by 200 mg/day maintenance dose of aspirin and 75 mg/day of clopidogrel thereafter.	
Kang, 2010{Kang, 2010 40 /id} 20724801 Korea NR	215 Asian 100% 136 (63.3) 63.5±10.8	NR NR 3(1.4) PCI:21(9.8)/CABG: 3(1.4) NR NR NR 14 (6.5) NR	33(15.4) 84 (39.1) 127 (59.1) 65 (30.2)	NR 100% 100% 4 (1.9)	NR NR 58 (27.5)	Scheduled coronary stenting	A 300-mg LD of clopidogrel and aspirin was administrated 12-24 hours before scheduled PCI, followed by 200 mg/day MD of aspirin and 75 mg/day clopidogrel	None
Liu 2010{Liu, 2010 38 /id} 21163112 China NR	722 Whites: 0 568 (78.7) 67.4±8.9	NR NR NR PCI:139 (19.5)/ CABG: 37 (5.1) NR NR NR 144 (19.9) NR	281 (34.9) NR 453 (62.7) 187 (25.9)	NR 100% 100% NR	NR NR NR	Elective PCI for symptomatic stable CAD	A loading dose of 300 mg clopidogrel was given to all patients and a daily maintenance dose of 75 mg for a minimum of 12 months.	None
Maeda, 2011{Maeda, 2011 30 /id} 21178986 Japan NR	97 Asian 100% 67 (69) 67±10	NR NR NR NR NR NR NR NR NR	NR 12(12) NR 6(18)	NR NR NR NR	NR NR NR	with CAD after percutaneous coronary intervention	(i) aspirin (100 mg, q.d.), (ii) aspirin (100 mg, q.d.) plus clopidogrel (75 mg, q.d.; Plavix, Sanofi-Aventis, Tokyo, Japan), or (iii) aspirin (100 mg, q.d.) plus ticlopidine (100 mg, b.i.d.;	None
Malek,{Malek, 2010 43 /id} 2010 20924183 Poland NR	261 NR 67.4 60.4±10.9	NR 6.5 1.5 10.0 NR NR 9.2 17.7 78.5/NR	72.7 39.8 HTN 83.5 31.6	NR 100 96.9 NR	NR NR NR	AMI with or without STE; PCI with stenting was attempted.	Pre-hospital 300 or 600 mg loading dose followed by 75 mg daily for at least 1 month	None
Simon 2011{Simon, 2011 27 /id} 21262992 France	2353 NR	NR 2.9	44.4 34.6	NR 100	NR NR	ACS patients undergoing PCI (<80%)	NR	NR

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
FAST-MI	72.3 63.4±13.4	3.2 PCI 8, CABG 3.3; NR NR NR 11.3 NR	52.3 31.7	94.9 NR	NR			
Yamamoto 2011{Yamamoto, 2011 25 /id} 21168310 Japan NR	123 Asian 100% 81(66%) 68.6 ± 10	NR NR NR NR NR NR NR NR NR	61 16 HTN 78 49	NR 61 39 26	NR NR NR	Cardiac catheterization upon diagnosis of stable CAD	300mg loading dose and 75mg/day clopidogrel maintenance dose plus 100mg aspirin	None
Park 2011{Park, 2011 21 /id} 21345843 Korea CILON-T	474 NR 69.6 63.3±8.7	NR 0.2 NR PCI 10.5, CABG 3.6; 47.7 46.6 NR 5.6 NR	44.3 20.7 HTN 67.9 33.5	NR NR NR 0.8	NR NR NR	Angina pectoris or positive stress test, native coronary artery lesions for which DES implantation was feasible.	Clopidogrel loading dose 300-600 mg and 75mg daily for at least 6 months	None
Tiroch, 2010{Tiroch, 2010 62 /id} 20826260 Germany NR	928 NR 75 64.8±12.9	NR NR NR CABG 6.1	51.9 36.5 HTN 74.5 24.1	NR NR NR NR	97.5 NR NR	ACS patients (M)I, >90% PCI with BMS	All patients received a loading dose of 600mg clopidogrel. Post procedural therapy consisted of aspirin (100mg twice daily, indefinitely) and clopidogrel (75mg once	None

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
		NR NR NR 13.9 NR					Daily for at least 6months).	
Sorich, 2010{Sorich, 2010 49 /id} 20492467 707 sites in 30 countries Substudy of TRITON-TIMI 38	2943 Caucasian 91.9 Hispanic 4 African 3 Asian 0.9 Other 0.2 75 60.9±11.2	NR NR 2.7 NR NR NR NR 18 74/30.2	55.6 38.3 HTN 64.1 23.1	NR NR NR NR	NR NR NR	Acute coronary syndromes (representative of the entire spectrum of those syndromes) with scheduled PCI	clopidogrel (300-mg loading dose and 75-mg daily maintenance dose) for 6–15 months.	None
Sibbing, 2010{Sibbing, 2010 48 /id} 20492469 Germany NR	986 NR 77.2 67.3±10.3	NR NR NR 17 NR NR NR 40.2 NR	77.6 10.9 68.1 25.9	NR 100 100 NR	NR NR NR	CAD patients in a stable condition and were on dual antiplatelet treatment with aspirin and clopidogrel	Aspirin (dose NR) and clopidogrel (75 mg/day)	
Sawada, 2010{Sawada, 2010 36 /id} 21099121 Japan NR	100 NR 85 69.6±9.2	NR NR NR NR NR NR	69 41 HTN 81 42	NR 100 NR 50	NR NR NR	CAD, PCI with DES implantation	All patients with DES implantation received dual antiplatelet therapy consisting of aspirin and clopidogrel	NR

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
		NR NR NR						
Pare, 2010{Pare, 2010 46 /id} 20979470 Multiple countries CURE	2549 Whites: 86.2 58.8 63.8±11	NR NR NR PCI=3.2% & CABG=9.8 NR/NR NR/NR NR/NR NR/NR NR/NR	NR 23.1 135.5±22.3&78.6±13.6 NR 20.7	NR NR NR NR	15.5 NR NR	ACS & Stroke	Clopidogrel (at a dose of 75 mg per day)	None
Pare, 2010{Pare, 2010 46 /id} 20979470 Multiple countries ACTIVE-A	570 Whites: 100 54.4 70.8±10.1	NR NR NR NR NR NR NR NR NR	NR 8.4 136.6±19&80.9±11.5 NR 21.8	NR NR NR NR	NR NR NR	ACS & Stroke	Clopidogrel (at a dose of 75 mg per day)	None
Mega, 2010{Mega, 2010 57 /id} 20801494 707 sites in 30 countries TRITON-TIMI 38	2932 Whites: 97.6 72% 60.2±10.9	NR NR NR NR NR NR NR 868 (30)	NR NR NR NR	NR NR NR NR	NR NR NR	Patients with acute coronary syndromes undergoing planned percutaneous coronary interventions	clopidogrel (300-mg loading dose and 75-mg daily maintenance dose) for 6–15 months.	None

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
		2064 (70)						
Bouman 2011{Bouman, 2011 9 /id} 21628721 Netherlands Genetic substudy of the Popular study	1024 NR 75.1% 64±11	100 NR NR NR NR NR NR NR	NR 1.2 76.9 18.5	NR 41.1 NR 15.1	100 DES 63.2 BMS 36.8	CAD patients undergoing PCI with stenting	pretreated with clopidogrel (75 mg daily for >5 days, or a loading dose of 300 mg ≥24 h or 600 mg ≥4 h before (PCI)) and aspirin (80-100 mg daily ≥10 days prior to PCI) unless on long-term anticoagulation with coumarin derivatives. All patients (after receiving drug-eluting or bare-metal stenting) were treated with clopidogrel for at least 1 year. Clopidogrel and aspirin maintenance doses were 75 mg and 80 to 100 mg daily, respectively.	NR
Campo 2011{Campo, 2011 13 /id} 21679849 Italy NR	300 NR 77 66 ± 13	NR NR NR PCI 16, CABG 11 NR NR NR 27 Non-STEMI ACS 61	51 24 HTN 72 24	NR 100 at 6month 97 100 at 6month 99 53	NR DES 71 Multivessel PCI 36	Patients with ischemic HD undergoing PCI with stenting	aspirin (300 mg as loading dose [LD] at hospital admission, followed by 100 mg daily, independently to previous or not chronic use). Clopidogrel 600 mg was given as LD at least 12 h before PCI. After intervention, clopidogrel 75 mg/day was continued for 12 months.	Anticoagulant and glycoprotein IIb/IIIa inhibitors treatment was administered at the interventionalist's discretion.
Fernando 2011{Fernando, 2011 233 /id} 21696537 Australia NR	31 NR 93 62 ± 11	NR NR NR NR NR 24 NR See next row	76 3 HTN 83 3	NR 0 100 NR	See next row BMS 62 DES 38 NR	ACS patients undergoing PCI	open label clopidogrel 75 mg daily and randomized to either esomeprazole 40 mg or placebo (sugar filled) capsule daily for a period of 6 weeks. All patients continued routine medications, including aspirin (100 mg). This was followed by a 2-week wash-out period after the first treatment period where study medications were ceased. Patients then	NR

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
		41/34					resumed clopidogrel 75 mg daily and the opposite therapy to which they were randomized in the first 6-week period (crossed-over to alternative therapy).	
Geisler 2008{Geisler, 2008 161 /id} 18781853 Germany NR	237 Caucasian 100 76.4 69(11.3) median and IQR	NR NR NR NR NR NR NR NR 12.7/22.8	73.8 NR HTN 85.2 34.6	NR NR NR NR	NR NR NR	CAD patients undergoing PCI	Loading dose of 600 mg clopidogrel was given prior to PCI, followed by a daily dose of 75 mg; also 500 mg IV aspirin given PCI, followed by 100 mg orally per day after, unless contraindicated because of GI bleeding or allergy; 70 units per kg body weight of unfractionated heparin given before PCI	NR
Gladding 2008{Gladding, 2008 149 /id} 19463375 New Zealand PRINC (Plavix Response in Coronary Intervention) Trial	60 Caucasian 95 83 68 (10)	NR CHF 3 NR PCI 20, CABG 10; NR NR NR NR 5/7	NR 10 HTN 57 18	NR 0 98 NR	Multi stent 15 DES 35 DES NR	CAD patients undergoing elective PCI	All patients: 600-mg clopidogrel at the start of the PCI procedure. At 2 hours after, 37 patients received 600 mg clopidogrel and 23 received placebo. Starting the next day, all patients were separately randomized to receive clopidogrel 75 or 150 mg once daily for 1 week, followed by 75 mg once daily thereafter.	glycoprotein IIb/IIIa inhibitor and medications inhibiting CYP3A4. Patients on warfarin were eligible if the international normalized ratio was <1.5 at study entry and warfarin could be withheld for the 7-day study duration
Gurbel 2010{Gurbel, 2010 91 /id} 19817997 USA NR	36 Whites: 70% NR NR	NR NR NR NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR	CAD patients undergoing PCI with stenting now in stable condition	chronic daily 75 mg clopidogrel and 81 mg aspirin therapy PLUS one 60-mg dose of elinogrel	NR

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
		NR NR						
Harmsze 2010{Harmsze, 2010 6 /id} 20833683 Netherlands NR	176 cases, 334 controls NR 77.8, 79.5 64.1(10.5), 62.1(9.4)	NR NR NR NR NR NR NR 23.9, 42.4; NR	52.3, 50.5; 22,2, 12.1; HTN 46.6, 49.5; 17.6, 16.4;	NR 100 100 29.0, 22.7;	100, 100 DES 31.3, 47.4; NR	CAD patients undergoing PCI with stenting	Cases: still on aspirin and clopidogrel at the time of stent thrombosis. All control subjects were on clopidogrel maintenance therapy and aspirin (80– 100 mg) during the entire follow-up period.	NR
Kim 2011{Kim, 2011 18 /id} 21511217 South korea ACCELAMI2C19 (High-dose clopidogrel group)	62 pts on 150 mg clopidogrel daily NR 69.4 59.4±12.2	NR NR 3.2 NR NR NR NR 6.5 56.5/43.5	25.8 62.9 NR 45.2 24.2	NR 100 100 0	93.5, 96.9; DES 93.5, BMS 0; DES 95.3, BMS 1.6; Multivessel 25.8 20.3;	Patients with ACS (AMI undergoing PCI with stenting)	all patients received a 600-mg loading-dose (LD) of clopidogrel, followed by a maintenance dose (MD) of 75 mg daily before randomization. All patients also took a 300-mg LD of aspirin, followed by aspirin 200 mg daily throughout the study period. After blood sampling pre-discharge, the patients were randomly assigned to high-MD clopidogrel of 150 mg daily (high-dose group) or adjunctive cilostazol 100 mg twice daily to clopidogrel 75 mg daily (standard dose + cilostazol group).	Use of low-molecular-weight heparin (enoxaparin) or unfractionated heparin was at the physician's discretion, and only tirofiban with a short half-life was administered if needed.
Kim 2011{Kim, 2011 18 /id} 21511217 South korea ACCELAMI2C19 (cilostazol group)	64 pts on 75 mg clopidogrel +cilostazol daily NR 76.6 63.9±11.9	NR NR 7.8 NR NR NR	29.7 56.3 NR 48.4 31.3;	NR 100 100 1.6				

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
		NR 4.7 48.4/51.6						
Lee 2011{Lee, 2011 4 /id} 21786436 South korea NR	166 NR 69 64.4±11.6	NR NR NR NR NR NR NR NR NR	NR 49 HTN 68 30	NR NR NR NR	NR NR NR	Patients with cerebrovascular disease	75 mg clopidogrel daily for at least six days before platelet testing	NR
Malek 2008{Malek, 2008 167 /id} 18577829 Poland NR	105 NR 70 60.0±11.6	NR NR 4 10 NR NR 8 16 82	34 47 HTN NR 17	NR 100 100 NR	NR NR NR	Patients with ACS undergoing PCI	loading dose of 300 mg of aspirin followed by a daily regimen of 75 mg and a loading dose of either 300 or 600 mg of clopidogrel followed by 75 mg daily	NR
Pettersen 2011{Pettersen, 2011 228 /id} 21426546 Norway Aspirin and Clopidogrel non-responsiveness clinical Endpoint Trial (ASCET)	219 Caucasian 100 79 62 (8.5)	100 NR NR PCI 38, CABG 19; NR NR NR 37	NR 16 Diastolic 82.1±9.2 /systolic 138.2±18.6 11	NR 100 100 14	NR NR NR	CAD patients undergoing PCI (<80% PCI)	75 mg/day clopidogrel; also possibly aspirin but details NR	NR

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
		NR						
Sibbing 2011{Sibbing, 2011 2 /id} 21527445 Germany NR (cohort)	1524 NR 77 67.4±10.6	NR NR NR CABG 14.6 NR NR NR 31.9 NR	NR 13.6 NR HTN 91.3 28.2	NR 100 100 18.1	100 NR NR	CAD pts undergoing PCI	Pretreatment with a loading dose of 600 mg of clopidogrel prior to the procedure. The recommended pr-treatment interval was ≥ 2 h.	Excluded patients on GP IIb/IIa during the 10 days before the PCI
Sibbing 2011{Sibbing, 2011 2 /id} 21527445 Germany NR (case control)	1566 NR 78 67.6	NR NR NR 13 NR NR NR 32.3 NR	NR 14.6 NR 90 29.1	NR 100 100 NR	NR NR NR	CAD pts undergoing PCI	Pretreatment with a loading dose of 600 mg of clopidogrel prior to the procedure.	Excluded patients on GP IIb/IIa during the 10 days before the PCI
Simon 2009{Simon, 2009 142 /id} 19106083 France FAST-MI	2208 NR 71 66.2/13.7	23 4 TIA 3, stroke 5; PCI 14, CABG 5; NR NR NR 9 STEMI 53	49 NR diastolic 81/17, systolic 141/28 32	NR 14 23 at screening and 98 in hospital 73	NR NR NR	ACS patients undergoing PCI (<80% PCI)	Mean loading dose, 300 mg/day; mean maintenance dose at time of hospital discharge, 75 mg/day	NR
Hwang	65 Whites:0	NR	30.8	NR	96.9	CAD patients undergoing PCI	All patients	The high-MD

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
2010{Hwang, 2010 55 /id} 20823393 Korea ACCEL-RESISTANCE, DM, COMPLEX (High-dose clopidogrel group)	NR 69.2±7.9	NR 6.2 18.4 NR NR NR 9.2 NR	40 NR 58.5 26.2	89.2 NR 15	DES 30.8		received a 300-mg loading dose of clopidogrel at least 12 hours before PCI (n=98) or were receiving chronic clopidogrel therapy (75 mg daily for >=7 days, n=36). All patients received a 300-mg loading dose of aspirin, followed by 200 mg daily for 1 month. They were randomly assigned to adjunctive cilostazol (triple group) or high-MD clopidogrel (high-MD group) .	group received clopidogrel 150 mg daily for 30 days.
Hwang 2010{Hwang, 2010 55 /id} 20823393 Korea ACCEL-RESISTANCE, DM, COMPLEX (Triple antiplatelet therapy group)	69 Whites:0 NR 63.4±9.4	NR NR 4.3 29 NR NR NR 17.4 NR	18.8 36.2 NR 55.1 28.9	NR 99.5 NR 4.3	95.7 DES 30.4	CAD patients undergoing PCI	All patients received a 300-mg loading dose of clopidogrel at least 12 hours before PCI (n=98) or were receiving chronic clopidogrel therapy (75 mg daily for >=7 days, n=36). All patients received a 300-mg loading dose of aspirin, followed by 200	The triple group (n=69) received adjunctive cilostazol 100 mg twice daily to clopidogrel 75 mg daily for 30 days

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year UID Country Study name	Total N Enrolled Race (% by group) Male (%) Age[3]	Previous CAD (%) Previous heart failure (%) Previous TIA/stroke (%) History of PCI or CABG (%) Stable angina (%) Unstable angina (%) Previous PAD (%) History of MI (%) STEMI/non-STEMI (%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist (%) Clopidogrel (%) Aspirin (%) PPI (%)	Stent implantation (%) Type of stent (%) Multi-or single vessel (%)			
							mg daily for 1 month. They were randomly assigned to adjunctive cilostazol (triple group) or high-MD clopidogrel (high-MD group) .	

Appendix Table D4: Patient characteristics for studies reporting analytic validity information

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Collet, 2009[1] 19108880 France AFIJI (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) registry	Prospective observational, registry based study	YES	Convenience sample of patients from a registry of AMI in patients <45 yr, on clopidogrel for ≥1 mo, with available genotyping information	Young patients with AMI (STE MI or NSTE MI)	The registry covers the period from April, 1996 to April, 2008; patients entered before 1999 (year when clopidogrel became available in the study population) were excluded	Median clopidogrel exposure = 1.07 yr (IQR = 0.28, 3.0) Maximum FU = 8 yr Mean followup = 2.7 yr for CYP2C19 *2 carriers; 2.9 yr for CYP2C19 non-carriers Mean followup = 2.84 yr	Patients were survivors of AMI enrolled in a multicenter registry; followup was on an outpatient basis	Not performed	Non-industry
Fontana, 2008[2] 17681590 Switzerland	Prospective observational study	YES	Consecutive patients who received PCI with stenting in a single center	Patients undergoing PCI with stent placement	NR	Measurements after ≥15 d under clopidogrel (median FU = 19 d; IQR = 15-47)	Inpatient for PCI; outpatient for followup after discharge	Power calculations performed; enrolled 81 patients out of a planned sample size of 100	Non-industry only
Giusti, 2007[3] 18004210 Italy NR	Observational study, prospective (measurements 24 h after PCI)	NO	Consecutive patients	Patients with ACS, undergoing primary PCI	NR	24 h post PCI	Inpatient	no (posthoc only)	Non-industry only
Giusti, 2009[4] 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Prospective observational study of patients enrolled in the RECLOSE study in a single center	NO (single center recruitment for this study)	Consecutive patients consenting to genetic study identified from the RECLOSE study population	Patients with ACS or CAD undergoing PCI with stenting	July 2005 to August 2006 [recruitment period of the RECLOSE study; information from pmid = 17572245]	6 months (unclear what metric; from the KM curves implied maximum FU)	In hospital (PCI)	Not performed	Non-industry only

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Gladding, 2009[5] 19926050 New Zealand NR	Prospective "open label dose escalation study with molecular randomization"	No	NR	Patients who had undergone PCI >2 weeks previously and were on clopidogrel	NR	Total 7 days	Inpatient, with outpatient followup after the inpatient procedure	Yes ("~90%")	NR (except "genotyping" was "supplied" by AutoGenomics, which is the affiliation of one of the authors)
Jinnai, 2009[6] 19531897 Japan Partly industry funded	Prospective	Unclear	Convenience sample	Patients scheduled for PCI	NR	Maximum 28 days; results reported only up to 48 hours	In-patient; patients undergoing elective PCI	Not performed	Partly industry funded
Mega, 2009[7] 19106084 Multinational Genetics substudy of TRITON-TIMI 38 [Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction]	Prospective cohort study (genetics substudy of RCT, only one of the randomized arms included)	YES	Sub study of RCT	Patients with ACS (STE MI, NSTE MI ,UA) planned for PCI	2004-2007	15 months	Inpatient	Not performed	Industry funding
Shuldiner, 2009[8] 19706858 USA Sinai Hospital of	Unclear *Retrospective, based on medical records (based on followup procedures)*	NO	Convenience	CAD patients undergoing non-emergent	January 2004 - May 2007	12 months post-PCI	In-patient in a single catheterization laboratory (non-	Not performed	Non-industry only

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Baltimore Study				PCI			emergent PCI)		
Sibbing, 2009[9] 19193675 Germany NR	Prospective observational study	NO	Convenience sample; patients participating in several randomized clinical trials of abciximab	CAD patients undergoing PCI	May 2000 – December 2005	Complete followup to 30 days	Inpatient for PCI, outpatient followup for the duration of the study followup. Patients with cardiac symptoms were seen in the outpatient clinic for further investigation	Not performed [power analysis was performed post hoc, based on the observed effect size]	Non-industry only (several authors with COI)
Sibbing, 2010[10] 20083681 Germany Part of a prospective study of the Multiplate analyzer	Observational study, prospective	NO	Consecutive patients recruited from a study of the Multiplate analyzer	Patients with CAD with planned DES implantation; patients were eligible regardless of clinical presentation (stable angina, UA, STE MI, or NSTE MI).	February 2007 – April 2008	30 d ±7 days (all outcomes adjudicated at that time-point by phone interview with outpatient clinic visits for those reporting cardiac symptoms)	Inpatient for elective PCI (patients were hospitalized for ≥2 days); patients were the interviewed by phone (outpatient) and those reporting symptoms were examined in the outpatient clinic (for clinical, EKG, and laboratory checkup)	Not performed	Partly industry supported (material provided by manufacturer of the Multiplate analyzer, which was used here as a reference standard)
Varenhorst, 2009[11] 19429918 Sweden NR	Prospective observational study (genetics sub study of RCT comparing antiplatelet regimens)	Yes (2 centers in Sweden)	Sub study of RCT	Patients with CAD (~98% had received PCI before inclusion in the parent trial)	April 2006 to December 2006 [for the parent study]	Maximum followup 29 d±3 d (last measurements obtained)	Outpatients who had regular visits for reactivity measurements	Not performed (for the genetic sub-study)	Industry funded
Frere, 2008[12] 18394438 France	Prospective	NO	Consecutive patients	NSTE ACS patients	2004-2006	≥12 h after loading	Inpatient	NO	NR

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
NR				undergoing angiography					
Frere, 2009[13] 19496924 France Part of larger observational study	Retrospective	NO	Convenience	NSTE ACS patients undergoing angiography	2004-2006	NR (measurements appear to have been obtained after the clopidogrel loading dose)	In-patient, single cardiology department	Not performed	NR (authors' stated that there was "no conflict of interest")
Bonello-Palot[14] 2009 19932784 France NR	Prospective observational study	YES	Convenience sample	Patients undergoing percutaneous coronary intervention (PCI) for ACS; Patients with acute coronary syndromes (ACS),	Aug 2007 – Mar 2008	NR (patients were followed up from admission till the PCI was performed)	Inpatient	Not performed	Partly Industry
Harmsze 2010[15] 19934793 Netherlands NR	Prospective observational cohort	NO	Consecutive patients	Patients undergoing percutaneous coronary intervention (PCI) for ACS	NR	NR	Inpatient	NO	Partly Industry
Trenk 2008[16] 18482659 Germany EXCELSIOR (Impact of Extent of	Prospective observational study	NO	Substudy of the EXCELSIOR prospective study	CAD patients undergoing elective PCI with stent implantation	NR	30 day follow up for all patients, and 12 month follow up for 795 patients (99.1%)	followup after intervention	no (power analysis for the parent study)	Non-industry only

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)									
Tantry 2010[17] 21079055 Multicountry - North America and Europe Genetic substudy of ONSET/OFFSET and RESPOND	RESPOND and ONSET/OFFSET were randomized, double-blind, double-dummy, multicenter studies. RESPOND was crossover; ONSET/OFFSET was parallel-group (prospective)	YES	Sub study of RCT	Adults with stable coronary artery disease receiving aspirin who consented to genotyping	RESPOND, May 19, 2008, to March 25, 2009 ONSET/OFFSET, October 2007 toMarch 2009	2-6 weeks	Outpatient	For both RESPOND and ONSET/OFFSET, YES [YES] Not done for genetic substudy (they took whoever consented)	All industry
Wallentin, 2010[18] 20801498 Multinational (43 countries in North America, South America, Europe, Asia, Australia) PLATO	Prospective observational study	YES	Sub study of RCT	ACS patients with <80% undergoing PCI	October 2006 through July 2008	Median, 277 days	Inpatient	NO (not prospectively powered and had to be based on the maximum number of patients consenting to provide a blood sample for genetic analysis)	All Industry
Hochholzer,	Prospective cohort	No	Unclear	Patients	NR	30 days to 6 months	inpatient	Not performed	NR

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
2010[19] 20510210 Germany EXCELSIOR				undergoing PCI with stenting					
Jeong 2010[20] 20650435 Korea ACCEL-DOUBLE	Cohort	No	Sub study of RCT	Patients with CAD undergoing PCI	Jan 2008-June 2009	≥1 mo	inpatient	it was estimated that a total of 95 patients (57 carriers and 38 noncarriers of the *CYP2C19* variant allele) would be required to provide a power of 90% to detect a statistically significant difference with a 2-sided alpha-level of 0.05.	NR
Barker, 2010[21] 20965456 USA NR	Prospective cohort	No	Selected CAD patients; unclear methods	CAD patients had clopidogrel for >7 days or high OTR	NR	Mean 8 days	Unclear	Yes, 90%	Non-industry
Bonello, 2010[22] 20708365 France NR	Prospective cohort	Yes	Selected sample of Patients with PCI	Patients with PCI	Jan 2009-Jan 2010	NR	Inpatient	Not performed	NR
Gurbel 2011[23] 21392617 USA NR	Cohort	No	Unclear	Patients had established coronary artery disease (CAD) and	NR	NR	Outpatient	Yes. Given the frequency of the *2 allele in the population, to determine a 20% absolute	Non-industry

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
				were on aspirin (81-325 mg/d) therapy for a minimum of 2 weeks were studied (N = 261).				difference in the prevalence of HPR between these 2 groups, a sample size of 105 patients was required with an a = .05 and power of 80%.	
Hwang 2011[24] 21075428 South Korea NR	Cohort	No	Consecutive patients	CAD patients undergoing elective PCI with stent implantation	Jan 2008-March 2009	NR	Inpatients from Department of Cardiology of the Gyeongsang National University Hospital	Not performed	Non-industry
Kang, 2010[25] 20724801 Korea NR	Cohort	No	Consecutive	CAD patients with elective stent implantation	July 2008-June 2009	NR	Hospital	Not performed	Non-industry
Liu 2010[26] 21163112 China NR	Cohort	No	Consecutive	Patients were admitted for elective coronary intervention with symptomatic stable CAD.	Oct 2006-Sep 2007	12 months minimum	Hospital	Not performed	NR
Maeda, 2010[27] 21178986 Japan NR	Cohort	No	NR	CAD	NR	>4 weeks	Unclear	Not performed	NR

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Malek, 2010[28] 20924183 Poland NR	Cohort	No	Consecutive	AMI with and without ST-elevation, PCI with stenting was attempted.	2005-2005	4 years	Hospital	Not performed	Non-industry
Simon 2011[29] 21262992 France FAST-MI	Prospective observational study (registry-based)	Yes	Consecutive	AMI patients undergoing PCI (<80%)	2005-2006	1 year	Inpatient (from ICU)	Not performed	Partly industry
Simon 2011[29] 19106083 France FAST-MI	Prospective observational study (registry-based)	Yes	Consecutive	AMI patients undergoing PCI (<80%)	2005-2006	1 year	Inpatient (from ICU)	Not performed	Partly industry
Yamamoto 2011[30] 21168310 Japan NR	cohort	No	Consecutive	CAD undergoing angiography (and PCI when needed); PCI(for those assessed for clinical outcomes)	NR	340 days	Inpatient	Not performed	NR
Park 2011[31] 21345843 Korea CILON-T	Randomized trial	yes	Sub study of RCT	CAD patients undergoing PCI with stenting	2006-2009	6 months	Inpatient	Yes 18 non-carriers and 11 carriers of CYP2C19-LOF would be needed to provide a power of 95% to detect a statistically significant difference between groups with a	Non-industry

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
								two-sided a-level of 0.05.	
Tiroch, 2010[32] 20826260 Germany NR	Cohort	No	Consecutive	AMI patients with >90% of them undergoing PCI with BMS placement	2005-2008	1 year	Inpatients in a Hospital	No (posthoc only)	NR
Sorich, 2010[33] 20492467 707 sites in 30 countries Substudy of TRITON-TIMI 38	Substudy of RCT	Yes	Selected sample	PCI	November 2004 and January 2007.	6 to 15 months.	Hospital (inpatient)	Not performed	Industry
Sibbing, 2010[34] 20492469 Germany NR	Cohort	No	Consecutive	Stable CAD patients undergoing angiography	Aug 2007 to Sep 2008	NR	Inpatients in a Hospital	Not performed	NR [Speaker fee from industry by first author]
Sawada, 2010[35] 21099121 Japan NR	Cohort	No	NR	PCI	Jan 2008-Jan 2010	243.8±88.1 days Median 223.5 days, range 7-546 days	In patients at Kobe University Hospital	Not performed	NR
Pare, 2010[36] 20979470 Multinational CURE	Prospective cohort study	Yes	Sub-study of RCT	Patients with ACS-NSTE	1998- 2000	3.6 years	Inpatient	NO	Industry
Pare, 2010[36] 20979470 Multinational ACTIVE-A	Prospective cohort study	Yes	Sub-study of RCT	Patients with AFIB	2000-2006	3-12 months	Outpatient	NO	Industry
Mega, 2010[37] 20801494 707 sites in 30 countries	Prospective cohort study	Yes	Sub study of RCT	ACS	November 2004 and January 2007.	6 -15 months.	Inpatient	Not performed	Industry

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
TRITON-TIMI 38									
Bouman 2011[38] 21628721 Netherlands Genetic substudy of the Popular study	Prospective, observational, single-center cohort study	NO	Consecutive sampling (but then patients without DNA samples were excluded)	Patients with CAD taking clopidogrel undergoing elective coronary stent implantation and who were genotyped	December 2005 and December 2007	Total 1 year	Inpatient/outpatient followup after intervention	Not performed	NR (Popular study received platelet-testing equipment from industry)
Campo 2011[39] 21679849 Italy NR	Prospective cohort	No	Consecutive	Patients undergoing PCI for ischemic heart disease who had a baseline and 1 month PRU evaluation and a baseline blood sample for genotyping	December 2008 to May 2009	Max, 1 year	Inpatient followed by outpatient followup	Not performed	NR but authors have COIs with drug companies
Fernando 2011[40] 21696537 Australia NR	Prospective (randomized crossover study design)	NO	Unclear	Patients with ACS and stents on aspirin but not clopidogrel	NR	Duration for all patients who completed study, 14 weeks (6 weeks in each study arm with 2-wk washout in between)	Outpatient	YES [YES]	Non-industry only
Geisler 2008[41] 18781853 Germany NR	Prospective cohort	NO	Consecutive	Caucasian patients undergoing PCI for CAD	July 2006-March 2007	NR	Inpatient only?	YES (86%)	NR except "The authors have no relevant financial

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
									involvement with any…entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes…grants…received or pending…"
Gladding 2008[42] 19463375 New Zealand PRINC (Plavix Response in Coronary Intervention) Trial	2 by 2 factorial, randomized, placebo-controlled, double-blind study over the first 24 h, followed by a 1-week randomized, placebo-controlled, double-blind study	NR	Sub study of RCT	Patients undergoing elective PCI	NR	7 Days total	Inpatient, with outpatient followup after the inpatient procedure	YES [YES ("~80%")]	Non-industry (except VerifyNow analyzer was provided by Sanofi Aventis)
Gurbel 2010[43] 19817997 USA NR	Prospective comparative?	NO	Unclear	Patients with stenting and stable condition who were screened for HPR	Feb. 1,-Sept. 15, 2008	NR (max. follow-up, 7 to 10 days)	Outpatient	Not performed	All industry
Harmsze 2010[44] 20833683 Netherlands NR	Retrospective case-control	YES	Consecutive enrollment	Patients undergoing PCI with stenting	Cases: January 2004 to February 2007 Controls:	Total, 1 yr from the time of PCI	Hospital/outpatient	Not performed	Partly industry?

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
					December 2005 and December 2006				
Kim 2011[45] 21511217 South Korea ACCELAMI2C19 High-dose clopidogrel	Randomized prospective	NO	Sub study of RCT	62 AMI patients treated with emergent PCI receiving a high-MD of clopidogrel	2007-2009	30 days	Inpatient	YES [YES]	Partly industry
Kim 2011[45] 21511217 South Korea ACCELAMI2C19 Cilostazol group	Randomized prospective	NO	Sub study of RCT	64 AMI patients treated with emergent PCI receiving an adjunctive dose of cilostazol	2007-2009	30 days	Inpatient	YES [YES]	Partly industry
Lee 2011[46] 21786436 South Korea NR	Retrospective	NO	Selection of patients with testing for resistance and polymorphism	Patients with cerebrovascular disease who received clopidogrel and were tested for clopidogrel resistance and CYP2C19 polymorphism	January 2009 to June 2010	NR	Outpatient	Not performed	Non-industry only
Malek 2008[47] 18577829 Poland NR	Prospective observational	Unclear	NR	Patients with any ACS undergoing PCI and receiving clopidogrel and aspirin	NR	12 months	Inpatient and then outpatient followup (by phone)	Not performed	Non-industry only
Pettersen 2011[48]	Prospective observational	NO	Consecutively	CAD patients	October 2005 to	NR	Outpatient	Not performed	Non-industry

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
21426546 Norway Aspirin and Clopidogrel non-responsiveness clinical Endpoint Trial (ASCET)	study		included randomized clopidogrel group from ASCET (n=219)	randomized to receive maintenance clopidogrel (<80% PCI)	June 2008				only
Sibbing 2011[49] 21527445 Germany NR	Prospective cohort	NO	For PCI cohort: volunteers for DNA sampling from prospective trial (1524/1608 [95%]) For early ST cohort, consecutive recruitment and DNA sample availability	CAD patients undergoing PCI with stenting (>95%) and receiving clopidogrel and aspirin and who had DNA samples	For PCI cohort (who were the control cohort also), Feb 2007-April 2008	NR	Inpatient	Not performed [	Non-industry only [except "material for platelet function analysis on the Multiplate device was provided free of charge from Dynabyte"]
Sibbing 2011[49] 21527445 Germany NR	Case-control	NO	Consecutive	CAD patients undergoing PCI with stenting	1999-2008	NR	Inpatient	Not performed	Non-industry only [except "material for platelet function analysis on the Multiplate device was provided free of charge from Dynabyte"]
Simon 2009[50] 19106083 France	Prospective observational	YES	Consecutive	Patients with AMI in a French registry	October 1-December 24, 2005	Total 1 year	Inpatient (for the subgroup undergoing PCI); outpatient	Not performed	Partly industry

Author, Year PMID Country Study name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrollment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
FAST-MI				receiving clopidogrel			followup		
Hwang 2010[51] 20823393 Korea ACCEL-RESISTANCE, DM, COMPLEX (High-dose clopidogrel group)	Prospective cohort Hwang	No	Sub study of RCT	High-risk CAD patients undergoing PCI	Jan 2008-June 2009	30 days	Inpatient	No	N on industry
Hwang 2010[51] 20823393 Korea ACCEL-RESISTANCE, DM, COMPLEX (Triple antiplatelet therapy group)	Prospective cohort Hwang	No	Sub study of RCT	High-risk CAD patients undergoing PCI	Jan 2008-June 2009	30 days	Inpatient	No	N on industry
Bouman 2011 Multinational 21170047 NR	Case-cohort study	Yes	Random (for controls); incident cases (convenience because of refusals)	Patients with CAD undergoing PCI with stenting	2003 – 2007	18 mo	Inpatient	Yes (but not for CYP2C19 variants)	No funding information; reported that the authors had no financial conflicts of interest
Bouman 2011 Multinational 21170047 NR	Prospective cohort	Yes	Convenience sample	Patients undergoing PCI with stenting	2007-2009	12 months	Inpatient	Yes	No funding information; reported that the authors had no financial conflicts of interest

Appendix Table D4: Genotypic test information

Author, year UID Country Study name	Genotyping assay (manufacturer):	Type of sample from which DNA extracted Interval between clopidogrel doses and DNA sampling (in days) Interval between sampling and genotyping results (in days): Interval between collection and DNA extraction:	N genotyped: Genotyping success (%):	Alleles tested Genotypes tested: Frequency of genotype:	Rational for the grouping of genotypes reported (Yes/No) [short description]	Grouping of genotypes: Frequency of group:
Collet, 2009 19108880 France AFIJI (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) registry	TaqMan Validated SNP assays (Applied Biosystems, Foster City, CA, USA) with the 7900HT sequence detection system (Applied Biosystems)	Periph. blood NR NR NR	259 (only included patients with available genotyping information)	CYP2C19 *2 rs4244285 *3 *4 *5 *6 *2/*2 = 9 (3.5%) *2/*1 = 64 (24.7%) *1/*1 = 186 (71.8%) A *3 was detected in two patients; *4 in 3 patients; *5 and *6 were not detected in any patient.	Not explicitly provided	Carriers (*2/*2 or *2/*1) = 73 (28.2%) Non-carriers (*1/*1) = 186 (71.8%)
Fontana, 2008[1] 17681590 Switzerland NR	PCR-RFLP	Blood NR NR NR	81 (100%)	CYP2C19 *2 (rs4244285) *2/*2 = 2 (2.5%) *2/*1 = 25 (30.7%) *1/*1 = 54 (66.7%)	In analyses relevant to this Key Question, no grouping was used. For other analyses heterozygotes and homozygotes for the rare variant (*2) were combined. Small sample size of the *2/*2 group was given as the reason for this grouping.	For this key question no grouping was performed. However, for analyses relevant to KQ3 analyses were performed by contrasting carriers with non-carriers (a dominant model).
Giusti, 2007[2] 18004210 Italy NR	PCR-RFLP	Whole blood Blood was collected "after PCI intervention" NR NR	1419 (not clear if genotyping failed on some patients)	CYP2C19 *2 (rs4244285) *2/*2 = 40 (2.8%) *2/*1 = 405 (28.6%) *1/*1 = 974 (68.6%)	Not explicitly reported.	Carriers (*2/*2 or *2/*1) [for some analyses] = 445 (31.4%) *1/*1 = 974 (68.6%)
Giusti, 2009[3] 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	PCR-RFLP	Whole Blood Venous blood samples were obtained 12-18 h from clopidogrel loading (assuming that blood for genetic and phenotypic testing was obtained at the same time); NR	772 (100%)	CYP2C19*2 (rs4244285) *2/*2 = 26 (3.4%) *2/*1 = 221 (28.6%) *1/*1 = 525 (68.0%)	Not explicitly reported (analyses were reported both with grouped and ungrouped genotypes).	"Carriers (*2/*2 or *2/*1) [for some analyses] = 247 (32%) Non-carriers (*1/*1) [for some analyses] = 525 (68%) "

Author, year UID Country Study name	Genotyping assay (manufacturer):	Type of sample from which DNA extracted Interval between clopidogrel doses and DNA sampling (in days) Interval between sampling and genotyping results (in days): Interval between collection and DNA extraction:	N genotyped: Genotyping success (%):	Alleles tested Genotypes tested: Frequency of genotype:	Rational for the grouping of genotypes reported (Yes/No) [short description]	Grouping of genotypes: Frequency of group:
		NR				
Gladding, 2009[4] 19926050 New Zealand NR	Autogenomics 2C19+ assay involving BioFilmChip microarray on the INFINITI analyzer	Whole blood "Genotyping was done after the second platelet function test [7 days after enrollment] and the results were retrospectively assessed" so patients had been receiving clopidogrel for a mean of over 10 weeks before genotyping. NR NR	39 (100%)	CYP2C19*2 (rs4244285) = 33% carriers CYP2C19*3 (rs1057910) = 0% carriers CYP2C19*17 (rs28399504) = 46% carriers	Not explicitly reported	CYP2C19*2 (and CYP2C9*3 though this is not of interest) carriers (poor metabolizers) = NR (but could try and count from Fig. 4) CYP2C19*2 (and CYP2C9*3 though this is not of interest) carriers (poor metabolizers) = NR (but could try and count from Fig. 4)
Jinnai, 2009[5] 19531897 Japan Partly industry funded	Direct sequencing (ABI 3100 genetic analyzer; PE Applied Biosystems, Foster City, CA)	Peripheral whole blood NR NR NR	25 (100%) (Of the 30 patients included 2 patients were not evaluated at 48 hours; 1 died of cancer; 1 refused genomic analysis; 1 was lost to followup)	CYP2C19*2 and *3 [Additional genes, not relevant to the report, were also genotyped] *2/*2 = 3 (12%) *3/*3 = 0 (0%) *2/*3 = 3 (12%) "*3/*1 = 2 (8%) *2/*1 = 6 (24%) *1/*1 = 11 (44%)	Not explicitly reported.	PM = *2/*2 or *2/*3 = 6 (24%) IM = *2/*1 or *3/*1 = 8 (32%) EM = *1/*1 = 11 (44%)
Mega, 2009[6] 19106084 Multinational Genetics substudy of TRITON-TIMI 38 [Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction]	98% of genotyping procedures were done with the Affymetrix Targeted Human DMET (drug metabolizing enzymes and transporters) 1.0 Assay (Affymetrix); for missing data from the DMET chip additional genotyping was performed with bi-directional sequencing or exon-specific PCR followed by RFLP	NR NR NR NR	1477 of which 1459 could be classified as CYP2C19 carriers or non-carriers (> 98.8% -this excludes patients that could not be assigned to a functional category based on genotype – exact count not provided)	CYP2C19 *1A;*2A;*3;*4;*5A;*6;*7;*8;*9;*10;*12;*13;*14 *1A/*1A = 1064 (73%) *1/*2A, *1A/*3, *1A/*4, *1A/*8 = 357 (24%) *2A/*2A, *2A/*3, *2A/*4, *2A/*5A, *2A/*8 = 38 (3%) *1A/*9, *1A/*10, *2A/*17, *6/*17= NR	CYP alleles were classified a priori by their effects on enzymatic function based on the literature. For each CYP gene, subjects were dichotomized a priori into 2 groups on the basis of whether they possessed at least one allele with significantly reduced function.	Non-carrier (includes extensive and ultra-metabolizers) = 1064 Carriers (intermediate + poor metabolizers) = 395 Unknown corresponding phenotype (not included in main analyses)= Excluded & Frequency NR

Author, year UID Country Study name	Genotyping assay (manufacturer):	Type of sample from which DNA extracted Interval between clopidogrel doses and DNA sampling (in days) Interval between sampling and genotyping results (in days): Interval between collection and DNA extraction:	N genotyped: Genotyping success (%):	Alleles tested Genotypes tested: Frequency of genotype:	Rational for the grouping of genotypes reported (Yes/No) [short description]	Grouping of genotypes: Frequency of group:
	analysis.					
Shuldiner, 2009[7] 19706858 USA Sinai Hospital of Baltimore Study	TaqMan SNP assay (Applied Biosystems, Foster City, California)	Blood 90 patients were already on clopidogrel when entering the study; all pther patients received clopidogrel loading followed by maintenance treatment NR NR	227 (99.1% - 225 patients included in analyses)	CYP2C19*2 (rs4244285) [Additional CYP2C19 variants were genotyped in healthy volunteers] CYP2C19 *2/*2 = 3 (1.6%) CYP2C19 *2/*1 = 54 (28.7%) CYP2C19 *1/*1 = 131 (69.7%)	Not explicitly reported	Carriers (*2/*2 or *2/*1) = 67 (29.8%) Non-carriers (*1/*1) = 158 (70.2%)
Sibbing, 2009[8] 19193675 Germany NR	TaqMan (ABI Prism Sequence Detector 7000, Applied Biosystems)	Whole blood Median = 5.1 h (IQR = 3.0 to 14.0 h) NR NR	2485 (100%)	CYP2C19 rs4244285 CYP2C19 *2/*2 = 47 (2%) CYP2C19 *2/*1 = 633 (25%) CYP2C19 *1/*1 = 1805 (73%)	Carriers vs. non-carriers was used in the majority of analyses. A dominant model was chosen because the mutant *2 allele results in a complete loss of enzyme function. A citation was provided to a paper on the functional relevance of CYP alleles.	Carriers = 680 (27%) Non-carriers = 1805 (73%)
Sibbing, 2010[9] 20083681 Germany Part of a prospective study of the Multiplate analyzer	TaqMan assay (ABI Prism Sequence Detector 7000, Applied Biosystems, Foster City, CA)	Arterial blood All patients received a clopidogrel loading dose with a recommended pre-treatment interval of 2h; blood was sampled directly before PCI. NR NR	1524 which is 95% of all eligible patients (100%)	CYP2C19 *17, (rs12248560) *17/*17 = 76 (5%) *17/*1 = 546 (35.8%) *1/*1 = 902 (59.2%)	Some analyses were reported without grouping the genotypes. No rationale was presented for the choice of model.	Carriers (*17/*17 or *17/*1) = 622 (40.8%) Non-carriers (*1/*1) = 902 (59.2%)
Varenhorst, 2009[10] 19429918 Sweden Genetic sub-study	Affymetrix Targeted Human Drug Metabolizing Enzyme and Transporter (DMET) 1.0 assay (Affymetrix, Santa Clara, CA, USA) for all alleles except *17; Conventional PCR-RFLP	Peripheral Blood NR NR NR	51 in the clopidogrel group consented to testing (100%)	*1A; *2A;*3;*4;*5A;*6;*7;*8;*9; *10; *12;*13;*14;*17 Ungrouped (by locus) data were not reported		Extensive metabolizers (*17/*17, *1A/*17, *1A/*1A) = 37 (79%) Reduced metabolizers (*1A/*2A, *1A/*8, *2A/*2A) = 9 (19%) *2A/*17=1 (2%)

Author, year UID Country Study name	Genotyping assay (manufacturer):	Type of sample from which DNA extracted Interval between clopidogrel doses and DNA sampling (in days) Interval between sampling and genotyping results (in days): Interval between collection and DNA extraction:	N genotyped: Genotyping success (%):	Alleles tested Genotypes tested: Frequency of genotype:	Rational for the grouping of genotypes reported (Yes/No) [short description]	Grouping of genotypes: Frequency of group:
	for *17 (no other information provided)					
Frere, 2008[11] 18394438 France NONE	Allele-specific PCR	DNA extracted from peripheral blood leucocytes NR NR NR	603 (99.7% [601-based on genotypes reported])	CYP2C19*2 (rs4244285) CYP2C19 *2/*2 = 23 (3.8%) CYP2C19 *2/*1 = 143 (23.8%) CYP2C19 *1/*1 = 435 (72.4%)	Not explicitly reported (also presents analyses from a general linear model where polymorphism was treated as the independent variable)	Recessive and codominant models were analyzed (Frequency NR)
Frere, 2009[12] 19496924 France Part of larger observational study	Allele-specific PCR	NR NR NR NR	598 (99.7% for CYP2C19 *4; 10% for CYP2C19 *5; 99.8% for CYP2C19 *6; 99.7% for CYP2C19 *17)	CYP2C19 *4; CYP2C19 *5; CYP2C19 *6; CYP2C19 *17 CYP2C19 *17/*4 = 25 (4.2) CYP2C19 *17/*1 = 189 (31.7) CYP2C19 *17/*1 = 382 (64.1) CYP2C19 *4/*4 = 0 (0%) CYP2C19 *4/*1 = 8 (1.3%) CYP2C19 *1/*1 = 589(98.7%) CYP2C19 *5/*5 = 0 (0) CYP2C19 *5/*1 = 0 (0) CYP2C19 *1/*1 = 598(100%) CYP2C19 *6/*6 = 0 (0) CYP2C19 *6/*1 = 1 (0.2) CYP2C19 *1/*1 = 596 (99.8)	Recessive, dominant (carriers vs. non-carriers), and co-dominant models were analyzed. No rationale was reported for these groupings.	*17/*17 + *17/*1 (carriers, also referred to as extensive metabolizers) = 214 (35.9%) *1/*1 (non-carriers) = 382 (64.1%) Frequency of grouping NR Frequency of grouping NR Frequency of grouping NR
Bonello-Palot[13] 2009 19932784 France NR	PCR amplification using primer oligonucleotides designed with Primer3 software tool.	Whole blood NR NR	73 (100%)	CYP2C19 2* (rs4244285) "*2/*2 = 7 (9.6%) Wild-type/*2 = 15 (20.5%) Wild-type/wild-type = 51 (69.9%)"	Not explicitly reported	≥ 1 CYP2C19*2 allele (*2/*2 or Wild-type/*2) = 22 (30.1%) Wild-type genotype (Wild-type/wild-type) = 51 (69.9%)

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		NR				
Harmsze 2010[14] 19934793 Netherlands NR	Real-time PCR (manufacturer NR)	Whole blood NR NR NR	428 (100%)	CYP2C19 G681A (*1>*2) (rs4244285) CYP2C19 G636A (*1>*3) (rs4986893) CYP2C19 G681A (*1>*1) = 296 (69%) CYP2C19 G681A (*1>*2) = 120 (28%) CYP2C19 G681A (*2>*2) = 12 (3%) CYP2C19 G636A (*1>*1) = 426 (99.5%) CYP2C19 G636A (*1>*3) = 2 (0.5%) CYP2C19 G636A (*3>*3) = 0 (0%)	Not explicitly reported	Carriers of variant allele of CYP2C19 G681A = 132 (31%) Noncarriers of variant allele of CYP2C19 G681A = 296 (69%) Allele frequencies (not used for grouping) "CYP2C19 G681A *2 = 17% CYP2C19 G636A *3 = 3%
Trenk 2008[15] 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel- Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	TaqMan PCR (Applied Biosystems;Germany; part no. C_25986767_70)	Whole blood NR; Blood was drawn before administration of clopidogrel, at time of PCI and after clopidogrel. It was NR which one was used for genomic analysis NR 1 hr	797 (100%)	CYP2C19*2 681G>A (rs4244285) CYP2C19 wildtype homozygotes (*1/*1) = 552 (69.3%) CYP2C19 (*1/*2) heterozygote = 228 (28.6%)	They reported allele frequencies of 83.6% for CYP2C19*1 (G) and 16.4% for CYP2C19*2 (A) but grouping was done by carriers of the CYP2C19*2 allele and wild-type homozygotes due to low numbers of *2/*2 homozygotes. Background talked about how the role of the CYP2C19*2 loss-of-function polymorphism is not clear.	Noncarriers (*1/*1) = 552 (69.3%) Carriers (*1/*2 or *2/*2) = 245 (30.7%)
Tantry 2010[16] 21079055 Multicountry - North America and Europe Genetic substudy of	TaqMan Assays (Life Technologies; Pleasanton, Calif)	NR NR NR	82 (100%)	CYP2C19 (*1, *2, *3, *4, *5, *6, *7, *8, *17 "CYP2C19*1/*1 Extensive metabolizer = 31 (38%)	Not explicitly reported	Group I: metabolizer status Ultrametaboloizers (UM) (=ultrarapid+rapid heterozygous, i.e., *17/*17 or *1/*17) = 28 (34%)

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ONSET/OFFSET and RESPOND		NR		CYP2C19*1/*2 = 13 (16%) CYP2C19*1/*3 = 1 (1%) CYP2C19*1/*2-*8 Intermediate metabolizer [NB Seems like *2-*8 thoughout really means just *2 or *3. Not sure whether they tested for 4-8.] = NR CYP2C19*2/*2 = 3 (4%) CYP2C19*2-*8/*2-*8 Poor metabolizer = NR CYP2C19*1/*17 Rapd heterozygous = 28 (34%) CYP2C19*2/*17 = 6 (7%) CYP2C19*8/*17 = 0 (0%) CYP2C19*2–8/*17 Poor/rapd heterozygous = NR CYP2C19*17/*17 Ultrarapid metabolizer = 0 (0%)		Extensive metabolizers (EM) = 31 (38%) Intermediate metabolizers (IM) (=intermediate+poor/rapid heterozygous; i.e., *1/*2-*8 or *2-*8/*17) = 20 (24%) Poor metabolizers (PM) = 3 (4%) Group II: LOF-allele carrier status LOF carrier (=IM+PM) = 23 (28%) LOF noncarrier (=UM+EM) = 59 (72%) Group III: GOF-allele carrier status GOF carriers (=UM) = 28 (34%) EM = 31 (38%) LOF carriers (=IM+PM) = 23 (28%)
Wallentin, 2010[17] 20801498 Multiple countries (43 countries in North America, South America, Europe, Asia, Australia) PLATO	TaqMan assays (Applied Biosystems, Life Technologies, Pleasanton, CA, USA)	Blood NR NR NR	5148 (98.8–99.5%)	CYP2C19 loss-of-function alleles *2, *3, *4, *5, *6, *7, and *8; CYP2C19 gain-of-function allele *17 *1/*1 = 1862 (36%) *1/*17 = 1386 (27%) *1/*2 = 898 (17%) *1/*3 = 6 (<1%) *1/*4 = 8 (<1%) *1/*6 = 2 (<1%) *1/*8 = 21 (<1%) *17/*17 = 268 (5%) *2/*17 = 318 (6%) *2/*2 = 115 (2%)	Phenotype groupings were based on the presence or absence of loss-of-function alleles (ie, extensive, ultra rapid, and rapid heterozygote vs intermediatee, poor, and poor or rapid heterozygote) to allow direct comparisons with previous reports. NB: Authors noted that "In outcomes within each treatment group in relation to the CYP2C19 genotype and predicted phenotype groupings, we did not identify any model explaining the variation in	Extensive (*1/*1) = 1862 (36%) intermediate (*1/*2–*8) = 935 (18%) poor (*2–*8/*2–*8) = 125 (2%) poor or rapid heterozygote (*2–*8/*17) = 328 (6%) rapid heterozygote (*1/*17) = 1386 (27%) ultra rapid (*17/*17) = 268 (5%) Missing = 244 (5%)

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				*2/*4 = 3 (<1%) *2/*5 = 1 (<1%) *2/*8 = 6 (<1%) *3/*17 = 1 (<1%) *4/*17 = 1 (<1%) *8/*17 = 8 (<1%) Missing = 244 (5%)	clinical outcomes so genotype groupings in the fi nal comparisons were based on the presence or absence of any loss-of-function allele." Hence results aren't based on the above phenotypic categories.	
Hochholzer, 2010[18] 20510210 Germany EXCELSIOR	Drug Metabolism Genotyping Assay(Applied Biosystems, Frankfurt, Germany). [this is based on TaqMan]	Blood NR NR NR	760 (NR)	CYP2C19*2 Frequency NR	NR	Grouping NR
Jeong 2010[19] 20650435 Korea NR	ABI SNaPshot	Blood NR NR NR	126 (100%)	CYP2C19*1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3 *1/*1 Normal = 46 (36.5) *1/*2 Decreased = 45 (35.7) *1/*3 Decreased = 15 (11.9) *2/*2 Decreased or absent = 13 (10.3) *2/*3 Decreased or absent = 7 (5.6) *3/*3 Decreased or absent = 0(0)	NR	NR
Barker, 2010[20] 20965456 USA NR	the Illumina CYP2C19 Panel and Fast Goldengate assay on the BeadXpress Platform (Illumina, San Diego, California).	Blood NR NR NR	41 (100%)	The CYP2C19 genotyping for the *2, *3, *4, *5, *6, *7, *8, and *17 single nucleotide polymorphisms CYP2C19 *1/*1 = 15(36.6) CYP2C19 *1/*2 = 14(14.1) CYP2C19 *1/*3 = 1(2.4) CYP2C19 *1/*4 = 1(2.4) CYP2C19 *1/*17 = 3(7.3) CYP2C19 *17/*17 = 3(7.3) CYP2C19 *2/*2 = 2(4.8) CYP2C19 *2/*3 = 1(2.4)	Metabolize status	EM, CYP2C19 *17/*17, *1/*17,*1/*1 = 21(52.5) IM, CYP2C19 *1/*2, *1/*3, *1/*4 = 16(40) PM, CYP2C19 *2/*2, *2/*3 = 3 (7.5) CYP2C19 *1 = 0.6 CYP2C19 *2 = 0.24 CYP2C19 *3 = 0.024 CYP2C19 *4 = 0.012 CYP2C19 *17 = 0.122

Author, year UID Country Study name	Genotyping assay (manufacturer):	Type of sample from which DNA extracted Interval between clopidogrel doses and DNA sampling (in days) Interval between sampling and genotyping results (in days): Interval between collection and DNA extraction:	N genotyped: Genotyping success (%):	Alleles tested Genotypes tested: Frequency of genotype:	Rational for the grouping of genotypes reported (Yes/No) [short description]	Grouping of genotypes: Frequency of group:
				CYP2C19 *2/*17 = 1(2.4)		
Bonello, 2010[21] 20708365 France NR	Home made with the primers from (Invitrogen, Carlsbad, California) [PCR]	Blood NR NR NR	411 (100%)	CYP2C19 *2 *2/*2 = 11 (2.7) Wt/*2 = 123 (29.9) Wt/wt = 277 (67.4)	NR	NR
Gurbel 2011[22] 21392617 USA NR	Taqman SNP genotyping assays (Applied Biosystems, Foster City, CA)	Blood NR NR NR	261 (NR)	CYP2C19 *1, *2, *3, *17 Frequency: White/African America/Asian American CYP2C19 *17/*17 = 7(5)/ 2 (2)/0(0) CYP2C19 *1/*17 = 43 (28)/ 27 (27)/ 3 (60) CYP2C19 *1/*1 = 55 (35)/ 42 (42)/0(0) CYP2C19 *2/*17 = 9 (6)/ 3 (3)/0(0) CYP2C19 *1/*2 = 38 (25)/ 24 (23)/2 (20) CYP2C19 *2/*2 = 3 (2)/ 3 (3)/0(0) Alleles: White/African America/Asian American CYP2C19*2 = 53 (17)/ 32 (15)/2(20) CYP2C19*1 = 257 (83)/170 (85)/ 8(80) CYP2C19*17 = 66 (21)/33(17)/ 2(20)	NR	Frequency: White/African America/Asian American EM = 50 (32)/29 (28)/ 2 (40) NM = 64 (41)/ 45 (45)/ 1 (25) IM = 38 (25)/24 (24)/2 (40) PM = 3 (2)/3 (3)/0(0)
Hwang 2011[23] 21075428 South Korea NR	ABI SNaPshot reaction and the ABI 3100 automated genetic analyzer (Applied Biosystems,	Blood Immediately after insertion of the arterial sheath in the catheterization laboratory, blood samples were obtained.	190 (100%)	CYP2C19 *1, *2, *3 CYP2C19 *1 = 62.9 CYP2C19 *2 = 30.3 CYP2C19 *3 = 6.8	NR	*1/*1 extensive metabolizers = 75(39.5) *1/*2 intermediate metabolizers = 71 (37.3) *1/*3 intermediate

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	Foster City, CA, USA).	NR NR				metabolizers = 18 (9.5) *2/*2 poor metabolizers = 18 (9.5) *2/*3 poor metabolizers = 8 (4.2) *3/*3 poor metabolizers = 0(0)
Kang, 2010[24] 20724801 Korea NR	ABI Snap- shot reaction and the ABI 3100 automated genetic analyzer (Applied Biosystems, Foster City, CA, USA)	Blood Immediately after insertion of the arterial sheath in the catheterization lab. NR NR	176 (82%)	CYP2C19*1/*2, *1/*3, *2/*2, *2/*3, *3/*3 *1/*2 = 61(34.7%) *1/*3 = 14 (8%) *2/*2 = 21(11.8%) *2/*3 = 7 (4%) *3/*3 = 1(0.6%)	NR	NR
Liu 2010[25] 21163112 China NR	PCR-RFLP	Blood Patient blood samples were collected before clopidogrel administration, and at least 24 hours after the first 300 mg clopidogrel dose to make sure maximum platelet inhibition has been achieved. NR NR	722 (100%)	SNP rs4244285 NR	NR	NR
Maeda, 2010[26] 21178986 Japan NR	Applied Biosystems StepOnePlus real-time PCR system. Specific sets of primers and TaqMan probes (TaqMan SNP genotyping assays) were obtained from Applied Biosystems.	Blood NR NR NR	165 (100%)	Assay IDs were C_25986767_70 for CYP2C19*2 and C_27861809_10 for CYP2C19*3 CYP2C19*1/*1 = 0.33 CYP2C19*1/*2 = 0.36 CYP2C19*1/*3 = 0.14 CYP2C19*2/*2 = 0.08 CYP2C19*2/*3 = 0.08 CYP2C19*3/*3 = 0.006	NR	EM CYP2C19*1/*1 = 34(35) IM CYP2C19*1/*2 and *1/*3 = 46(47) PM CYP2C19*2/*2, *2/*3 and *3/*3 = 17(18)
Malek, 2010[27]	PCR-RFLP	Blood	261 (94.6%)	CYP2C19*2	NR	NR

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20924183 Poland NR		NR NR NR		NR		
Simon 2011[28] 21262992 France NR	NR	NR NR NR NR	1579 (NR)	CYP2C19 loss of function alleles NR	NR	NR
Yamamoto 2011[29] 21168310 Japan NR	home made with AmpliTaq DNA polymerase (Hoffmann-La Roche, Ltd., Base& Switzerland)	Whole blood NR NR NR	201 (NR)	*1/*1, *1/*2, *1/*3, *2/*2,*2/*3,*3/*3 CYP2C19 *1/*1 = 37 CYP2C19 *1/*2 = 33 CYP2C19 *1/*3 = 11 CYP2C19 *2/*2 = 11 CYP2C19 *2/*3 = 7 CYP2C19 *3/*3 = 1 CYP2C19 *1 = 145 (58.9%) CYP2C19 *2 = 76 (30.9%) CYP2C19 *3 = 25 (10.2%)	NR	EM = 47 IM = 51 PM = 25
Park 2011[30] 21345843 Korea CILON-T	TaqMan fluorogenic 59 nuclease assay (ABI, Foster City, California, USA).	Blood NR NR NR	478 (99%)	CYP2C19 *2, *3, *17 NR	NR	NR
Tiroch, 2010[31] 20826260 Germany NR	Home made or BigDye Terminator V1.1 Cycle Sequencing Kit (Applied Biosystems, patent no. 4336776)	Blood NR NR	928 (100%)	CYP2C19*17, *2 NR	NR	NR

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		NR				
Sorich, 2010[32] 20492467 707 sites in 30 countries Substudy of TRITON-TIMI 38	Affymetrix Targeted Human DMET Assay	Blood NR NR NR	2943 (99%)	CYP2C19 alleles detected included *1A, *2A, *3, *4, *5A, *6, *7, *8, *9, *10, *12, *13 and *14, of which *2A, *3, *4, *5A, *6, *7 and *8 were considered to result in significantly reduced function NR	Carrier of allele status	EMs (no reduced function alleles). 72% RMs(with one or two reduced function allels) 28%
Sibbing, 2010[33] 20492469 Germany	Genotypes were determined with a TaqMan assay, using an ABI Prism Sequence Detector 7000 (Applied Biosystems, Darmstadt, Germany),	Blood Peripheral venous blood samples were drawn Directly at hospital admission, after the daily dose of 75mg of Clopidogrel had been taken and before any in-hospital drug. NR NR	986 (100%)	CYP2C* 2, *17 CYP2C19 *2 (wt/wt) = 738 (74.8) CYP2C19 *2 (wt/*2) = 229 (23.2) CYP2C19 *2 (*2/*2) = 19 (1.9) CYP2C19 *17 (wt/wt) = 608 (61.7) CYP2C19 *17 (wt/*17) = 335 (34) CYP2C19 *17 (*17/*17) = 43 (4.4)	Carrier of allele status	Wild type allele = 86.5 Carrier for at least one*2 allele = 248 (25) *2 allele = 13.5 Wild type carrier = 78.7 Carrier for at least one*17 allele = 378 (38.4) *17 allele = 21.3
Sawada, 2010[34] 21099121 Japan NR	CYP2C19*2 polymorphisms were genotyped using TaqMan™ Drug Metabolism Genotyping Assays (Applied Biosystems, Foster City, CA, USA) with the Applied Biosystems 7500 Real-Time PCR System.	Blood NR NR NR	100 (NR)	CYP2C19*2 NR	NR	NR
Pare, 2010[35] 20979470 Multiple countries	TaqMan	NR (ACTIVE-A) “stored-DNA” (CURE) NR	1156 (ACTIVE-A) + 5059 (CURE) (>98%)	CYP2C19 *2, *3, *17 NR	NR	NR

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CURE and ACTIVE		NR NR				
Mega, 2010[36] 20801494 707 sites in 30 countries TRITON-TIMI 38	Affymetrix Targeted Human DMET Assay	Blood NR NR NR	2932 (NR)	CYP2C19 alleles detected included *1A, *2A, *3, *4, *5A, *6, *7, *8, *9, *10, *12, *13 and *14, of which *2A, *3, *4, *5A, *6, *7 and *8 were considered to result in significantly reduced function NR	NR	NR
Bouman 2011[37] 21628721 Netherlands Genetic substudy of the Popular study	Real-time PCR (company not given)	blood NR NR NR	Unclear NR	*1/*1 n=737 (72%) *1/*2 n=260 (25.4%) *2/*2 n=27 (2.6%)	Not explicitly provided	NR
Campo 2011[38] 21679849 Italy NR	allelic discrimination assay (TaqMan Assays, Applied Biosystems, Foster City, California) on the Chromo4 Real-Time PCR System detection (Bio-Rad Laboratories, Hercules, California) using TaqMan Universal Master Mix. The data were analyzed by Opticon Monitor 3.1 software (Bio-Rad Laboratories).	Whole blood NR NR NR	300 NR	CYP2C19*2 heterozygote n=76(25%) CYP2C19*2 homozygote n=5(2%) CYP2C19*2 noncarrier n =219 (73%) CYP2C19*17 heterozygote n=85 (28%) CYP2C19*17 homozygote n=17 (6%) CYP2C19*17 noncarrier n =198 (66%)	Poor response threshold from Price MJ, Endemann S, Gollapudi RR, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 2008;29:992–1000.	*2 carrier (heterozygote or homozygote) n=81 (27%) *17 carrier (heterozygote or homozygote) n=102 (34%) Poor responders at baseline n=107 (36%)
Fernando 2011[39] 21696537	PCR with probe hybridization and single	Whole blood	29 NR	*1/*17 Heterozygous ultrarapid extensive metabolizer n=10(34%)	Gain and loss of function given for interest, not analysis, and based	Gain of function n=10 (34%)

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Australia NR	base extension	NR NR NR		*1/*1 Extensive metabolizer n=13 (45%) *1/*2 Intermediate metabolizer n=5(17%) *2/*2 Poor metabolizer n=1(3%)	on known allele function. Groupings for analysis: No difference found between extensive and heterozygous ultrarapid extensive (data not shown) Poor and intermediate combined because of small n's in each group.	Loss of function N= 6(20%) Extensive and heterozygous ultrarapid extensive (*1/*17 or *1/*1) n=23 (74%) Poor/intermediate metabolizers (*1/*2 or *2/*2) n=6(26%)
Geisler 2008[40] 18781853 Germany NR	Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) using the MassARRAY Compact system (Sequenom, CA)	Blood NR NR NR	273 100%	CYP2C19*1/*1 (*2 noncarriers) n=175 (74%) CYP2C19*1/*2 n=52 (22%) CYP2C19*2/*2 n=10 (4%) CYP2C19*2/*2 n=15.2% *3 frequency n=0% CYP2C19*1/*1 (*17 noncarriers) n=137 (58%) CYP2C19*1/*17 n=79 (33%) CYP2C19*17/*17 n=21 (9%) *17 frequency n= 25.5%	Not explicitly reported	*2 carriers (*1/*2 or *2/*2) n=62 (26%)
Gladding [41]2008 19463375 New Zealand PRINC (Plavix Response in Coronary Intervention) Trial	PCR with TaqMan kits (Applied Biosystems, Foster City, California) and ABI PRISM 7000 Sequence Detection System (Applied Biosystems); genotyping using the Sequenom mass spectrometer	Whole blood Dose came first. Interval varied over study period. Platelet function was tested (blood was taken) at baseline, 2, 4, and 7 h from the first clopidogrel loading dose; and at 7 days. Clopidogrel given at baseline and on days 1-7 after PCI in all patients as well as at 2 hours after PCI in 37 patients. NR NR	60 NR	CYP2C19*1 (normal function) n=24/60 (40%) CYP2C19*2 (19154G>A, rs4244285) n=0/60 (0%) CYP2C19*3 n=0/60 (0%) CYP2C19*4 (1A>G, rs28399504) n=0/60 (0%) CYP2C19*17 (-806C>T, rs12248560) n=17 (28%)	Reference: Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007:5:2429 –36.	[good?] response genotype (CYP2C19*1*1 or CYP2C9*1*/*2) =NR poor response genotype (CYP2C19*2 or *4 or *17 OR CYP2C9*3 [note is not only CYP2C19])=NR CYP2C19*2 or *4 carriers n=19/60 (32%)
Gurbel 2010[42] 19817997	TaqMan SNP genotyping assay (Applied	NR(Probably blood)	36	CYP2C19*2 N=13/17 with HPR (77%)	Not explicitly reported	≥1 CYP2C19*2 allele N=44% of all genotyped

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USA NR	Biosystems, Foster City CA)	NR NR NR	NR	N=3/19 without HPR (16%) CYP2C19*3 n=0% in both groups CYP2C19*5 n=0% in both groups CYP2C19*17 N=75% of patients with HPR N=NR for those without HPR		patients (17 w/HPR, 19 without HPR)
Harmsze 2010[43] 20833683 Netherlands NR	Real-time PCR (company NR)	Blood for all controls and 38 cases; saliva for remaining 138 cases NR NR NR	176 cases and 420 controls NR	*2 allele n=Cases 70/176 (39.8%) [allele frequency, 22.6%] N=Controls 123/420 (29.3%) [allele frequency, 17.0%] *1/*1 n= Cases 60.0% N=Controls 70.5% *1/*2 n= Cases 34.9% N=Controls 25.7% *2/*2 n= Cases 5.1% N=Controls 3.8% CYP2C19*3 SNP *3 allele n= Cases 0% N=Controls 0.2% *1/*1 n= Cases 100% N=Controls 99.8% *1/*3 n= Cases 0% N=Controls 0.2% *3/*3 n= Cases 0% N=Controls 0%	NA	NA (carriage of the CYP2C19*2 allele was only variable used)
Kim 2011[44] 21511217 South korea CCELAMI2C19	PCR + ABI SNaPshot	Leukocytes in whole blood NR	126 (62+64) Unclear	High-dose clopidogrel n=62 *1/*1 Extensive metabolizer (noncarrier) = 24 (38.7%) 1/*2 Intermediate metabolizer =	Not explicitly stated	High-dose clopidogrel (N=62) Noncarrier/extensive metabolizer (*1/*1) = 24

Author, year UID Country Study name	Genotyping assay (manufacturer):	Type of sample from which DNA extracted Interval between clopidogrel doses and DNA sampling (in days) Interval between sampling and genotyping results (in days): Interval between collection and DNA extraction:	N genotyped: Genotyping success (%):	Alleles tested Genotypes tested: Frequency of genotype:	Rational for the grouping of genotypes reported (Yes/No) [short description]	Grouping of genotypes: Frequency of group:
		NR NR		22 (35.5%) *1/*3 Intermediate metabolizer = 6 (9.7%) *2/*2 Poor metabolizer = 6 (9.7%) *2/*3 Poor metabolizer = 4 (6.4%) *3/*3 Poor metabolizer = 0 (0%) Standard-dose clopidogrel plus cilostazol (n=64) *1/*1 Extensive metabolizer (noncarrier) = 25 (39.1%) 1/*2 Intermediate metabolizer = 24 (37.5%) *1/*3 Intermediate metabolizer = 6 (9.4%) *2/*2 Poor metabolizer = 5 (7.8%) *2/*3 Poor metabolizer = 4 (6.2%) *3/*3 Poor metabolizer = 0 (0%)		(38.7%) Carrier (of *2 or *3)/intermediate or poor metabolizer [=*1/*2, *1/*3, *2/*2, *2/*3, or *3/*3) = 38 (61.3%) Any intermediate metabolizer (1/*2 or *1/*3) = 28 (45.2%) Any poor metabolizer (*2/*2, *2/*3, or *3/*3) = 10 (16.1%) Standard-dose clopidogrel plus cilostazol (n=64) Noncarrier/extensive metabolizer (*1/*1) = 25 (39.1%) Carrier (of *2 or *3)/intermediate or poor metabolizer [=*1/*2, *1/*3, *2/*2, *2/*3, or *3/*3) = 39 (60.9%) Any intermediate metabolizer (1/*2 or *1/*3) = 30 (46.9%) Any poor metabolizer (*2/*2, *2/*3, or *3/*3) = 9 (14.1%)
Lee 2011[45] 21786436 South korea NR	Seeplex CYP2C19 ACE Genotyping system (Seegene, Seoul, Korea)	Blood NR NR NR	166 NR	CYP2C19 *1/*1 = 68 (40.9%) *1/*2 = 56 (33.7%) *1/*3 = 18 (10.8%) *2/*2 = 14 (8.4%) *2/*3 = 9 (5.4%) *3/*3 = 1 (0.6%)	Not explicitly reported	extensive metabolizer (*1/*1) = 68 (40.9%) Intermediate metabolizer (*1/*2, *1/*3) = 74 (44.6%) poor metabolizer (*2/*2, *2/*3, *3/*3) = 24 (14.5%)
Malek 2008[46] 18577829 Poland NR	PCR-RFLP	Peripheral vein blood NR NR	105 100%	CYP2C19*1/*1 = 84 (80%) *1/*2 = 20 (19%) *2/*2 = 1 (1%)	Not explicitly reported	Group 1: mutant P2Y12 and *2 CYP2C19 = 7 Group 2: wild type P2Y12 and *2CYP2C19 = 14 Group 3: mutant P2Y12 and

Author, year UID Country Study name	Genotyping assay (manufacturer):	Type of sample from which DNA extracted Interval between clopidogrel doses and DNA sampling (in days) Interval between sampling and genotyping results (in days): Interval between collection and DNA extraction:	N genotyped: Genotyping success (%):	Alleles tested Genotypes tested: Frequency of genotype:	Rational for the grouping of genotypes reported (Yes/No) [short description]	Grouping of genotypes: Frequency of group:
		NR				*1 CYP2C19 = 17 Controls: wild-type P2Y12 and *2 CYP2C19 = 67
Pettersen [47]2011 21426546 Norway Aspirin and Clopidogrel non-responsiveness clinical Endpoint Trial (ASCET)	ABI Prism 7900 HT Sequence Detection System using allele-specific primers and probes included in the TaqMan Drug Metabolism Assay mix (Applied Biosystems, Foster City, CA	Whole blood Blood drawn 1 month after first clopidogrel dose NR NR	219 (99%)	CYP2C19*2 homozygote = 3/218 (1%) CYP2C19*2 heterozygote = 61/218 (28%) CYP2C19*2 carrier = 64/218 (29%)	NA	NA
Sibbing 2011[48] 21527445 Germany NR	TaqMan assay using an ABI Prism Sequence Detector 7000 (Applied Biosystems)	Blood NR NR NR	1525 (cohort) 1566 (case-control) (100%)	PCI cohort (n=1524) CYP2C19*1/*1 = 32 (2.1%) CYP2C19*1/*2 = 345 (22.6%) CYP2C19*2/*2 = 1147 (75.3%) St cohort (n=127) CYP2C19*1/*1 = 81 (64%) CYP2C19*1/*2 = 43 (34%) CYP2C19*2/*2 = 3 (2%)	NA	NA
Simon 2009[49] 19106083 France FAST-MI	For *2 or *3, oligonucleotide ligation assay (SNPlex, Applied Biosystems) after initial amplification by PCR For *4,*5,*17: custom TaqMan	whole blood Drawn at time of admission NR NR	2208 *2: 2178 (99%) *3: 2187 (99%) *4: 2189 (99%) *5: 2176 (99%) Any LOF (*2,3,4, or 5): 2208 (100%) *17: 2164 (98%)	CYP2C19*2 noncarrier = 1571/2178 (72%) CYP2C19*2 heterozygote = 564/2178 (26%) CYP2C19*2 homozygote = 53/2178 (2%) CYP2C19*3 noncarrier = 2186/2187 (99.9%) CYP2C19*3 heterozygote = 1/2187 (<1%) CYP2C19*4 heterozygote = 2168/2189 (99%) CYP2C19*4 homozygote = 21/2189 (1%) CYP2C19*5 noncarrier =	Not explicitly reported	No CYP2C19 loss-of-function SNP (*2, *3, *4, or *5) = 1573/2208 (71%) Any CYP2C19 loss-of-function SNP (*2, *3, *4, or *5) = 577/2208 (26%) Any 2 CYP2C19 loss-of-function SNPs (*2, *3, *4, or *5) = 58/2208 (3%)

Author, year UID Country Study name	Genotyping assay (manufacturer):	Type of sample from which DNA extracted Interval between clopidogrel doses and DNA sampling (in days) Interval between sampling and genotyping results (in days): Interval between collection and DNA extraction:	N genotyped: Genotyping success (%):	Alleles tested Genotypes tested: Frequency of genotype:	Rational for the grouping of genotypes reported (Yes/No) [short description]	Grouping of genotypes: Frequency of group:
				2175/2176 (99.9%) CYP2C19*5 heterozygote = 1/2176 (<1%) CYP2C19*17 noncarrier = 1390/2164 (64%) CYP2C19*17 heterozygote = 674/2164 (31%) CYP2C19*17 homozygote = 100/2164 (5%)		
Hwang 2010[50] 20823393 Korea ACCEL	SNaPshot single base primer extension	Blood NR NR NR	65 (from the high-dose clopidogrel group) + 69 (from the triple antiplatelet therapy group) Unclear	*1/*1: 44 (32.8) *1/*2: 47 (35.1) *1/*3: 16 (11.9) *2/*2: 18 (13.4) *2/*3: 8(6.0) *3/*3: 1(0.7)	previous publication	*1: 56.3% *2: 34% * 3: 9.7%

Appendix Table D5: Mortality outcomes

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Collet, 2009{Collet, 2009 140 /id} 19108880 France AFIJI	Clopidogrel (75 mg maintenance dose for at least 1 mo)	CYP2C19 *2	CV death	Death with a demonstrable cardiovascular cause or any death not clearly attributable to non-cardiovascular cause.	Mean FU = 2.8 yr	Carriers (*2/*2 or *2/*1) N = 73	2 1.45 events per 100 person-years	HR = 5.74 Adjusted HR = NON EVALUABLE (small number of events)	0.52, 63.48 NA	0.10 NA	Unadjusted NA	NO	None.
						Non-carriers (*1/*1) N = 186	1 0.26 events per 100 person-years						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19* 2	Cardiac mortality	NR	Maximum FU of 6 mo	*2/*2 or *2/*1 N = 247	10 (4%)	NR	NR	0.037 (chi square test)	NO	NO	Component of composite secondary outcome
						*1/*1 N = 525	8 (1.5%)						
Mega, 2009{Mega, 2009 141 /id} 19106084 Multinational Genetics substudy of TRITON-TIMI 38 [Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction]	Clopidogrel 300 mg loading dose, 75 mg maintenance	CYP2C19	Death from cardiovascular causes	NR; all outcomes were adjudicated by a committee unaware of group assignments	Up to 15 mo (maximum duration of treatment on trial)	IM or PM (1/*2A, *1A/*3, *1A/*4, *1A/*8, *2A/*2A, *2A/*3, *2A/*4, *2A/*5A, *2A/*8) N = 395	NR Rate = 2.0% (Kaplan-Meier)	HR = 4.79	1.40, 16.37	NR	ACS subtype (STE or NSTE was used as a stratification factor)	NO	Secondary outcome
						EM (*1A/*1A) N = 1064	NR Rate = 0.4% (Kaplan-Meier rate)						
Sibbing, 2009{Sibbing, 2009 133 /id} 19193675 Germany NR	Clopidogrel 600 mg loading dose before stent placement	CYP2C19 *2	Death	NR	30 days	CYP2C19 *2 carriers (*2/*2 and *2/*1) N = 680	5 (<1%)	HR = 0.83	0.30, 2.26	0.71 [Cox proportional hazards regression; carriers vs. non-carriers]	NO	NO	None
						CYP2C19 non-carriers (*1/*1) N = 1805	16 (1%)						
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	Clopidogrel 600 mg loading dose; clopidogrel 75 mg (1/d) and aspirin 100 mg (2/d) maintenance.	CYP2C19 *17	Mortality	Death within 30 days	30 d	*17/*17 N = 76	1 (1.3%)	OR = 0.87	0.23, 3.31	(carriers vs. non-cariers)[logistic regression] P = 0.84 (across 3 groups) [chi-square test for trend]	NO	NO	Secondary efficacy endpoint
						*17/*1 N = 546	2 (0.4%)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
						*1/*1 N = 902	5 (0.6%)						
Bonello{Bonello, 2010 45 /id} 2010 20708365 France NR	All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement	CYP2C19	Death	Death	In hospital	Wild-type N = 277	0 (0%)	NR	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	0 (0%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						
Malek{Malek, 2010 43 /id} 2010 20924183 Poland NR	Aspirin + clopidogrel	CYP2C19*2	All cause mortality	All cause mortality	4 years	*2/*2 or *2/*1 N = 56	10 (17.9%); count calculated based on proportion	HR = 1.9	0.9, 4.0	0.09 [noncarrier Vs. carrier of *2; Kaplan-Meier]	NR	NR	curve in figure 1b
						*2 noncarriers N = 205	20 (9.8%); count calculated based on proportion						
Yamamoto 2011{Yamamoto, 2011 25 /id} 21168310 Japan NR	clopidogrel	CYP2C19*2 or *3	Cardiovascular death	Cardiovascular death	74 days	Carriers N = 61	1 ()	NR	NR	NR	NR	NR	
		CYP2C19*2/*2	Cardiovascular death	Cardiovascular death	NR	CYP2C19*2/*2	NR	NR	NR	NR	NR	NR	
Tiroch, 2010{Tiroch, 2010 62 /id} 20826260 Germany NR	aspirin (100mg twice daily) and clopidogrel (75mg once Daily)	CYP2C19*2 GG	Death	Death	1 year	CYP2C19*2 GG N = 680	54 (7.9)	NR	NR	0.08, CYP2C19*2 GG vs *2 A allele	NR	NR	
		CYP2C19*2 A allele	Death	Death	1 year	CYP2C19*2 A allele N = 248	11 (4.4)	NR	NR		NR	NR	
		CYP2C19*17 CC	Death	Death	1 year	CYP2C19*17 CC N = 565	34 (6)	NR	NR	0.203 CYP2C19*17 CC vs T allele	NR	NR	
		CYP2C19*17 T allele	Death	Death	1 year	CYP2C19*17 T allele N = 363	30 (8.3)	NR	NR		NR	NR	
Sorich, 2010{Sorich, 2010 49 /id} 20492467 707 sites in 30 countries Substudy of TRITON-TIMI 38	300-mg loading dose and 75-mg daily maintenance dose	CYP2C19	CV death	CV death	15 months	RM(with one or two reduced function alleles) vs EM(no reduced function allele) N = 802	4.2%	OR=4.79	1.4-16.37	NR	NR	No	

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95% CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
			CV death,	CV death,	15 months	EM N = ???	0.9%		0.3-1.7	NR	NR	No	
			CV death,	CV death,	15 months	RM	NR		2.2-6.1	NR	NR	No	
Sawada, 2010{Sawada, 2010 36 /id} 21099121 Japan NR	loading dose of clopidogrel (300 mg) and maintenance dose of clopidogrel (75 mg/day) and aspirin (100 mg/day)	CYP2C19	Death	Death	Mean 243.8 days	Non-carrier	58	0 (0%)	NR	0.87, Non-carrier vs *2 carrier	No	No	
			Death	Death	Mean 243.8 days	*2 carrier	42	1 (2.4%)	NR	NO	NO	NO	
Campo 2011 21679849 Italy NR	Clopidogrel + aspirin	TaqMan	Death	All cause death	1 mo to 1 yr after PCI	*2 noncarriers	4 (1.8%)	NR	NR	NR	NR	NO	
						*2 carriers	2 (2.5%)	NR	NR				
						*17 noncarriers	5 (2.5%)	NR	NR				
						*17 carriers	1 (1.0%)	NR	NR				

AFIJI = Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention registry; NR = not reported; RECLOSE = Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis study.

Appendix Table D6: Acute Coronary Syndromes

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Collet{Collet, 2009 140 /id} 2009 19108880 France AFIJI	Clopidogrel (75 mg maintenance dose for at least 1 mo)	CYP2C19 *2	MI	Recent ischemic symptom with EKG abnormalities in the ST segmen (depression or elevation of at least 0.1 mV)t and a positive troponin measurement as defined locally.	Mean FU = 2.8 yr	Carriers (*2/*2 or *2/*1) N = 73	N = 10 7.27 events per 100 person-years	HR = 4.57 Adjusted HR = 5.57	1.64, 12.53 1.94, 16.01	0.001 0.001	Unadjusted Adjusted [baseline BMI, smoking status, diabetes status, stent implantation, initial STE MI, use of PPI]	NO	None.
						Non-carriers (*1/*1) N = 186	N = 6 1.58 events per 100 person-years						
Mega{Mega, 2009 141 /id} 2009 19106084 Multinational TRITON-TIMI 38	Clopidogrel 300 mg loading dose, 75 mg maintenance	CYP2C19	Non-fatal MI	NR; all outcomes were adjudicated by a committee unaware of group assignments	Up to 15 mo (maximum duration of treatment on trial)	IM or PM (1/*2A, *1A/*3, *1A/*4, *1A/*8, *2A/*2A, *2A/*3, *2A/*4, *2A/*5A, *2A/*8) N = 395	NR Rate = 10.1% (Kaplan-Meier)	HR = 1.38	0.94, 2.02	NR	ACS subtype (STE or NSTE was used as a stratification factor)	NO	Secondary outcome
						EM (*1A/*1A) N = 1064	NR Rate = 7.5% (Kaplan-Meier rate)						
Sibbing{Sibbing, 2009 133 /id} 2009 19193675 Germany NR	Clopidogrel 600 mg loading dose before stent placement	CYP2C19 *2	MI	Thrombolysis in Myocardial Infarction Criteria (TIMI), based on new abnormal Q-wave appearance in the EKG or increase in CK-MB value to three or more times the upper limit of normal; appears to have included NSTE-ACS	30 days	CYP2C19 *2 carriers (*2/*2 and *2/*1) N = 680	48 (7%)	HR = 1.15	0.82, 1.61	P = 0.42 [Cox proportional hazards regression; carriers vs. non-carriers]	NO	NO	None
						CYP2C19 non-carriers (*1/*1) N = 1805	111 (6%)						
			STEMI	NR	30 days	CYP2C19 *2 carriers (*2/*2 and *2/*1) N = 680	10 (1%)	HR = 2.96	1.20, 7.28	0.02 [Cox proportional hazards regression; carriers vs. non-carriers]	NO	NO	None
						CYP2C19 non-carriers (*1/*1) N = 1805	9 (<1%)						
			NSTE-ACS	NSTE-ACS	30 days	CYP2C19 *2 carriers (*2/*2 and *2/*1) N = 680	38 (6%)	HR = 0.99	0.68, 1.44	0.96 [Cox proportional hazards regression; carriers vs. non-carriers]	NO	NO	None
						CYP2C19 non-carriers (*1/*1) N = 1805	102 (6%)						
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	Clopidogrel 600 mg loading dose; clopidogrel 75 mg (1/d) and aspirin 100 mg (2/d) maintenance.	CYP2C19 *17	MI	Based on TIMI criteria (new abnormal Q-wave appearance in EKG or increase in CK-MB ≥3 x normal)	30 d	*17/*17 N = 76	4 (5.3%)	OR = 1.05	0.59, 1.85	(carriers vs. non-cariers)[logistic regression] P = 0.61 (across 3 groups) [chi-square test for trend]	NO	NO	Secondary efficacy endpoint

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95% CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
						*17/*1 N = 546	17 (3.1%)						
						*1/*1 N = 902	29 (3.2%)						
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement	CYP2C19	ACS	Non–ST-segment elevation acs= clinical symptoms of acute myocardial ischemia within 12 h before admission + at least 1 of the following: a new finding of ST-segment depression >0.05 mV, T-wave inversion >0.3 mV in at least 2 leads, or elevated levels of cardiac markers.	In hospital	Wild-type N = 277	0 (0%)	NR	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	0 (0%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						
Yamamoto 2011{Yamamoto, 2011 25 /id} 21168310 Japan NR	clopidogrel	CYP2C19*2 or *3	Nonfatal myocardial infarction	Nonfatal myocardial infarction	NR	carriers	2/62	NR	NR	NR	NR	NR	
		CYP2C19*1/*2	Myocardial infarction	Myocardial infarction	21 days	CYP2C19*1/*2	NR	NR	NR	NR	NR	NR	
		CYP2C19*1/*3	Myocardial infarction	Myocardial infarction	340 days	CYP2C19*1/*3	NR	NR	NR	NR	NR	NR	
Tiroch, 2010{Tiroch, 2010 62 /id} 20826260 Germany NR	aspirin (100mg twice daily) and clopidogrel (75mg once Daily)	CYP2C19*2 GG	Repeat MI	Repeat MI	1 year	CYP2C19*2 GG	680	N(%) 17 (2.5)	NR	0.666, CYP2C19*2 GG vs *2 A allele	NR	NR	
		CYP2C19*2 A allele	Repeat MI	Repeat MI	1 year	CYP2C19*2 A allele	248	N(%) 5(2)	NR		NR	NR	
		CYP2C19*2 GG	Repeat MI	Repeat MI	1 year	CYP2C19*2 GG	565	N(%) 15 (2.7)	NR	0.48 CYP2C19*17 CC vs T allele	NR	NR	
		CYP2C19*2 A allele	Repeat MI	Repeat MI	1 year	CYP2C19*2 A allele	363	N(%) 7 (1.9)	NR		NR	NR	
Sorich, 2010{Sorich, 2010 49 /id} 20492467 707 sites in 30 countries Substudy of TRITON-TIMI 38	300-mg loading dose and 75-mg daily maintenance dose	CYP2C19	Non-fatal MI	Non-fatal MI	15 months	RM vs EM	802	OR=1.38	0.94-2.02	NR	NR	No	

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95% CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
			Non-fatal MI	Non-fatal MI	15 months	EM	NR	8.3%	7.0-9.6	NR	NR	No	
			Non-fatal MI	Non-fatal MI	15 months	RM	NR	11.6%	8.7-14.8	NR	NR	No	
Sawada, 2010{Sawada, 2010 36 /id} 21099121 Japan NR	loading dose of clopidogrel (300 mg) and maintenance dose of clopidogrel (75 mg/day) and aspirin (100 mg/day)	CYP2C19	MI	MI	Mean 243.8 days	Non-carrier	58	2(3.4)	NR	0.76, Non-carrier vs *2 carrier	No	No	
			MI	MI	Mean 243.8 days	*2 carrier	42	1 (2.4)	NR		No	No	
Malek 2008{Malek, 2008 167 /id} 18577829 Poland NR	Clopidogrel and aspirin	CYP2C19	CV Death or MI	NR	Within 12 months after PCI	Group 1	0	NR	NR	NR	NR	NR	NR
						Group 2	1	NR	NR	NR	NR	NR	NR
						Group 3	0	NR	NR	NR	NR	NR	NR
						Controls	5	NR	NR	NR	NR	NR	NR

Appendix Table D7: Stent Thrombosis

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Collet, 2009 19108880 France AFIJI (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) registry	Clopidogrel (75 mg maintenance dose for at least 1 mo)	CYP2C19 *2	Definite stent thrombosis	Based on definitions from the Academic Research Consortium. Definite = total occlusion originating or within 5 mm of the stent; or visible thrombus within the stent or within 5 mm of the stent in the presence of an acute ischemic clinical syndrome within 48 h	Mean FU = 2.8 yr	Carriers (*2/*2 or *2/*1) N = 61 (patients with stent implantation)	N = 8 6.79 events per 100 person-years	HR = 6.02 Adjusted HR = 6.04	1.81, 20.04 1.75, 20.80	0.0009 0.004	Unadjusted Adjusted [baseline BMI, smoking status, diabetes status, stent implantation, initial STE MI, use of PPI]	NO	NO
						Non-carriers (*1/*1) N = 162 (patients with stent implantation)	N = 4 1.14 events per 100 person-years						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19*2	Stent thrombosis	Definite or probable stent thrombosis. Definite = ACS + angiographic or pathologic confirmation of thrombosis; probable = unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	Maximum FU of 6 mo	*2/*2 N = 26	2 (7.7%)	NR	NR	0.046 across groups (chi square test)	NO	NO	Primary outcome
						*2/*1 N = 221	11 (5.0%)						
						*1/*1 N = 525	11 (2.1%)						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19*2 (see also KQ2b extraction form)	Stent thrombosis	Definite or probable stent thrombosis. Definite = ACS + angiographic or pathologic confirmation of thrombosis; probable = unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	Maximum FU of 6 mo	*2/*2 + RPR N = 40	6 (15%)	NR OR=5.79	NR (1.04, 39.01)	<0.0001 across groups (chi square test) 0.033 (logistic regression)	NO Adjusted ("for traditional cardiovascular risk factors and clinical and procedural risk factors for stent thrombosis")	NO	Primary outcome
						*1/*1 or low RPR N = 732	18 (2.5%)						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19*2	Stent thrombosis	Definite or probable stent thrombosis. Definite = ACS + angiographic or pathologic confirmation of thrombosis; probable = unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	Maximum FU of 6 mo	*2/*2 or *2/*1 N = 247	13 (5.3%)	NR OR=2.59 OR=3.43	NR (1.15, 5.88) (1.01, 12.78)	0.025 (chi square test) 0.022 (logistic regression) 0.047 (logistic regression)	NO NO (univariate) YES (ADP-RPR, traditional cardiovascular risk factors, clinical and procedural risk factors for ST)	NO	Primary outcome

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
						*1/*1 N = 525	11 (2.1%)						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19*2	Stent thrombosis	Definite or probable stent thrombosis. Definite = ACS + angiographic or pathologic confirmation of thrombosis; probable = unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	Maximum FU of 6 mo	*2/*2 or *2/*1 N = 247	13 (crude proportion 5.3%)	NR	NR	<0.01 (log rank)	NO	NO	Primary outcome
						*1/*1 N = 525	11 (crude proportion 2.1%)						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19*2	Definite stent thrombosis	ACS + angiographic or pathologic confirmation of thrombosis	Maximum FU of 6 mo	*2/*2 or *2/*1 N = 247	6 (2.4%)	NR	NR	0.100 (chi square test)	NO	NO	Component of composite secondary outcome
						*1/*1 N = 525	5 (1%)						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19*2	Probable stent thrombosis	Unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	Maximum FU of 6 mo	*2/*2 or *2/*1 N = 247	7 (2.8%)	NR	NR	0.083 (chi square test)	NO	NO	Component of composite secondary outcome
						*1/*1 N = 525	6 (1%)						
Mega{Mega, 2009 141 /id} 2009 19106084 TRITON-TIMI 38	Clopidogrel 300 mg loading dose, 75 mg maintenance	CYP2C19 (multiple alleles)	Stent thrombosis	Definite or probable, as defined by the Academic Research Consortium	Up to 15 mo (maximum duration of treatment on trial)	IM or PM (1/*2A, *1A/*3, *1A/*4, *1A/*8, *2A/*2A, *2A/*3, *2A/*4, *2A/*5A, *2A/*8) N = 375 (patients who had stent placement)	N = NR Rate = 2.6% (Kaplan-Meier)	HR = 3.09	1.19, 8.00	0.02 [Kaplan-Meier]	ACS subtype (STE or NSTE was used as a stratification factor)	NO	Secondary outcome
						EM (*1A/*1A) N = 1014 (patients who had stent placement)	N = NR Rate = 0.8% (Kaplan-Meier rate)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
		CYP2C19*2	Stent thrombosis	Definite or probable, as defined by the Academic Research Consortium	Up to 15 mo (maximum duration of treatment on trial)	*2 carriers (*2/*2 or *2/*1) 95% of all carriers = 375	N = NR Rate = 2.7% (Kaplan-Meier)	HR = 3.33	1.28, 8.62	0.004 [Kaplan-Meier]	ACS subtype (STE or NSTE was used as a stratification factor)	NO	Secondary outcome
						Non-*2 carriers (*1/*1) N = 1084 (= 1459 - 375)	N = NR Rate = 0.8% (Kaplan-Meier rate)						
Sibbing, 2009{Sibbing, 2009 133 /id} 19193675 Germany NR	Clopidogrel 600 mg loading dose before stent placement	CYP2C19 *2	Stent thrombosis (definite)	Definite stent thrombosis according to the Academic Research Consortium criteria (ACS with angiographic or pathologic confirmation of thrombosis)	30 days	CYP2C19 *2/*2 N = 47	NR	NR	NR	P = 0.002 [chi-square test for trend]	NO	NO	Additional data on the cumulative incidence is presented in Figure 2
						CYP2C19 *2/*1 N = 633	NR	NR	NR				Additional data on the cumulative incidence is presented in Figure 2
						CYP2C19 *1/*1 N = 1805	NR	NR	NR				Additional data on the cumulative incidence is presented in Figure 2
Sibbing, 2009{Sibbing, 2009 133 /id} 19193675 Germany NR	Clopidogrel 600 mg loading dose before stent placement	CYP2C19 *2	Stent thrombosis (definite)	Definite stent thrombosis according to the Academic Research Consortium criteria (ACS with angiographic or pathologic confirmation of thrombosis)	30 days	CYP2C19 *2 carriers (*2/*2 and *2/*1) N = 680	10	HR = 3.81 HR = 3.86	1.45, 10.02 1.47, 10.14	P = 0.007 [Cox proportional hazards regression; carriers vs. non-carriers] P = 0.006 [Cox proportional hazards regression; carriers vs. non-carriers]	Unadjusted Adjusted [age, diabetes, ACS, type of stent, substudy from which patient was selected, use of abciximab]	NO	None
						CYP2C19 non-carriers (*1/*1) N = 1805	7						
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	Clopidogrel 600 mg loading dose; clopidogrel 75 mg (1/d) and aspirin 100 mg (2/d) maintenance.	CYP2C19 *17	Definite or probable stent thrombosis	Definite stent thrombosis according to Academic Research Consortium Criteria = ACS with either angiographic or pathological confirmation of thrombosis; probable = any unexplained death or target vessel MI, without angiographic confirmation of thrombosis or other identified culprit lesion	30 d	*17/*17 N = 76	1 (1.3%)	OR = 1.09	0.39, 3.02	(carriers vs. non-cariers)[logistic regression] P = 0.79 (across 3 groups) [chi-square test for trend]	NO	NO	Primary efficacy endpoint
						*17/*1 N = 546	5 (0.9%)						
						*1/*1 N = 902	8 (0.9%)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Wallentin, 2010{Wallentin, 2010 56 /id} 20801498 Multiple countries (43 countries in North America, South America, Europe, Asia, Australia) PLATO	75 mg clopidogrel once daily (300–600 mg loading dose)	CYP2C19 genotyping	Definite stent thrombosis			Any LOF allele (*2-*8)	934						
						No LOF allele	2300						
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement	CYP2C19	Stent thrombosis	Stent thrombosis	In hospital	Wild-type N = 277	0 (0%)	NR	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	1 (1%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						
Tiroch, 2010{Tiroch, 2010 62 /id} 20826260 Germany NR	aspirin (100mg twice daily) and clopidogrel (75mg once Daily)	CYP2C19*2 GG	Stent thrombosis	Stent thrombosis	1 year	CYP2C19*2 GG	680	N(%) 7 (1.0)	NR	0.822 CYP2C19*2 GG vs *2 A allele	NR	NR	
		CYP2C19*2 A allele	Stent thrombosis	Stent thrombosis	1 year	CYP2C19*2 A allele	248	N(%) 3(1.2)	NR				
Tiroch, 2010{Tiroch, 2010 62 /id} 20826260 Germany NR	aspirin (100mg twice daily) and clopidogrel (75mg once Daily)	CYP2C19*2 GG	Stent thrombosis	Stent thrombosis	1 year	CYP2C19*2 GG	565	N(%) 6 (1.1)	NR	0.964 CYP2C19*17 CC vs T allele	NR	NR	
		CYP2C19*2 A allele	Stent thrombosis	Stent thrombosis	1 year	CYP2C19*2 A allele	363	N(%) 4 (1.1)	NR		NR	NR	
Sawada, 2010{Sawada, 2010 36 /id} 21099121 Japan NR	loading dose of clopidogrel (300 mg) and maintenance dose of clopidogrel (75 mg/day) and aspirin (100 mg/day)	CYP2C19	Intra-stent thrombus	Intra-stent thrombus	Mean 243.8 days	Non-carrier	58	9(15.5)		0.0002 Non-carrier vs *2 carrier	No	No	
			Intra-stent thrombus	Intra-stent thrombus	Mean 243.8 days	*2 carrier	42	22 (52.3)			No	No	
			Intra-stent thrombus	Intra-stent thrombus	Mean 243.8 days	Non-carrier	100		2.475-16.812	0.0001 *2 carrier vs non-carrier	No	No	

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
			Intra-stent thrombus	Intra-stent thrombus	Mean 243.8 days	Non-carrier	100		3.401-36.018	0.00006 *2 carrier vs non-carrier	Yes, age, sex, factors with p<0.2	No	
Campo 2011 21679849 Italy NR	Clopidogrel	TaqMan	Definite or probable stent thrombosis (Academic Research Consortium classification)	Definite or probable stent thrombosis (Academic Research Consortium classification)	1 mo to 1 yr after PCI	*2 noncarriers N = 219	3 (1.4%)	NR	NR	NR	NO	NO	NO
						*2 carriers N = 81	1 (1.2%)						
						*17 noncarriers N = 198	4 (2.0%)	NR	NR	NR	NO	NO	NO
						*17 carriers N = 102	0 (0.0%)						
Harmsze 2010{Harmsze, 2010 6 /id} 20833683 Netherlands NR	Clopidogrel+aspirin	Real-time PCR	Stent thrombosis	NR	Any time within 1 yr after PCI	CYP2C19*2 carriers	fNR	Crude OR 1.6 Adjusted OR 1.7	Crude CI 1.1-2.3 Adjusted CI 1.0-2.6	Crude P 0.013 Adjusted P 0.018 [Logistic regression]	YES for potential confounders (i.e., a ge, gender, body mass index (BMI), smoking, diabetes mellitus, prior MI, the use of PPIs, the use of CCBs, acute coronary syndrome (ACS) as the indication for PCI, peri-procedural variables being stent length, stent diameter, and stent type (bare metal or drug eluting), and the use of glycoprotein IIb/IIIa antagonists during the procedure)	YES (by performing the false discovery rate test (q-value threshold 0.20))	NO
						CYP2C19*2 noncarriers							
						CYP2C19*2 carriers		OR 1.7	1.0 –3.1	0.040 [Multivariate analysis]			
						CYP2C19*2 noncarriers							
			Acute stent thrombosis	Occurrence within the first 24 h after PCI	**first 24 h after PCI**	CYP2C19*2 carriers		Crude OR 1.3 Adjusted OR 1.7	Crude CI 0.8–2.3 Adjusted CI 0.8–3.5	Crude P 0.34 Adjusted P 0.11 [Logistic regression]			NO
						CYP2C19*2 noncarriers							
			Subacute stent thrombosis	from 24 h to 30 days after PCI	**24 h to 30 days after PCI**	CYP2C19*2 carriers		Crude OR 2.0 Adjusted OR 2.5	Crude CI 1.3–3.3 Adjusted CI 1.1–5.5	Crude P 0.003 Adjusted P 0.026 [Logistic regression]			NO

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
						CYP2C19*2 noncarriers							
			Late stent thrombosis	from 30 days to 1 year after PCI	**30 days to 1 year after PCI**	CYP2C19*2 carriers		Crude OR 1.0 Adjusted OR 1.4	Crude CI 0.4 –2.6 Adjusted CI 0.6–9.5	Crude P 0.92 Adjusted P 0.54 [Logistic regression]			NO
						CYP2C19*2 noncarriers							
Sibbing 2011{Sibbing, 2011 2 /id} 21527445 Germany NR	Clopidogrel	TaqMan assay	Early ST	Stent thrombosis ≤30 days after stenting	**≤30 days after stenting**	*2/*1	Had event 33.9% of patients	Adjusted OR 2.27 vs *1/*1 Unadjusted OR 2.25	Adjusted 1.08 – 4.74 Undadjusted 1.17 – 4.32	Adjusted 0.03 (multivariable logistic regression model that assumed a codominant allele effect) Undadjusted 0.015	YES for adjusted [all baseline variables] NO for unadjuseted	NR	NONE
						*2/*2	Had event 2.4%						
						*2 noncarrier (*1/*1)	Had event 63.7%						
						*2/*2	Did not have event 22.9%						
						*2/*1	Did not have event 2.2%		OR 1.51 vs. *1/*1	1.04 – 2.18			
						*2 noncarrier (*1/*1)	Did not have event 74.9%			P=0.019 for comparison of frequencies in this row and all above rows (chi-square)			

Appendix Table D8: Major Adverse Cardiovascular Events

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95% CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Collet{Collet, 2009 140 /id} 2009 19108880 France AFIJI	Clopidogrel (75 mg maintenance dose for at least 1 mo)	CYP2C19 *2	First MACE	First death, non-fatal MI, or urgent revascularization during FU. See below for definitions of components.	Mean FU = 2.8 yr	*2/*2 N = 9	2 (22%)	NR	NR	NR	NA	NO	Only counts provided
						*2/*1 N = 64	13 (20%)						
						*1/*1 N = 186	11 (5.9%)						
			First MACE	First death, non-fatal MI, or urgent revascularization during FU. See below for definitions of components.	Mean FU = 2.8 yr	Carriers (*2/*2 or *2/*1) N = 73	15 (21%) 10.9 events per 100 person-years	HR = 3.69 Adjusted HR = 5.38	1.69, 8.05 2.32, 12.47	0.0005 <0.0001	Unadjusted Adjusted [baseline BMI, smoking status, diabetes status, stent implantation, initial STE MI, use of PPI]	NO	Primary endpoint; survival curve in Figure 3A
						Non-carriers (*1/*1) N = 186	11 (6%) 2.89 events per 100 person-years						
			First MACE, landmark analysis (from 6 mo after clopidogrel initiation)	First death, non-fatal MI, urgent revascularization, for patients on clopidogrel for at least 6 mo	Mean FU = 2.8 yr [for the whole cohort; does not account for patient with FU shorter than 6 mo, or for person time during the first 6 mo]	Carriers (*2/*2 or *2/*1) N = 61 (landmark analysis)	10 (16%)	HR = 3.00	1.27, 7.10	0.009	Unadjusted (based on the other HR reported in the same graph)	NO	Landmark analysis; survival curve in Figure 3b.
						Non-carriers (*1/*1) N = 122 (landmark analysis)	9 (7%)						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19*2	MACE	Composite of cardiac mortality and stent thrombosis (definite or probable)	Maximum FU of 6 mo	*2/*2 N = 26	2 (7.7%)	NR	NR	0.061 across groups (chi square test)	NO	NO	Secondary outcome
						*2/*1 N = 221	13 (5.9%)						
						*1/*1 N = 525	14 (2.7%)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95% CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
		CYP2C19*2 (see also KQ2b extraction form)	MACE	Composite of cardiac mortality and stent thrombosis (definite or probable)	Maximum F U of 6 mo	*2/*2 + RPR N = 40	7 (17.5%)	NR OR=11.45	NR (1.84, 71.27)	<0.0001 (chi square test) 0.009 (logistic regression)	NO Adjusted ("for traditional cardiovascular risk factors and clinical and procedural risk factors for stent thrombosis")	NO	Secondary outcome
						*1/*1 or low RPR N = 732	22 (3%)						
		CYP2C19*2	MACE	Composite of cardiac mortality and stent thrombosis (definite or probable)	Maximum F U of 6 mo	*2/*2 or *2/*1 N = 247	15 (6.1%)	NR OR=2.36 OR=2.70	NR (1.12, 4.97) (1.00, 8.42)	0.020 (chi square test) 0.024 (logistic regression) 0.049 (logistic regression)	NO NO (univariate) YES (ADP-RPR, traditional cardiovascular risk factors, clinical and procedural risk factors for ST)	NO	Secondary outcome
						*1/*1 N = 525	14 (2.7%)						
		CYP2C19*2	MACE	Composite of cardiac mortality and stent thrombosis (definite or probable)	Maximum F U of 6 mo	*2/*2 or *2/*1 N = 247	15 (crude proportion 6.1%)	NR	NR	<0.01 (log rank)	NO	NO	Secondary outcome
						*1/*1 N = 525	14 (crude proportion 2.7%)						
Mega{Mega, 2009 141 /id} 2009 19106084 Multinational TRITON-TIMI 38	Clopidogrel 300 mg loading dose, 75 mg maintenance	CYP2C19	MACE	Death from cardiovascular causes, myocardial infarction, or stroke	Up to 15 mo (maximum duration of treatment on trial)	IM or PM (1/*2A, *1A/*3, *1A/*4, *1A/*8, *2A/*2A, *2A/*3, *2A/*4, *2A/*5A, *2A/*8) N = 395	N = 46 Rate = 12.1% (Kaplan-Meier)	HR = 1.53	1.07, 2.19	0.01 carriers vs. non-carriers [Gehan-Wilcoxon test]	ACS subtype (STE or NSTE was used as a stratification factor)	NO	Primary outcome
						EM (*1A/*1A) N = 1064	N = 83 Rate = 8.0% (Kaplan-Meier rate)						
		CYP2C19	MACE	Death from cardiovascular causes, myocardial infarction, or stroke	Up to 15 mo (maximum duration of treatment on trial)	*2 carriers (*2/*2 or *2/*1) 95% of all carriers = 375	N = NR Rate = 11.7% (Kaplan-Meier)	HR = 1.42	0.98, 2.05	0.04 [Kaplan-Meier]	ACS subtype (STE or NSTE was used as a stratification factor)	NO	Primary outcome
						Non-*2 carriers (*1/*1) N = 1084 (= 1459 - 375)	N = NR Rate = 8.3% (Kaplan-Meier rate)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95% CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Shuldiner{Shuldiner, 2009 116 /id} 2009 19706858 USA Sinai Hospital of Baltimore Study	Clopidogrel LD 600 mg (n=112) or 300 mg (n=25) or maintenance therapy with 75 mg daily (n=90) + 81-325 mg aspirin daily before PCI and LD 325 mg. Aspirin 325 mg/d & clopidogrel 75 mg/d at discharge	CYP2C19 *2	Post-discharge ischemic events	MI, ischemic stroke, stent thrombosis (definite), unplanned TVR, unplanned non-TVR, hospitalization for coronary ischemia without revascularization, and death due to CV cause	At one and 12 mo (results reported from time to event analyses covering the whole time period)	*2/*2 or *2/*1 N = 67	14 (20.9%)	HR = 2.42 HR = 1.58	1.18, 4.99 0.68, 3.66	P = 0.02 (carriers vs. non-carriers) P = 0.29 (carriers vs. non-carriers) Based on proportional hazards model (time-to-event)	Adjusted (age, sex, race) Adjusted (age, sex, race, and ADP-stimulated platelet reactivity as a covariate)	NO	KM plots in figure 4, with number at risk. Also reports analyses stratified by clopidogrel treatment status at the time of the outcome event
						*1/*1 N = 158	16 (10%)						
Sibbing{Sibbing, 2009 133 /id} 2009 19193675 Germany NR	Clopidogrel 600 mg loading dose before stent placement	CYP2C19 *2	MACE	Death or MI	30 d	CYP2C19 *2 carriers (*2/*2 and *2/*1) N = 680	52 (8%)	HR = 1.14	0.83, 1.58	0.42 [Cox proportional hazards regression; carriers vs. non-carriers]	NO	NO	None
						CYP2C19 non-carriers (*1/*1) N = 1805	121 (7%)						
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	Clopidogrel 600 mg loading dose; clopidogrel 75 mg (1/d) and aspirin 100 mg (2/d) maintenance.	CYP2C19 *17	MACE	Death, MI, or urgent TVR	30 d	*17/*17 N = 76	4 (5.3%)	OR = 0.94	0.5, 1.61	(carriers vs. non-cariers)[logistic regression] P = 0.94 (across 3 groups) [chi-square test for trend]	NO	NO	Secondary efficacy endpoint
						*17/*1 N = 546	18 (3.3%)						
						*1/*1 N = 902	34 (3.8%)						
Trenk{Trenk, 2008 171 /id} 2008 18482659 Germany EXCELSIOR	600 mg clopidogrel loading dose + 75 mg/day clopidogrel (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	CYP2C19 *2	Composite of death and MI	MI = new rise in troponin T ≥0.03 mg/l associated with typical symptoms and/or typical electrocardiogram changes and/or typical angiographic finding; death = as reported in phone interview	1 year	Carriers (*1/*2 or *2/*2) N = 245	5 (2%) (3/90 when limited to patients with at least 1 drug eluting stent implanted)	NR	NR	P=0.371 (between carriers and noncarriers) P=0.684 (same contrast; limited to patients with at least one drug eluting stent implanted)	NO	NR	NO
						Noncarriers (*1/*1) N = 552	19 (3.4%) (4/190 when limited to patients with at least 1 drug eluting stent implanted)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Wallentin{Wallentin, 2010 56 /id} 2010 20801498 Multiple countries (43 countries in North America, South America, Europe, Asia, Australia) PLATO	75 mg clopidogrel once daily (300–600 mg loading dose)	CYP2C19 genotyping	Cardiovascular death, MI, and stroke	NR	From baseline through end of followup (≤360 days)	Any LOF allele (*2-*8) N = 1388	149 (10.7% crude, 11.2% actuarial)	NR	NR	NR	NO	NO	Primary efficacy end point
						No LOF allele N = 3516	332 (9.4% crude, 10.0% actuarial)						
			Cardiovascular death, MI, and stroke	NR	At 30 days	Any LOF allele (*2-*8) N = 1388	5.7% crude	NR	NR	NR	NO	NO	Additional data (daily) in Fig. 1 (K-M)
						No LOF allele N = 3516	3.8% crude						
			Cardiovascular death, MI, and stroke	NR	From 31 days through end of followup (≤360 days)	Any LOF allele (*2-*8) N = 1302	5.8% actuarial	NR	NR	NR	NO	NO	Additional data (daily) in Fig. 2 (K-M)
						No LOF allele N = 3370	6.4% actuarial						
			Cardiovascular death or MI	NR	From baseline through end of followup (≤360 days)	Any LOF allele (*2-*8) N = 1388	138 (9.9% crude, 10.4% actuarial)	NR	NR	NR	NO	NO	None
						No LOF allele N = 3516	306 (8.7% crude , 9.2% actuarial)						
nello, 2010{Bonello, 2010 45 /id} 20708365 France NR	All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement	CYP2C19	All MACE	All MACE	In hospital	Wild-type N = 277	1 (<1%)	Count	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	1 (1%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						
Simon 2011{Simon, 2011 27 /id} 21262992 France NR	Clopidogrel	CYP2C19	Death , MI or stroke	Death , MI or stroke	1 year	No PPI, No variant allele	41/485 (8.5)	HR= 1.13	0.74-1.74	NR	Yes. GRACE score, sex, current smoking, hyperlipidemia, hypertension, diabetes mellitus	NR	Supplement data for whole population, N=3670

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
			Death , MI or stroke	Death , MI or stroke	1 year	PPI, No variant allele	50/545 (9)			NR		NR	
			Death , MI or stroke	Death , MI or stroke	1 year	No PPI, 1variant allele	11/171 (6)	HR= 1.02	0.44-2.4	NR	Yes	NR	
			Death , MI or stroke	Death , MI or stroke	1 year	PPI, 1variant allele	11/190 (6)			NR		NR	
			Death , MI or stroke	Death , MI or stroke	1 year	No PPI, 2 variant allele	3/19 (16)	HR= 0.25	0.02-3.58	NR	NR		
			Death , MI or stroke	Death , MI or stroke	1 year	PPI, 2 variant allele	1/15 (7)						
Tiroch, 2010{Tiroch, 2010 62 /id} 20826260 Germany NR	aspirin (100mg twice daily) and clopidogrel (75mg once Daily)	CYP2C19*2 GG	Death or MI	Death or MI	1 year	CYP2C19*2 GG N = 680	680	63 (9.2%)	NR	0.086 CYP2C19*2 GG vs *2 A allele	NR	NR	
		CYP2C19*2 A allele	Death or MI	Death or MI	1 year	CYP2C19*2 A allele N = 248	248	14 (5.7%)	NR		NR	NR	
		CYP2C19*2 GG	MACE	MACE	1 year	CYP2C19*2 GG N = 680	680	N(%) 179 (26.3)	NR	0.525 CYP2C19*2 GG vs *2 A allele	NR	NR	
		CYP2C19*2 A allele	MACE	MACE	1 year	CYP2C19*2 A allele	248	N(%) 60 (24.2)	NR		NR	NR	
		CYP2C19*2 GG	MACE or stroke	MACE or stroke	1 year	CYP2C19*2 GG	680	N(%) 184 (27.1)	NR	0.378 CYP2C19*2 GG vs *2 A allele	NR	NR	
		CYP2C19*2 A allele	MACE or stroke	MACE or stroke	1 year	CYP2C19*2 A allele	248	N(%) 60 (24.2)	NR		NR	NR	
		CYP2C19*2 GG	Death or MI	Death or MI	1 year	CYP2C19*2 GG	565	N(%) 42 (7.4)	NR	0.255 CYP2C19*17 CC vs T allele	NR	NR	
		CYP2C19*2 A allele	Death or MI	Death or MI	1 year	CYP2C19*2 A allele	363	N(%) 35 (936)	NR		NR	NR	
		CYP2C19*2 GG	MACE	MACE	1 year	CYP2C19*2 GG	565	N(%) 159 (28.1)	NR	0.04 CYP2C19*17 CC vs T allele	NR	NR	
		CYP2C19*2 A allele	MACE	MACE	1 year	CYP2C19*2 A allele	363	N(%) 80 (22)	NR		NR	NR	

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Sorich, 2010{Sorich, 2010 49 /id} 20492467 707 sites in 30 countries Substudy of TRITON-TIMI 38	300-mg loading dose and 75-mg daily maintenance dose	CYP2C19	CV death, non-fatal MI or non-fatal stroke	CV death, non-fatal MI or non-fatal stroke	15 months	RM(with one or two reduced function alleles) vs EM(no reduced function allele)	802	OR=1.53	1.07-2.19	NR	NR	No	
			CV death, non-fatal MI or non-fatal stroke	CV death, non-fatal MI or non-fatal stroke	15 months	EM	NR	9.8%	8.3-11.3	NR	NR	No	
			CV death, non-fatal MI or non-fatal stroke	CV death, non-fatal MI or non-fatal stroke	15 months	RM	NR	15%	11.6-18.8	NR	NR	No	
Sawada, 2010{Sawada, 2010 36 /id} 21099121 Japan NR	loading dose of clopidogrel (300 mg) and maintenance dose of clopidogrel (75 mg/day) and aspirin (100 mg/day)	CYP2C19	Total MACE	Total MACE	Mean 243.8 days	Non-carrier	58	11(19)	NR	0.25, Non-carrier vs *2 carrier	No	No	
			Total MACE	Total MACE	Mean 243.8 days	*2 carrier	42	13(31)	NR				
Pare, 2010{Pare, 2010 46 /id} 20979470 Multinational ACTIVE	clopidogrel dose of 75 mg per day in combination with aspirin	CYP2C19	MACE (first definition)	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke	12 months	Poor metabolizers N = 61	4 (7%)	NR	NR	NR	NR	NR	NR
						Intermediate metabolizers N = 437	37 (9%)						
						Extensive metabolizers N = 1033	112 (11%)						
						Ultra metabolizers N = 847	66 (8%)						
						Unknown status N = 152	11 (7%)						
			MACE (second definition)	Composite of death from cardiovascular causes, nonfatal myocardial infarction, stroke, recurrent ischemia, or hospitalization for unstable angina	12 months	Poor metabolizers N = 61	13 (21%)	NR	NR	NR	NR	NR	NR
						Intermediate metabolizers N = 437	70 (16%)						
						Extensive metabolizers N = 1033	193 (19%)						
						Ultra metabolizers N = 847	123 (15%)						
						Unknown status N = 152	19 (13%)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Pare, 2010{Pare, 2010 46 /id} 20979470 Multiple countries ACTIVE-A	clopidogrel dose of 75 mg per day in combination with aspirin	CYP2C19	composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke - ACTIVE trial	composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke	Median 3.6 y	Poor metabolizers N = 9	1 (11%)	NR	NR	NR	NR	NR	NR
						Intermediate metabolizers N = 93	21 (23%)						
						Extensive metabolizers N = 199	34 (17%)						
						Ultra metabolizers N = 222	49 (22%)						
						Unknown status N = 37	7 (19%)						
Mega, 2010{Mega, 2010 57 /id} 20801494 707 sites in 30 countries TRITON-TIMI 38	clopidogrel (300-mg loading dose and 75-mg daily maintenance dose)	CYP2C19	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	15 months	Reduced-function allele carrier vs non-carrier		HR=1.77	1.11-2.80	0.0155, Reduced-function allele carrier vs non-carrier	NR	NR	
		CYP2C19 and ABCB1 3435 C-T	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	15 months	No risk gene of either CYP2C19 and ABCB1 3435 C-T	KM rate 6.3% 48/773		NR	NR	NR	NR	
		CYP2C19	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	15 months	CYP2C19 reduced-function allele only	KM rate 11.5%, 29/268		NR	NR	NR	NR	
		ABCB1 3435 TT homozygotes only	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	15 months	ABCB1 3435 TT homozygotes only	KM rate 12.6%, 35/288		NR	NR	NR	NR	
		CYP2C19 and ABCB1 3435 C-T	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	15 months	risk gene of both CYP2C19 and ABCB1 3435 C-T	KM rate 13.6%, 17/125		NR	NR	NR	NR	
		CYP2C19	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	30 days	No risk gene of either CYP2C19 and ABCB1 3435 C-T	KM rate 4%, 31/773		NR	NR	NR	NR	
		CYP2C19	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	30 days	ABCB1 3435 TT homozygotes	KM rate 7%, 20/288		NR	NR	NR	NR	
		CYP2C19	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	30 days	carriers of CYP2C19 reduced function allele		KM rate 6%, 16/268	NR	NR	NR	NR	
		CYP2C19	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	30 days	Carriers of either Reduced-function allele vs carriers of neither		HR=1.64	1.01-2.65	0.0441, Carriers either of Reduced-function allele vs carriers of neither	NR	NR	

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
		CYP2C19	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	30 days	carriers of both CYP2C19 reduced function allele and ABCB1 3435 TT homozygotes		KM rate 12% 15/125	NR				
		CYP2C19	Cardiovascular death, myocardial infarction, or stroke	Cardiovascular death, myocardial infarction, or stroke	30 days	Carriers of either Reduced-function allele vs carriers of neither		HR=3.16	1.71-5.85	0.0003, Carriers of both Reduced-function allele vs carriers of neither	NR	NR	
Campo 2011 21679849 Italy NR	Clopidogrel	TaqMan	Death, MI (Recurrence of ischemic symptoms and elevation of creatine kinase-myocardial band ≥3x ULN), or stroke	Death, MI (Recurrence of ischemic symptoms and elevation of creatine kinase-myocardial band ≥3x ULN), or stroke	1 mo to 1 yr after PCI	*2 noncarriers	219	11 (5.0%)	NR	0.02 vs, next row [Fisher exact test]	NO	NO	NO
						*2 carriers	81	10 (12.3%)					
						*17 noncarriers	198	16 (8.1%)	NR	0.1 vs, next row [Fisher exact test]	NO	NO	NO
						*17 carriers	102	5 (4.9%)					
Malek 2008{Malek, 2008 167 /id} 18577829 Poland NR	Clopidogrel and aspirin	CYP2C19 *2	CV Death or MI	NR	Within 12 months after PCI	Group 1	0	NR	NR	NR	NR	NR	NR
						Group 2	1	NR	NR	NR	NR	NR	NR
						Group 3	0	NR	NR	NR	NR	NR	NR
						Controls	5	NR	NR	NR	NR	NR	NR
Simon {Simon, 2009 142 /id}2009 19106083 France FAST-MI	Clopidogrel	CYP2C19*2	Death from any cause, nonfatal stroke, or MI	Primary outcome	Within 1 yr	CYP2C19*2 noncarrier N = 1561	214 (14%)	NR	NR	0.17 (univariate Cox across genotype groups)	NO	NO	Check Table 2—should ensure P values are for these comparisons exactly Also %s here dif't from those reporter but not sure it's the best data to present
						CYP2C19*2 heterozygote N = 564	64 (11%)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
						CYP2C19*2 homozygote N = 53	10 (19%)						
		CYP2C19*3	Death from any cause, nonfatal stroke, or MI	Primary outcome	Within 1 yr	CYP2C19*3 noncarrier N = 2186	291 (13%)	NR	NR	0.97 (univariate Cox across genotype groups)	NO	NO	NO
						CYP2C19*3 heterozygote N = 1	0 (0%)						
						CYP2C19*2 homozygote N = 0	NA						
		CYP2C19*4	Death from any cause, nonfatal stroke, or MI	Primary outcome	Within 1 yr	CYP2C19*4 noncarrier N = 2168	286 (13%)	NR	NR	0.31 (univariate Cox across genotype groups)	NO	NO	NO
						CYP2C19*4 heterozygote N = 21	4 (19%)						
						CYP2C19*4 homozygote N = 0	NA						
		CYP2C19*5	Death from any cause, nonfatal stroke, or MI	Primary outcome	Within 1 yr	CYP2C19*5 noncarrier N = 2175	289 (13%)	NR	NR	0.97 (univariate Cox across genotype groups)	NO	NO	NO
						CYP2C19*5 heterozygote N = 1	0 (0%)						
						CYP2C19*5 homozygote N = 0	NA						
		CYP2C19*17	Death from any cause, nonfatal stroke, or MI	Primary outcome	Within 1 yr	CYP2C19*17 noncarrier N = 1390	199 (14%)	NR	NR	0.18 (univariate Cox across genotype groups)	NO	NO	NO
						CYP2C19*17 heterozygote N = 674	77 (11%)						
						CYP2C19*17 homozygote N = 100	11 (11%)						
		Any CYP2C19 loss-of-function SNP (*2, *3, *4, or *5)	Death from any cause, nonfatal stroke, or MI	Primary outcome	Within 1 yr	None of *2, *3, *4, or *5 N = 1573	218 (14%)	NR	NR		NO	NO	NO

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
						One of *2, *3, *4, or *5 N = 577	64 (11%)						
						Two of *2, *3, *4, or *5 N = 58	12 (21%)						
		Any CYP2C19 loss-of-function SNP (*2, *3, *4, or *5)	Death from any cause, nonfatal stroke, or MI	In the 1535/2208 patients undergoing PCI		None of *2, *3, *4, or *5 N = 1573	NR	Adjusted HR 3.58, vs. next two rows	1.71-7.51	0.005	NO	NO	From Table 3 (which is subgoup analysis—is this OK?)
						One of *2, *3, *4, or *5 N = 577	NR	Adjusted HR 0.78, vs. previous and next row	0.50-1.21				
						Two of *2, *3, *4, or *5 N = 58	NR						

Appendix Table D9: Bleeding Outcomes

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Mega, 2009{Mega, 2009 141 /id} 19106084 Multinational Genetics substudy of TRITON-TIMI 38 [Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction]	Clopidogrel 300 mg loading dose, 75 mg maintenance	CYP2C19	Minor or major bleeding	TIMI major or minor bleeding not related to CABG; all outcomes were adjudicated by a committee unaware of group assignments	Up to 15 mo (maximum duration of treatment on trial)	IM or PM (1/*2A, *1A/*3, *1A/*4, *1A/*8, *2A/*2A, *2A/*3, *2A/*4, *2A/*5A, *2A/*8)	N = 11 Rate = 12.1% (Kaplan-Meier)	HR = 1.01	0.51, 2.01	0.98 [Kaplan-Meier]	YES [ACS subtype (STE or NSTE was used as a stratification factor)]	NO	Secondary outcome
						EM (*1A/*1A) N = 1061 (patients who received clopidogrel treatment)	N = 30 Rate = 8.0% (Kaplan-Meier rate)						
Gladding, 2009{Gladding, 2009 248 /id} 19926050 New Zealand NR	Clopidogrel 150 mg daily	Autogenomics 2C19+ assay	Bleeding	NR	7 d	CYP2C19*2 (and CYP2C9*3) carriers N=NR	0	NR	NR	NR	NR	NR	NR
						CYP2C19*2/*17 N=NR	0						
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	Clopidogrel 600 mg loading dose; clopidogrel 75 mg (1/d) and aspirin 100 mg (2/d) maintenance.	CYP2C19 *17	TIMI major and minor bleeding	Combined major or minor bleeding according to TIMI criteria	30 d	*17/*17 N = 76	6 (7.9%)	OR = 3.27	1.33, 8.10	(*17/*17 vs. *1/*1) [logistic regression] P = 0.1 (across 3 groups) [chi-square test for trend]	NO	NO	Primary safety endpoint
						*17/*1 N = 546	22 (4%)						
						*1/*1 N = 902	23 (2.5%)						
			TIMI major and minor bleeding	Combined major or minor bleeding according to TIMI criteria	30 d	*17/*17 or *17/*1 N = 622	28 (4.5%)	OR = 1.80	1.03, 3.14	NR	NO	NO	Primary safety endpoint
						*1/*1 N = 902	23 (2.5%)						
			TIMI major and minor bleeding	Combined major or minor bleeding according to TIMI criteria	30 d	*17/*17 or *17/*1 N = 622	28 (4.5%)	OR = 1.85 OR = 3.41	1.19, 2.86 1.42, 8.17	P = 0.006 (carriers vs. non-carriers) [multivariable logistic regression] P = NR (*17/*17 vs. *1/*1) [multivariable logistic regression]	YES (age, sex, BMI, serum Creatinine, PPIs, abciximab, clopidogrel loading interval)	NO	Primary safety endpoint
						*1/*1 N = 902	23 (2.5%)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
			TIMI major bleeding	Major bleeding according to TIMI criteria	30 d	*17/*17 N = 76	1 (1.3%)	OR = 2.04 OR = 2.39	0.68, 6.12 0.95, 2.10	(carriers vs. non-cariers)[logistic regression] (*17/*17 vs. *1/*1) [logistic regression] P = 0.22 (across 3 groups) [chi-square test for trend]	NO	NO	Secondary safety endpoint
						*17/*1 N = 546	6 (1.1%)						
						*1/*1 N = 902	5 (0.6%)						
			TIMI minor bleeding	Minor bleeding according to TIMI criteria	30 d	*17/*17 N = 76	5 (6.6%)	OR = 1.72 OR = 3.46	0.92, 3.22 1.30, 9.27	(carriers vs. non-cariers)[logistic regression] (*17/*17 vs. *1/*1) [logistic regression] P = 0.025 (across 3 groups) [chi-square test for trend]	NO	NO	Secondary safety endpoint
						*17/*1 N = 546	16 (2.9%)						
						*1/*1 N = 902	18 (2%)						
			Fatal intracranial bleeding	Fatal intracranial bleeding	30 d	*17/*17 N = 76	1 (1.3%)	NR	NR	NR	NO	NO	Not mentioned as an explicit predefined endpoint
						*17/*1 N = 546	1 (0.2%)						
						*1/*1 N = 902	0 (0%)						
Wallentin, 2010{Wallentin, 2010 56 /id} 20801498 Multiple countries (43 countries in North America, South America, Europe, Asia, Australia) PLATO	75 mg clopidogrel once daily (300–600 mg loading dose)	CYP2C19 genotyping	Major bleeding	Major bleeding	Median treatment duration = 277 d	Any LOF allele (*2-*8) N = 1380	143 (10%)	NR	NR	NR	NO	NO	None
						No LOF allele N = 3506	340 (10%)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
			Major bleeding	Major bleeding	Median treatment duration = 277 d	No LOF or GOF allele N = 1856	161 (9%)	NR	NR	0.022 GOF allele vs. all others [Cox regression]	NO	NO	None
						Any LOF but no GOF allele N = 1053	108 (10%)						
						Any GOF allele N = 1977	214 (11%)						
			Major bleeding related to non-CABG	Major bleeding related to non-CABG	Median treatment duration = 277 d	Any LOF allele (*2-*8) N = 1380	41 (3%)	NR	NR	NR	NO	NO	None
						No LOF allele N = 3506	110 (3%)						
			Major bleeding related to CABG	Major bleeding related to CABG	Median treatment duration = 277 d	Any LOF allele (*2-*8) N = 1380	107 (8%)	NR	NR	NR	NO	NO	None
						No LOF allele N = 3506	246 (7%)						
Bonello{Bonello, 2010 45 /id} 2010 20708365 France NR	Oral LDs of 250 mg aspirin and 600 mg clopidogrel	CYP2C19*2	TIMI major bleeding	TIMI major bleeding	In hospital	Wild-type N = 277	0 (%)	NR	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	0 (0%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						
			TIMI minor bleeding	TIMI minor bleeding	In hospital	Wild-type N = 277	4 (1%)	NR	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	0 (0%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						
			TIMI major or minorbleeding	TIMI minor bleeding	In hospital	Wild-type N = 277	4 (1%)	NR	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	0 (0%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Sorich, 2010{Sorich, 2010 49 /id} 20492467 707 sites in 30 countries Substudy of TRITON-TIMI 38	clopidogrel (300-mg loading dose and 75-mg daily maintenance dose) for 6–15 months.	CYP2C19	Major or minor bleeding	Major or minor bleeding	15 months	extensive metabolizers	NR	3.4%	2.6-4.2	NR	NR	No	
			Major or minor bleeding	Major or minor bleeding	15 months	RM	NR	3.5%	2.0-5.5	NR	NR	No	
Pare{Pare, 2010 46 /id} 2010 20979470 Multinational CURE	clopidogrel (at a dose of 75 mg per day) in combination with aspirin	CYP2C19	Major Bleeding - CURE trial	Major bleeding	12 months	Poor metabolizers N = 61	0 (0%)	NR	NR	NR	NR	NR	None
						Intermediate metabolizers N = 437	19 (4%)						
						Extensive metabolizers N = 1033	42 (4%)						
						Ultra metabolizers N = 847	39 (5%)						
						Unknown status N = 152	2 (1%)						
Pare{Pare, 2010 46 /id} 2010 20979470 Multinational ACTIVE-A	clopidogrel (at a dose of 75 mg per day) in combination with aspirin	CYP2C19	Major Bleeding – ACTIVE trial	Major bleeding	Median 3.6 y	Poor N = 9	0 (0%)	NR	NR	NR	NR	NR	None
						Intermediate metabolizers N = 93	10 (11%)						
						Extensive metabolizers N = 199	10 (5%)						
						Ultra metabolizers N = 222	8 (4%)						
						Unknown status N = 37	4 (11%)						
Campo 2011 21679849 Italy NR	Clopidogrel + aspirin	TaqMan	Bleeding event	Major + minor (TIMI classification)	1 mo to 1 yr after PCI	*2 noncarriers N = 219	219	16 (7.3%)	NR	0.4 vs, next row [Fisher exact test]	NO	NO	For KQ4?
						*2 carriers N = 81	81	3 (3.7%)					
						*17 noncarriers N = 198	198	6 (3%)	NR	0.01 vs, next row [Fisher exact test]		NO	NO
						*17 carriers N = 102	102	13 (1.7%)					

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
				Superficial (BleedScore classification)	1 mo to 1 yr after PCI	*2 noncarriers N = 219	219	22 (10.1%)	NR	NR	NO	NO	NO
						*2 carriers N = 81	81	8 (9.8%)					
						*17 noncarriers N = 198	198	4 (2.0%)	NR	NR	NO	NO	NO
						*17 carriers N = 102	102	18 (9.1%)					
				Internal (melena, hematuria, hematemesis, epistaxis)+ alarming (intracranial or needing transfusion)	1 mo to 1 yr after PCI	*2 noncarriers N = 219	219	20 (9.1%)	NR	0.4 vs, next row [Fisher exact test]	NO	NO	NO
						*2 carriers N = 81	81	6 (7.4%)					
						*17 noncarriers N = 198	198	10 (5%)	NR	0.01 vs, next row [Fisher exact test]	NO	NO	NO
						*17 carriers N = 102	102	16 (16%)					
				"Composite bleeding endpoints"	1 mo to 1 yr after PCI	*17 carriers N = 102	NR	HR = 2.3	1.03-5.3	0.03 [Cox proportional hazards model]	YES [age, on-clopidogrel platelet reactivity at 30 d, additional clinical, angiographic, and genetic characteristics]	NO	NO
						*17 noncarriers N = 198	NR						

Appendix Table D10: Stroke Events

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95% CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Mega{Mega, 2009 141 /id} 2009 19106084 Multinational Genetics substudy of TRITON-TIMI 38 [Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction]	Clopidogrel 300 mg loading dose, 75 mg maintenance	CYP2C19	Non-fatal stroke	NR; all outcomes were adjudicated by a committee unaware of group assignments	Up to 15 mo (maximum duration of treatment on trial)	IM or PM (1/*2A, *1A/*3, *1A/*4, *1A/*8, *2A/*2A, *2A/*3, *2A/*4, *2A/*5A, *2A/*8) N = 395	N = NR Rate = 0.88% (Kaplan-Meier)	HR = 3.93	0.66, 23.51	NR	ACS subtype (STE or NSTE was used as a stratification factor)	NO	Secondary outcome
						EM (*1A/*1A) N = 1064	N = NR Rate = 0.24% (Kaplan-Meier rate)						
Sibbing, 2009{Sibbing, 2009 133 /id} 19193675 Germany NR	Clopidogrel 600 mg loading dose before stent placement	CYP2C19 *2	Ischemic stroke	Confirmed by brain CT or MRI	30 days	CYP2C19 *2 carriers (*2/*2 and *2/*1) N = 680	4	NR	NR	0.001	NO	NO	None
						CYP2C19 non-carriers (*1/*1) N = 1805	0						
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement	CYP2C19	stroke	stroke	In hospital	Wild-type N = 277	1 (<1%)	NR	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	0 (0%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						
Yamamoto 2011{Yamamoto, 2011 25 /id} 21168310 Japan NR	clopidogrel	CYP2C19*2 or *3	Ischemic stroke	Ischemic stroke	NR	carriers	2/62	NR	NR	NR	NR	NR	
		CYP2C19*1/*2	Stroke	Stroke	1 days	CYP2C19*1/*2	NR	NR	NR	NR	NR	NR	
			Stroke	Stroke	10 days	CYP2C19*1/*2	NR	NR	NR	NR	NR	NR	
		CYP2C19*2/*2	Cardiovascular death	Cardiovascular death	74 days	CYP2C19*2/*2	NR	NR	NR	NR	NR	NR	

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95% CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Tiroch, 2010{Tiroch, 2010 62 /id} 20826260 Germany NR	aspirin (100mg twice daily) and clopidogrel (75mg once Daily)	CYP2C19*2 GG	Stroke	Stroke	1 year	CYP2C19*2 GG	680	N(%) 8(1.2)	NR	0.085 CYP2C19*2 GG vs *2 A allele	NR	NR	
		CYP2C19*2 A allele	Stroke	Stroke	1 year	CYP2C19*2 A allele	248	N(%) 0(0)	NR		NR	NR	
		CYP2C19*2 GG	Stroke	Stroke	1 year	CYP2C19*2 GG	565	N(%) 5 (0.9)	NR	0.93 CYP2C19*17 CC vs T allele	NR	NR	
		CYP2C19*2 A allele	Stroke	Stroke	1 year	CYP2C19*2 A allele	363	N(%) 3 (0.8)	NR		NR	NR	

Appendix Table D11: Other Clinical Outcomes

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
Collet{Collet, 2009 140 /id} 2009 19108880 France AFIJI	Clopidogrel (75 mg maintenance dose for at least 1 mo)	CYP2C19 *2	Urgent revascularization	Coronary (any vessel) revascularization (any type of PCI or CABG) decided within 24 h of a recurrent episode of myocardial ischemia	Mean FU = 2.8 yr	Carriers (*2/*2 or *2/*1) N = 73	3 (4%) 2.18 events per 100 person-years	HR = 1.94 Adjusted HR = 3.24	0.43, 8.73 0.69, 15.09	0.38 0.13	Unadjusted Adjusted [baseline BMI, smoking status, diabetes status, stent implantation, initial STE MI, use of PPI]	NO	NO
						Non-carriers (*1/*1) N = 186	4 (2%) 1.05 events per 100 person-years						
			Ischemic endpoint not related to stent thrombosis	Acute coronary events occurring either in patients who did not receive a stent or in those with recurrent events affecting a non-stented artery	Mean FU = 2.8 yr	Carriers (*2/*2 or *2/*1) N = 73	6 (8%) 5.09 events per 100 person-years	HR = 2.38 Adjusted HR = 3.31	0.79, 7.13 1.05, 10.47	0.11 0.04	Unadjusted Adjusted [baseline BMI, smoking status, diabetes status, stent implantation, initial STE MI, use of PPI]	NO	The authors stated that "when we took into account the other CYP2C19 variants (*3 to *6) that were present in 3 patients without the CYP2C19*2 variant, the overall results did not change"
						Non-carriers (*1/*1) N = 186	7 (4%) 1.99 events per 100 person-years						
			First cardiovascular event	Survival free of a cardiovascular event	Mean FU = 2.8 yr	Carriers (*2/*2 or *2/*1) N = 73	NR	HR = 4.04	1.81, 9.02	0.0006	Adjusted (multivariable step-wise Cox regression, after elimination CYP2C19*2 was the only factor independently associated with the outcome) Stated that "we noted no significant effect of use of PPIs"	NO	Selection of covariates based on p-value criteria; additional information in Table 1 of the manuscript
						Non-carriers (*1/*1) N = 186	NR						
			First cardiovascular event; limited to stent implantation	Survival free of a cardiovascular event	Mean FU = 2.8 yr	Carriers (*2/*2 or *2/*1) N = 61 (patients with stent implantation)	NR	HR = 4.09	1.81, 9.25	0.0008	Adjusted (multivariable step-wise Cox regression, after elimination CYP2C19*2 was the only factor independently associated with the outcome) Stated that "we noted no significant effect of use of PPIs"	NO	Selection of covariates based on p-value criteria; additional information in Table 1 of the manuscript

Author,year UID Country Study name	Treatment	Genetic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Genotype groups	No. with outcome status within phenotype group	Comparative metric	95%CI	P (between which groups?) [statistical test]	Statistical Adjustment [If YES, for what factors?]	Procedures for multiple comparisons	Comments
						Non-carriers (*1/*1) N = 162 (patients with stent implantation)	NR						
Wallentin, 2010{Wallentin, 2010 56 /id} 20801498 Multiple countries (43 countries in North America, South America, Europe, Asia, Australia) PLATO	75 mg clopidogrel once daily (300–600 mg loading dose)	CYP2C19 genotyping	Net clinical benefit			Any LOF allele (*2-*8) N = 1388							
						No LOF allele N = 3516							
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement	CYP2C19	Urgent revascularization	Urgent revascularization	In hospital	Wild-type N = 277	0 (0%)	NR	NR	NS	NR	NR	None
						Heterozygotes 2C19*2 N = 123	0 (0%)						
						Homozygotes 2C19*2 N = 11	0 (0%)						
Sawada, 2010{Sawada, 2010 36 /id} 21099121 Japan NR	loading dose of clopidogrel (300 mg) and maintenance dose of clopidogrel (75 mg/day) and aspirin (100 mg/day)	CYP2C19	Target vessel revascularization	Target vessel revascularization	Mean 243.8 days	Non-carrier N = 58	9 (15.5)	NR	NR	0.11, Non-carrier vs *2 carrier	NO	NO	NO
			Target vessel revascularization	Target vessel revascularization	Mean 243.8 days	*2 carrier N = 42	13 (31%)	NR	NR				
			Target lesion revascularization	Target lesion revascularization	Mean 243.8 days	Non-carrier N = 58	6 (10.3)	NR	NR	0.06, Non-carrier vs *2 carrier	NO	NO	NO
			Target lesion revascularization	Target lesion revascularization	Mean 243.8 days	*2 carrier N = 41	11 (26.1)	NR	NR				

Appendix Table D12: Platelet Reactivity (categorical)

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Giusti, 2007{Giusti, 2007 190 /id} 18004210 Italy NR	LD:Clopidogrel 600 mg (orally) + 500 mg ASA (IV); MD: clopidogrel 75 mg and ASA 100 mg (both daily)	CYP2C19 *2	Aggregation with ADP 10 µmol/L	% maximal aggregation (discrete); cut-off based on previous literature	24 h after PCI (6 d for patients receiving IIb/IIIa inhibitors)	*2/*2 N = 40	High RPR	14 (35.0%)	≥70%	NR	NR	P=0.002 (across 3 groups) [chi-square test]	NO	NO	Additional data in combination with AA as the agonist were not extracted (not agonist of interest to the report)
						*2/*1 N = 406 [unclear why the sample size changed]		85 (20.9%)							
						*1/*1 N = 973 [unclear why the sample size changed]		156 (16.0%)							
Jinnai, 2009{Jinnai, 2009 120 /id} 19531897 Japan Partly industry funded	low-dose aspirin (81-100 mg/day) at enrollment; Clopidogrel LD= 300 mg on the first day + 75 mg/day MD.	CYP2C19 *2, *3 and *1	IPA	Change in platelet reactivity compared to baseline	48h	PM = *2/*2 or *2/*3 N = 6	Responders	1	IPA ≥ 30%	NR	NR	NR	NR	NO	None
						IM = *2/*1 or *3/*1 N = 8	Responders	1	IPA ≥ 30%						
						EM = *1/*1 N = 11	Responders	7	IPA ≥ 30%						
						PM = *2/*2 or *2/*3 N = 6	Hypo-responders	3	10% ≤ IPA <30%						
						IM = *2/*1 or *3/*1 N = 8	Hypo - responders	6	10% ≤ IPA <30%						
						EM = *1/*1 N = 11	Hypo - responders	3	10% ≤ IPA <30%						
						PM = *2/*2 or *2/*3 N = 6	Non-responders	2	IPA < 10%						

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						IM = *2/*1 or *3/*1 N = 8	Non-responders	1	IPA < 10%						
						EM = *1/*1 N = 11	Non-responders	1	IPA < 10%						

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Frere, 2008{Frere, 2008 176 /id} 18394438 France NONE	600 mg loading dose of clopidogrel + 250 mg aspirin	CYP2C19 *2 genotyping	ADP-induced reactivity by LTA	Measurement of ADP-stimulated aggregation	At the catheterization laboratory (≥12h after the loading dose)	*2/*2	HPR +	10	>70% of baseline	NR	NR	0.03 [using a recessive model for the prevalence of HPR+ among *2/*2 patients] 0.03 [comparing the prevalence of HPR+ among *2/*1 patients; unclear genetic model]	NR	NO	Unclear reporting of statistical analyses but 2x3 data are adequate to reconstruct the analysis
						*2/*2	HPR -	13	<70% of baseline	NR	NR				
						*2/*1	HPR +	28	>70% of baseline	NR	NR				
						*2/*1	HPR -	115	<70% of baseline	NR	NR				
						*1/*1	HPR +	110	>70% of baseline	NR	NR				
						*1/*1	HPR -	325	<70% of baseline	NR	NR				
Frere, 2009{Frere, 2009 117 /id} 19496924 France Part of larger observational study	600 mg clopidogrel loading dose	CYP2C19 *17	VASP phosphorylation assay	Proportion of patients with PRI VASP >50%	After clopidogrel loading dose (exact timing NR)	*17/*17 and *17/*1 (carriers vs. non-carriers) N = 214	HPR+ = 50% HPR- = 50%	HPR+ = 107 HPR- = 107	>50% vs. ≤50%	NR	NR	P=0.007 (carriers vs. non-carriers) [analysis method NR]	NO	NO	None
						*1/*1 N = 382	HPR+ = 63% HPR- = 37%	HPR+ = 241 HPR- = 141							
Bonello-Palot{Bonello-Palot, 2009 107 /id} 2009 19932784 France NR	600 mg clopidogrel LD	CYP2C19 *2	high on treatment platelet reactivity (HTPR)	Patients with a VASP index >50%	>6 to <12 hours after 600 mg clopidogrel LD	≥ 1 CYP2C19*2 allele (*2/*2 or Wild-type/*2)	HTPR+	17/43 (39.5%)	VASP index >50%	Calculated DOR: 3.27	1.04, 10.2	P=0.04 (≥ 1 CYP2C19*2 allele vs wild-type)	NO	NR	None
						Wild-type genotype (Wild-type/wild-type)	HTPR+	26/43 (60.5%)	VASP index >50%						

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			Good responders	Patients with a VASP index <50%	>6 to <12 hours after 600 mg clopidogrel LD	≥ 1 CYP2C19*2 allele (*2/*2 or Wild-type/*2)	HTPR-	5/30 (16.7%)	VASP index <50%						
						Wild-type genotype (Wild-type/wild-type)	HTPR-	25/30 (83.3%)	VASP index <50%						
	600 mg loading dose (LD) of clopidogrel in good responders & 4 subsequent doses LD of of 600-mg clopidogrel	CYP2C19 *2	Failed Dose adjustment	VASP reactivity <50% after 4 LD of 600 mg clopidogrel	>6 to <12 hours after 4th 600 mg clopidogrel LD	≥ 1 CYP2C19*2 allele (*2/*2 or Wild-type/*2)	Failed dose+	3/10 (30%)	VASP index >50%	Calculated DOR: 0.99	0.23, 4.25	P=0.01 (≥ 1 CYP2C19*2 allele vs wild-type)	NO	NR	The data reported in the table and text is discrepant with the calculate values; for example the percentages reported in the text varies
						Wild-type genotype (Wild-type/wild-type)	Failed dose+	7/10 (70%)	VASP index >50%						
			Successful Dose adjustment			≥ 1 CYP2C19*2 allele (*2/*2 or Wild-type/*2)	Failed dose-	19/63 (30.1%)	VASP index <50%						
						Wild-type genotype (Wild-type/wild-type)	Failed dose-	44/63 (69.9%)	VASP index <50%						
Harmsze 2010{Harmsze, 2010 102 /id} 19934793 Netherlands NR	clopidogrel maintenance: 75 mg/day	CYP2C19*2	Poor responder	>70% aggregation using 20 mmol/l ADP (LTA)	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	Poor responder +	20% (N calculated as 59)	>70% aggregation	OR: 3.7	2.0,6.9	P<0.001 (Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1))	NO	YES; false discovery rate test (q value threshold 0.20)	
										OR: 3.8	2.0,7.2	P<0.001 (Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1))	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca^{+} channel blockers, PPI, SSRIs, and NSAIDs.	YES; false discovery rate test (q value threshold 0.20)	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel maintenance: 75 mg/day	CYP2C19*2	Poor responder	PRU value greater than 235 (VerifyNow P2Y12 assay).	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	Poor responder +	NR	>235 PRU	OR: 2.8	1.6,5.0	P<0.001 (Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1))	NO	YES; false discovery rate test (q value threshold 0.20)	
										OR: 3.4	1.8,6.4	P<0.001 (Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1))	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca^+ channel blockers, PPI, SSRIs, and NSAIDs.	YES; false discovery rate test (q value threshold 0.20)	
	300 mg clopidogrel loading dose	CYP2C19*2	Poor responder	>70% aggregation using 20 mmol/l ADP (LTA)	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	Poor responder +	40% according to LTA (N calculated as 52)	>70% aggregation	OR: 3.7	2.0,6.9	P<0.001 (Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1))	NO	YES; false discovery rate test (q value threshold 0.20)	Responder status as per PRU was not reported (unlike for the chronic clopidogrel group)
										OR: 4.1	1.6,10.4	P=0.003 (Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1))	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca^+ channel blockers, PPI, SSRIs, and NSAIDs.	YES; false discovery rate test (q value threshold 0.20)	
Trenk 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-	600 mg clopidogrel loading dose + 75 mg/day clopidogrel (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	CYP2C19*2	High on-clopidogrel platelet reactivity	proportion of patients achieving an residual platelet aggregation >14% after	At PCI	Carriers (*1/*2 or *2/*2)	High on-clopidogrel platelet reactivity	153/245 (62.4%)	14%	OR=2.18	1.6,2.97	P<0.001 (between carriers and noncarriers)	NO	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)				stimulation with 5 µmol/l ADP											
						Noncarriers (*1/*1)	High on-clopidogrel platelet reactivity	239/552(43.3%)	14%						
					Pre-discharge	Carriers (*1/*2 or *2/*2)	High on-clopidogrel platelet reactivity	97/235 (41.3%)	14%	OR=2.43	1.74,3.38	P<0.001 (between carriers and noncarriers)	NO	NR	
						Noncarriers (*1/*1)	High on-clopidogrel platelet reactivity	118/525(22.5%)	14%						
					At PCI	Carriers (*1/*2 or *2/*2)	High on-clopidogrel platelet reactivity	153/245 (62.4%)	14%	NR	NR	NR	YES; clinical characteristics (active smoker, BMI, hypertension, previous PCI), drug therapy (angiotensin-1 blockers, diuretics, oral antidiabetics), or Angiographic parameters (American Heart Association/ American College of Cardiology coronary lesion type B2 or C, stenting in circumflex artery, vessel size, balloon size, minimal lumen diameter after PCI, stented	NR	OR was not reported; it can be estimate from digitizing Fig 1 & P value can be back calculated

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
													length)		

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Noncarriers (*1/*1)	High on-clopidogrel platelet reactivity	239/552(43.3%)	14%	NR	NR	NR			
					Pre-discharge	Carriers (*1/*2 or *2/*2)	High on-clopidogrel platelet reactivity	97/235 (41.3%)	14%	NR	NR	NR	YES; clinical characteristics (active smoker, BMI, hypertension, previous PCI), drug therapy (angiotensin-1 blockers, diuretics, oral antidiabetics), or Angiographic parameters (American Heart Association/ American College of Cardiology coronary lesion type B2 or C, stenting in circumflex artery, vessel size, balloon size, minimal lumen diameter after PCI, stented length)	NR	OR was not reported; it can be estimate from digitizing Fig 1 & P value can be back calculated
						Noncarriers (*1/*1)	High on-clopidogrel platelet reactivity	118/525(22.5%)	14%	NR	NR	NR			
Hochholzer, 2010{Hochholzer, 2010 76 /id} 20510210 Germany EXCELSIOR	clopidogrel	CYP2C19* polymorphism	Low response to clopidogrel	Residual platelet aggregation>14%	2-4 hours after maintenance dose	CYP2C19* polymorphism	Low response to clopidogrel	760	Residual platelet aggregation>14%	OR=2.738	1.925 - 3.895	<0.001	Yes, age, arterial hypertension, diabetes mellitus,body mass index, platelets, ACE inhibition, nitrates, verapamil/diltiazem,	NR	Figure 1 box and whisker plot

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
													previous balloon angioplasty, previous balloon angioplasty, previous CABG, impaired LV function, CCS angina class III or IV		

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel	CYP2C19* polymorphism	Low response to clopidogrel	Residual platelet aggregation after stimulation with 5 uM ADP	2-4 hours after maintenance dose	CYP2C19* polymorphism	Residual platelet aggregation	760	Residual platelet aggregation	Partial n2=0.052	NR	<0.001	Yes, age, arterial hypertension, diabetes mellitus,body mass index, platelets, ACE inhibition, nitrates, verapamil/diltiazem, previous balloon angioplasty, previous balloon angioplasty, previous CABG, impaired LV function, CCS angina class III or IV	NR	
Jeong 2010{Jeong, 2010 70 /id} 20650435 Korea NR	Clopidogrel	CYP2C19	HPPR	See below	2-4 hours	*1/*1	HPPR+ 4(8.7)	46	5uM ADP induced maximal platelet reactivity >50%	%	NR	0.012 comparing the following row	NR	Yes	Figure 3-6 bar graph of LTA and genotype
						Rms	23(28.8)	80							
	clopidogrel	CYP2C19	HPPR	See below	2-4 hours	CYP2C19 variant	HPPR+	126	5uM ADP induced maximal platelet reactivity >50%	OR=4.237	1.362 - 13.158	0.013	NO	NO	
	clopidogrel	CYP2C19	HPPR	See below	2-4 hours	CYP2C19 variant	HPPR+	126	5uM ADP induced maximal platelet reactivity >50%	OR=5.525	1.333 - 23.256	0.018	Yes, CYP3A5*3/*3 carriers, carriage of ABCB1 variant, female sex, age(per 10 yr increment), BMI, ACS, current cmoking, hypertension, diabetes mellitus,	NO	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
													chronic kidney disease, LV ejection fraction<45 %, CYP3A4-metabolized statin, beta-blocker, calcium-channel blocker, nitrate,		

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	Clopidogrel	CYP2C19	HTPR	High on treatment platelet reactivity	12h	*2 heterozygotes	HTRP+	97/123 (77%)	VASP index ≥50%	Proportion	NR	<0.001 compared with row 2 and 3	NR	NR	
	Clopidogrel	CYP2C19	HTPR	High on treatment platelet reactivity	12h	*2 homozygotes	HTPR+	6/11(54 %)	VASP index ≥50%	Proportion	NR		NR	NR	
	Clopidogrel	CYP2C19	HTPR	High on treatment platelet reactivity	12h	Wild-type genotype	HTPR+	154/277 (55.6)	VASP index ≥50%	proportion	NR		NR	NR	
	Clopidogrel	CYP2C19	HTPR	High on treatment platelet reactivity	12h	2C19*2 allele carriage	HTPR+	NR	VASP index ≥50%	OR=2.69	1.66-4.36	<0.0001	Yes, age, BMI	NR	
	Clopidogrel	CYP2C19	HTPR	High on treatment platelet reactivity	12h	No loss-of function allele	HTPR+	154/277 (55.6%)	VASP index ≥50%	NR	NR	NR	NR	NR	
	Clopidogrel	CYP2C19	HTPR	High on treatment platelet reactivity	3 additional 600-mg LDs	No loss-of function allele	HTPR+	137/154 (89%)	VASP index ≥50%	NR	NR	NR	NR	NR	
Gurbel 2011{Gurbel, 2011 24 /id} 21392617 USA NR	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 5um ADP	*2	HRP +	46%	5 µM ADP 46%	Freqency	NR	0.015 carriers vs noncarries	NR	NR	
						*2 non carrier	HRP -	25%			NR		NR	NR	
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 20um ADP	*2	HRP+	41%	20 µM ADP 59%	Freqency	NR	0.013 carriers vs noncarries	NR	NR	
						*2 non carrier	HRP-	18%			NR		NR	NR	
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 5um ADP	*17	HRP +	27%	5 µM ADP 46%	Freqency	NR	0.32 carriers vs noncarries	NR	NR	
						*17 non carrier	HRP -	36%			NR		NR	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 20um ADP	*17	HRP+	14%	20 µM ADP 59%	Freqency	NR	0.016 carriers vs noncarries	NR	NR	
						*17 non carrier	HRP-	35%			NR		NR	NR	
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 5um ADP	*2 N=41	HRP +	15/27	5 µM ADP 46%	Count	NR	NR	NR	NR	
							HRP-	26/91							
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 5um ADP	*2 noncarrier N=77	HRP +	12/27	5 µM ADP 46%	Count	NR	NR	NR	NR	
							HRP-	65/91							
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 5um ADP	*17 N=45	HRP +	8/27	5 µM ADP 46%	Count	NR	NR	NR	NR	
							HRP-	37/91							
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 5um ADP	*17 N=73	HRP +	19/27	5 µM ADP 46%	Count	NR	NR	NR	NR	
								54/91							
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 20um ADP	*2 N=41	HRP +	20/40	20 µM ADP 59%	Count	NR	NR	NR	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
							HRP-	21/78							
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 20um ADP	*2 noncarrier N=77	HRP +	20/40	20 µM ADP 59%	Count	NR	NR	NR	NR	
							HRP-	57/78							
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 20um ADP	*17 N=45	HRP +	9/40	20 µM ADP 59%	Count	NR	NR	NR	NR	
							HRP-	36/78							
	Clopidogrel	CYP2C19	High platelet reactivity (HPR)	defined by specific cutoff values by ROC	HPR 20um ADP	*17 N=73	HRP +	31/40	20 µM ADP 59%	Count	NR	NR	NR	NR	
							HRP-	42/78							
Hwang 2011{Hwang, 2011 35 /id} 21075428 South Korea NR	Clopidogrel	CYP2C19*2	HRP	5 umol/L ADP-MPA>50%	12h	Codominant	HPR+ 34	GG 93	5 umol/L ADP-MPA>50 %	Count	NR	0.003 comparing the following 2 groups	NR	Yes	
							HPR- 59								
	Clopidogrel	CYP2C19*2	HRP	5 umol/L ADP-MPA>50%	12h	Codominant	HPR+ 44	GA 79	5 umol/L ADP-MPA>50 %	Count	NR		NR	Yes	
							HPR- 35								
	Clopidogrel	CYP2C19*2	HRP	5 umol/L ADP-MPA>50%	12h	Codominant	HPR+ 13	AA 18	5 umol/L ADP-MPA>50 %	Count	NR		NR	Yes	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
							HPR 5								
	Clopidogrel	CYP2C19*2	HRP	5 umol/L ADP-MPA>50%	12h	dominant	HPR+ 34	GG 93	5 umol/L ADP-MPA>50%	Count	NR	0.001 comparing the following group	NR	Yes	
							HPR 59								
	Clopidogrel	CYP2C19*2	HRP	5 umol/L ADP-MPA>50%	12h	dominant	HPR+ 57	GA/AA 97	5 umol/L ADP-MPA>50%	Count	NR		NR	Yes	
							HPR- 40								
	Clopidogrel	CYP2C19*2	HRP	5 umol/L ADP-MPA>50%	12h	recessive	HPR+ 78	GG/GA 172	5 umol/L ADP-MPA>50%	Count	NR	0.107 comparing the following group	NR	Yes	
							HPR- 94								
	Clopidogrel	CYP2C19*2	HRP	5 umol/L ADP-MPA>50%	12h	recessive	HRP+ 13	AA 18	5 umol/L ADP-MPA>50%	Count	NR		NR	Yes	
							HPR- 5								
	Clopidogrel	CYP2C19*3	HRP	5 umol/L ADP-MPA>50%	12h	Codominant	HRP+ 76	GG 165	5 umol/L ADP-MPA>50%	Count	NR	0.008 comparing the following 2 groups	NR	Yes	
							HRP- 88								
	Clopidogrel	CYP2C19*3	HRP	5 umol/L ADP-MPA>50%	12h	Codominant	HRP+ 15	GA 25	5 umol/L ADP-MPA>50%	Count	NR		NR	Yes	
							HRP- 11								
	Clopidogrel	CYP2C19*3	HRP	5 umol/L ADP-MPA>50%	12h	Codominant	HRP+ -	AA 0	5 umol/L ADP-MPA>50%	Count	NR		NR	Yes	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
							HRP- -								
	Clopidogrel	CYP2C19*3	HRP	5 umol/L ADP-MPA>50%	12h	dominant	HRP+ 76	GG 165	5 umol/L ADP-MPA>50%	Count	NR	0.008 comparing the following group	NR	Yes	
							HRP- 88								
	Clopidogrel	CYP2C19*3	HRP	5 umol/L ADP-MPA>50%	12h	dominant	HRP+ 15	GA/AA 25	5 umol/L ADP-MPA>50%	Count	NR		NR	Yes	
							HRP- 11								
	Clopidogrel	CYP2C19*3	HRP	5 umol/L ADP-MPA>50%	12h	recessive	HRP+ 91	GG/GA 190	5 umol/L ADP-MPA>50%	Count	NR		NR	Yes	
							HRP- 99								
	Clopidogrel	CYP2C19*3	HRP	5 umol/L ADP-MPA>50%	12h	recessive	HRP+ -	AA 0	5 umol/L ADP-MPA>50%	Count	NR		NR	Yes	
							HRP- -								
Kang, 2010{Kang, 2010 40 /id} 20724801 Korea NR	clopidogrel	CYP2C19	HPPR	high post-treatment platelet reactivity	NR	Carrier of CYP2C19 varian	HPPR	112/215	5 umol/L ADP-induced PRmax>50%	OR 4.202	1.996 - 8.850	<0.001	Yes, sex, age, BMI, previous MI, previous stroke, current smoking, hypertension, diabetes mellitus, chronic kidney disease, LV ejection fraction<45 %, CYP3A4-metabolized statin, beta blocker, angiotension blocker, calcium	No	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
													channel blocker, proton pump inhibitor		

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Park 2011{Park, 2011 21 /id} 21345843 Korea CILON-T	DAT	CYP2C19	on-treatment platelet reactivity (High OPR)	on-treatment platelet reactivity (High OPR)	NR	Non-carrier	on-treatment platelet reactivity (High OPR)	104	NR	Odds ratio 1	-	-	Yes. Age, gender, cigarette smoking, chronic kidney disease, antiplatelet treatment regimen according to CYP2C19 genotype	Yes	Figure E multiple comparison
	DAT	CYP2C19	(High OPR	(High OPR	NR	Carrier	(High OPR	132	NR	Odds ratio 2.93	1.64-5.21	<0.001	NR	NR	
	TAT	CYP2C19	(High OPR	(High OPR	NR	Non-carrier	(High OPR	87	NR	Odds ratio 0.75	0.39-1.44	0.388	NR	NR	
	TAT	CYP2C19	(High OPR	(High OPR	NR	Carrier	(High OPR	151	NR	Odds ratio 1.19	0.68-2.05	0.545	NR	NR	
	Dual Clopidogrel	CYP2C19	OPR	on-treatment platelet reactivity	NR	Non-carrier vs Carrier of	on-treatment platelet reactivity	CYP2C19 LOF allele 236	NR	N=104 for non carrier N=132 for carrier		Non-carrier vs Carrier of <0.001	NR	NR	
	Triple Clopidogrel	CYP2C19	OPR	on-treatment platelet reactivity	NR	Non-carrier vs Carrier of	on-treatment platelet reactivity	CYP2C19 LOF allele 238	NR	N=87 for non carrier N=151 for carrier		Non-carrier vs Carrier of 0.139	NR	NR	
	Dual Clopidogrel	CYP2C19	High OPR proportion	OPR >240 PRU	NR	Non-carrier vs Carrier of	OPR >240 PRU	CYP2C19 LOF allele 236	OPR >240 PRU	37% for non carrier 61% for carrier		Non-carrier vs Carrier <0.001	NR	NR	
	Triple Clopidogrel	CYP2C19	High OPR proportion	OPR >240 PRU	NR	Non-carrier vs Carrier of	OPR >240 PRU	CYP2C19 LOF allele 238	OPR >240 PRU	33% for non carrier 44% for carrier		Non-carrier vs Carrier 0.115	NR	NR	
	Dual and triple Clopidogrel	CYP2C19	OPR	on-treatment platelet reactivity	NR	Dual versus triple	on-treatment platelet reactivity	CYP2C19 LOF allele non carrier 191	NR	N=104 for dual N=87 for triple		Dual versus triple 0.242	NR	NR	
	Dual and triple Clopidogrel	CYP2C19	OPR	on-treatment platelet reactivity	NR	Dual versus triple	on-treatment platelet reactivity	CYP2C19 LOF allele carrier 283	NR	N=132 for dual N=151 for triple		Dual versus triple <0.001	NR	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Dual and triple Clopidogrel	CYP2C19	High OPR proportion	OPR >240 PRU	NR	Dual versus triple	OPR >240 PRU	CYP2C19 LOF allele non carrier	OPR >240 PRU	37% for dual 33% for triple		Dual versus triple 0.241	NR	NR	
	Dual and triple Clopidogrel	CYP2C19	High OPR proportion	OPR >240 PRU	NR	Dual versus triple	OPR >240 PRU	CYP2C19 LOF allele carrier	OPR >240 PRU	61% for dual 44% for triple		Dual versus triple <0.001	NR	NR	
Sibbing, 2010{Sibbing, 2010 48 /id} 20492469 Germany NR	Clopidogrel	CYP2C19	Platelet aggregation	Platelet aggregation	NR	CYP2C19*17	Platelet aggregation	396	>188Au*min	1.3	1.1-1.6	*17 vs no *17	no	no	
	Clopidogrel	CYP2C19	Platelet aggregation	Platelet aggregation	NR	CYP2C19*17/*17	Platelet aggregation		>188Au*min	1.7	1.1-2.7	*17/*17 vs no *17	no	no	
	Clopidogrel	CYP2C19	Platelet aggregation	Platelet aggregation	NR	CYP2C19*17	Platelet aggregation	396	>188Au*min	1.4	1.1-1.7	*17 vs no *17	Yes, age, gender, smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia, omeprazole/pantoprazole or ca2+ channel inhibition or phenprocoumon, renal insufficiency, BMI,, fibrinogen levels.	no	
	Clopidogrel	CYP2C19	Platelet aggregation	Platelet aggregation	NR	CYP2C19*17/*17	Platelet aggregation	396	>188Au*min	1.9	1.2-3.0	*17/*17 vs no *17	Yes, age, gender, smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia, omeprazole/pantoprazole or ca2+ channel inhibition or phenprocoumon, renal insufficiency,	no	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
													BMI,fibrinogen levels.		
Bouman 2011{Bouman, 2011 9 /id} 21628721 Netherlands Genetic substudy of the Popular study	Clopidogrel	CYP2C19 genetic test (real-time PCR)	High on-treatment platelet reactivity	5 mmol/l ADP-induced LTA cutoff from ROC	Within 2 hr after blood sampling	*1/*1	HPR+	38% of 737 patients	>42.9% aggregation	NR	NR	<0.001 vs. each of next two rows [chi-square test]	YES (age, sex, BMI, current smoking, systolic BP >140 mm Hg or diastolic BP >90 mm Hg, diabetes mellitus, LVEF <45%, renal failure (creatinine level >1.36 mg/dl), platelet count, mean platelet volume, clopidogrel regimen, PPI use, and amlodipine use)	NR	NONE
						*1/*2		53% of 260 patients	>42.9% aggregation	NR	NR	0.006 vs. next row			
						*2/*2		70% of 27 patients	>42.9% aggregation	NR	NR				
				20 mmol/l ADP-induced LTA cutoff from ROC		*1/*1	HPR+	31% of 737 patients	>64.5% aggregation	NR	NR	<0.001 vs. each of next two rows			
						*1/*2		52% of 260 patients	>64.5% aggregation	NR	NR	0.013 vs. next row			
						*2/*2		78% of 27 patients	>64.5% aggregation	NR	NR				
				PlateletWorks assay cutoff from ROC		*1/*1	HPR+	33% of 737 patients	> 80.5% aggregation	NR	NR	<0.001 vs. next row			
						*1/*2		51% of 260 patients	> 80.5% aggregation	NR	NR	0.045 vs. next row			

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2/*2		91% of 27 patients	> 80.5% aggregation	NR	NR	0.001 vs. first row			
				VerifyNow cutoff from ROC		*1/*1	HPR+	34% of 737 patients	>236 PRU (P2Y12 reaction units)	NR	NR	<0.001 vs. each of next two rows			
						*1/*2		49% of 260 patients	>236 PRU (P2Y12 reaction units)	NR	NR	0.08 vs. next row			
						*2/*2		67% of 27 patients	>236 PRU (P2Y12 reaction units)	NR	NR				
			Risk of HPR	5 mcmol/l ADP-induced LTA		*1/*2 vs.*1/*1			>42.9% aggregation	Adjusted OR 1.80	1.28-2.54	0.001 [multivariate binary logistic regression]			
				20 mcmol/l ADP-induced LTA					>64.5% aggregation	Adjusted OR 2.53	1.78-3.60	<0.001 [multivariate binary logistic regression]			
				Platelet works assay					> 80.5% aggregation	Adjusted OR 1.96	1.24-3.09	0.004 [multivariate binary logistic regression]			
				VerifyNow P2Y12					>236 PRU (P2Y12 reaction units)	Adjusted OR 2.14	1.50-3.07	<0.001 [multivariate binary logistic regression]			
				5 mcmol/l ADP-induced LTA		*2/*2 vs.*1/*1			>42.9% aggregation	Adjusted OR 2.33	0.88-6.19	0.091 [multivariate binary logistic regression]			
				20 mcmol/l ADP-induced LTA					>64.5% aggregation	Adjusted OR 4.54	1.61-12.80	0.004 [multivariate binary logistic regression]			
				Platelet works assay					> 80.5% aggregation	Adjusted OR 12.92	1.52-109.98	0.019 [multivariate binary logistic regression]			
				VerifyNow P2Y12					>236 PRU	Adjusted OR 2.63	0.97-7.14	0.059 [multivariate binary logistic regression]			
Campo 2011{Campo, 2011 13 /id}	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
21679849 Italy NR															
Fernando 2011{Fernando, 2011 233 /id} 21696537 Australia NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Geisler 2008{Geisler, 2008 161 /id} 18781853 Germany NR	Clopidogrel	MassARRAY for *2	Residual platelet aggregation (RPA)	From turbidometry	Post-clopidogrel loading dose	*1/*1	Low RPA	144/175 patients with low RPA (82.3%)	RPA = or <47% at at least 6 hr after loading dose of clopidogrel	OR vs. *1/*2 + *2/*2, 4.6	2.5-8.7	<0.0001	NR	NR	ORs and chi-square values are fro having high RPA vs. low RPA among the three genotype subgroups
							High RPA	31//62 patients with high RPA (50%)	RPA >47% at at least 6 hr after loading dose of clopidogrel						
						*1/*2	Low RPA	28/175 (16%)		Chi-square statistic vs. *1/*2 vs. *2/*2, 27.17	NR	<0.001			
							High RPA	24/62 (38.7%)							
						*2/*2	Low RPA	3/175 (1.7%)							
							High RPA	7/62 (11.3%)							
		MassARRAY for *17				*1/*1	Low RPA	96/175 (54.9%)		OR vs. *1/*17 + *17/*17, 0.62	0.34-1.14	0.14			
							High RPA	41/62 (66.1%)							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*1/*17	Low RPA	65/175 (37.1%)		Chi-square statistic vs. *1/*17 vs. *17/*17, 4.48	NR	0.11			
							High RPA	14/62 (22.6%)							
						*17/*17	Low RPA	14/175 (8.0%)							
							High RPA	7/62 (11.3%)							
			Risk of high RPA development			*2 carriers	High RPA			Chi-square statistic 21.31 OR, 4.38	2.3-8.33	<0.0001 [Multivariable logistic regression including age, diabetes status, LVEF, renal failure, ACS)			NS for all other SNPs
						One *2 allele				OR 3.71	1.87-7.35				
						Two *2 alleles				OR 10.72	2.56-44.88				
Gurbel 2010{Gurbel, 2010 91 /id} 19817997 USA NR	75 mg clopidogrel daily	TaqMan	HPR	Upper tertile of 5 mcM ADP-induced platelet aggregation	NR	CYP2C19*2 carrier	HPR+	13/17	<43%	NR	NR	NR	NR	NO	
						CYP2C19*2 noncarrier		4/19							
Kim 2011{Kim, 2011 18 /id} 21511217 South Korea CCELAMI2C19	High-dose clopidogrel	PCR and SNaPshot assay kit	HPR	20 mcmol ADP-induced maximal platelet aggregation >59%	Predischarge	*2 or *3 noncarrier	Yes HPR	11/24 (45.8%)	20 mcmol ADP-induced maximal platelet aggregation >59%	NR	NR	0.666 vs. corresponiding cilostazol row below [chi-square statistics or Fisher exact test]	NR	NR	NONE

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2 or *3 carrier		20/38 (52.6%)				0.430 vs. corresponiding cilostazol row below [chi-square statistics or Fisher exact test]			
					At 30 days	*2 or *3 noncarrier		2/24 (8.3%)				0.235 vs. corresponiding cilostazol row below [chi-square statistics or Fisher exact test] Also P=0.002 vs next row [NR]			
						*2 or *3 carrier		17/38 (44.7%)				0.005 vs. corresponiding cilostazol row below [chi-square statistics or Fisher exact test]			
				Absolute change between baseline and 30 days		*2 or *3 noncarrier		24	NR	Mean 37.5% (SD NR)	NR				Data also in Fig. 4
						*2 or *3 carrier		38	NR	Mean 7.9% (SD NR)	NR				
	Standar-dose clopidogrel + cilostazol				Pre-discharge	*2 or *3 noncarrier		21/25 (52%)							
						*2 or *3 carrier		24/39 (61.5%)							
					At 30 days	*2 or *3 noncarrier		0/25 (0%)				P=0.174 vs. next row [NR]			
						*2 or *3 carrier		6/39 (15.4%)							
				Absolute change between baseline and 30 days		*2 or *3 noncarrier		25	NR	Mean 54.2% (SD NR)					Data also in Fig. 4
						*2 or *3 carrier		39	NR	Mean 46.1% (SD NR)					

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Pettersen 2011{Pettersen, 2011 228 /id} 21426546 Norway Aspirin and Clopidogrel non-responsiveness clinical Endpoint Trial (ASCET)	Clopidogrel	TaqMan Drug Metabolism Assay	Clopidogrel resistance	per VASPPRI	NR	*2 carrier	Resistant	46%	≥ 55% PRI	NR	NR	< 0.001 vs. row below (either Student 's unpaired t-test or Mann-Whitney U-test)	NR	NR	NONE
						*2 noncarrier	Resistant	22%							
				Per VerifyNow PRU		*2 carrier	Resistant	64 (54%)	≥ 170 PRU			0.003 vs. row below (either Student 's unpaired t-test or Mann-Whitney U-test)			
						*2 noncarrier	Resistant	104 (22%)							

Appendix Table D13: Platelet Reactivity (continuous)

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Fontana, 2008{Fontana, 2008 182 /id} 17681590 Switzerland NR	600 mg clopidogrel loading dose; 75 mg maintenance dose; all patient except one were on aspirin at baseline; data NR for aspirin maintenance	CYP2C19 *2	PRI VASP continuous outcome	Measurement of PRI	After a minimum 15 d of clopidogrel treatment	*2/*2	2	Mean = 66.1	SD = 5.6	Non-parametric tests for comparison of medians	NR	NR	0.65 (across all 3 groups) [Kruskall-Wallis test]	NO	NO	NO
						*2/*1	25	Mean = 50.6	SD = 17.1							
						*1/*1	54	Mean = 50.9	SD = 13.7							
Giusti, 2007{Giusti, 2007 190 /id} 18004210 Italy NR	Loading dose: clopidogrel 600 mg (orally) + 500 mg ASA (IV); maintenance dose: clopidogrel 75 mg and ASA 100 mg (both daily)	CYP2C19 *2	Aggregation with ADP 2 µmol/L	% maximal aggregation (continuous)	24 h after PCI (6 d for patients receiving IIb/IIIa inhibitors)	*2/*2	40	41 [median]	5, 84 [range]	Non-parametric comparison of medians	NR	NR	P < 0.0001 (across 3 groups) [Kruskall-Wallis] P < 0.0001 (*2/*1 vs. *1/*1) [Mann-Whitney] P < 0.0001 (*2/*2 vs. *1/*1) [Mann-Whitney] P = 0.028 (*2/*2 vs. *2/*1) [Mann-Whitney]	NO	NO	None.
						*2/*1	405	32 [median]	1, 94 [range]							
						*1/*1	974	26 [median]	1,100 [range]							
						*2/2 or *2/*1 (carriers)	445	33 [median]	1, 94 [range]	Non-parametric comparison of medians	NR	NR	P < 0.0001 (carriers vs. non-carriers) [Mann-Whitney]	NO	NO	None.

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*1/*1 (non-carriers)	974	26 [median]	1, 100 [range]							
						*2/*2	40	62 [median]	26, 100 [range]	Non-parametric comparison of medians	NR	NR	P < 0.0001 (across 3 groups) [Kruskall-Wallis] P < 0.0001 (*2/*1 vs. *1/*1) [Mann-Whitney] P < 0.0001 (*2/*2 vs. *1/*1) [Mann-Whitney] P = 0.015 (*2/*2 vs. *2/*1) [Mann-Whitney]	NO	NO	None.
						*2/*1	405	54 [median]	2, 100 [range]							
						*1/*1	974	49 [median]	1, 100 [range]							
						*2/2 or *2/*1 (carriers)	445	56 [median]	2, 100 [range]	Non-parametric comparison of medians	NR	NR	P < 0.0001 (carriers vs. non-carriers) [Mann-Whitney]	NO	NO	None.
						*1/*1 (non-carriers)	974	49 [median]	1, 100 [range]							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2/2 or *2/*1 (carriers)	445	NR	NR	Linear regression	Coefficient = 5.3 Coefficient = 4.9	SE = 1.0 SE = 1.3	P < 0.0001 (carriers vs. non-carriers) [univariable linear regression] P = 0.0001 (carriers vs. non-carriers) [linear regression]	NO YES (age, sex, HTN, diabetes mellitus, dyslipidemia, smoking habits)	NO	None.
						*1/*1 (non-carriers)	974	NR	NR							
						*2/2 or *2/*1 (carriers)	445	NR	NR	Linear regression	Coefficient = 5.8 Coefficient = 5.5	SE = 1.2 SE = 1.3	P < 0.0001 (carriers vs. non-carriers) [univariable linear regression] P = 0.0001 (carriers vs. non-carriers) [linear regression]	NO YES (age, sex, HTN, diabetes mellitus, dyslipidemia, smoking habits)	NO	None.
						*1/*1 (non-carriers)	974	NR	NR							
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	CYP2C19*2	ADP-RPR	Continuous measurement	12-18 h from clopidogrel loading	*2/*2 or *2/*1	N = 247	51% [median]	2%-100% [range]	Mann-Whitney U test	NR	NR	0.001	NO	NO	None
						*1/*1	N = 525	45% [median]	1%-100% [range]							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Gladding, 2009{Gladding, 2009 248 /id} 19926050 New Zealand NR	Clopidogrel 150 mg daily	Autogenomics 2C19+ assay	Platelet inhibition (%)	Per VerifyNow	Baseline	CYP2C19 *2 carrier	NR	Median (range) 18% (0% to 72%)	NR	NR	NR	NR	0.01 (vs. next row) [Wilcoxon]	NO	NO	NONE
						CYP2C19 *1/*1	NR	Median (range) 59% (11% to 95%)	NR							
					7 days	CYP2C19 *2 carrier	NR	NR	NR	NR	NR	NR	0.03 (vs. next row) [Wilcoxon]	NR	NR	NONE
						CYP2C19 *1/*1	NR	NR	NR							
			Change in platelet inhibition (%) from baseline		7 days	CYP2C19 *2 carrier	NR	Mean (SD) 9% (11%)	NR	NR	NR	NR	0.03 for this row's result (7 days vs. baseline) [Student's t]	NR	NR	Fig. 3 shows all raw data for this row and a P of 0.05 (?)
						CYP2C19 *2 and CYP2C9*3) carriers: poor or intermediate metabolizers	NR	Mean -10% 95% CI -20 to -0.1%	NR	NR	NR	NR	0.05 (vs. wild type) [Student's t]	NO	NO	Raw data (separate for poor and intermediate, though result here is combined?) in Fig 4
Jinnai, 2009{Jinnai, 2009 120 /id} 19531897 Japan Partly industry funded	Patients were on low-dose aspirin (81-100 mg/day) at study enrollment. They received clopidogrel 300 mg loading dose on the first day and 75 mg daily maintenance thereafter.	CYP2C19 *2, *3 and *1	IPA	Change in platelet reactivity compared to baseline	48h	PM = *2/*2 or *2/*3	N = 6	16.0 [Mean % IPA]	SD = 13.0	T-test	NR	NR	0.04 (IM vs. EM)	NO	NO	Patient level data in figure 2b; data for other time-points in Figure 3 (individual patient data)
						IM = *2/*1 or *3/*1	N = 8	18.4 [Mean % IPA]	SD = 10.0	T-test	NR	NR	0.02 (PM vs. EM)	NO	NO	
						EM = *1/*1	N = 11	31.6 [Mean % IPA]	SD = 14.3	T-test	NR	NR	0.73 (PM vs. IM)	NO	NO	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Shuldiner, 2009{Shuldiner, 2009 116 /id} 19706858 USA Sinai Hospital of Baltimore Study	Clopidogrel LD= 600 mg (n=112) or 300 mg (n=25); No LD for subjects on clopidogrel maintenance therapy (n=90). Aspirin: 81-325 mg aspirin daily for ≥1 week prior to PCI and 325 mg on the day of PCI. Post-PCI: Aspirin 325 mg/day and clopidogrel 75mg/day	CYP2C19 *2	Mean ADP-induced reactivity	Measurements of platelet reactivity before and after clopidogrel administration	Pre-clopidogrel vs. post clopidogrel	*2/*2 *2/*1 *1/*1	Pre clopidogrel N per group was *2/*2 = 4; *2/*1 = 37; *1/*1 = 102 (total=143) Post-clopidogrel N per group was *2/*2 = 3; *2/*1 = 54; *1/*1 = 131 (total=188)	Means can only be extracted from Figure 3.	NR	Additive genetic model within each treatment period (pre-clopidogrel and post-clopidogrel); no comparisons of the genetic effect across treatment periods	NR	NR	P=0.92 for the difference between the 3 genotypes (additive model) pre-clopidogrel. P=0.02 for the difference between the 3 genotypes (additive model) post-clopidogrel.	NO	NO	Measures were paired for some participants but data are not adequate to reconstruct before-after measurements. Patients receiving clopidogrel at baseline were excluded from baseline means.
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	Clopidogrel 600 mg loading dose; clopidogrel 75 mg (1/d) and aspirin 100 mg (2/d) maintenance.	CYP2C19 *17	Platelet aggregation	Continuous outcome, Multiplate analyzer	All patients received a clopidogrel loading dose with a recommended pre-treatment interval of 2h; blood was sampled directly before PCI. The median clopidogrel loading interval was 3.5h for *1/*1; 3.5 h for *17/*1; and 5.3 h for *17/*17.	*17/*17	N = 76	189 [median, in arbitrary units * minutes]	IQR = 119, 301	Comparison of medians using non-parametric tests	NR	NR	P = 0.007 (across all groups) P = 0.039 (*17/*1 vs *1/*1) P = 0.008 (*17/*17 vs. *1/*1)	NO	NO	Additional data in Figure (medians and bootstrap-based 95% CIs)
						*17/*1	N = 546	215 [median, in arbitrary units * minutes]	IQR = 140, 342							
						*1/*1	N = 902	238 [median, in arbitrary units * minutes]	IQR = 146, 388							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*17/*17 or *17/*1	N = 622	213 [median, in arbitrary units * minutes]	IQR = 136, 329	Linear regression	Coefficient values (adjusted mean difference) = -32.3	SE = 9.5	P = 0.0006 (carriers vs. non-carriers) [multivariable linear regression] P = 0.009 (non-parametric test, Wilcoxon)	YES (age, sex, BMI, serum creatinine, use of PPIs, clopidogrel loading interval)	NO	None
						*1/*1	N = 902	238 [median, in arbitrary units * minutes]	IQR = 146, 388							
Varenhorst, 2009{Varenhorst, 2009 122 /id} 19429918 Sweden Genetic sub-study	Clopidogrel 600 mg loading dose; 75 mg maintenance	CYP2C19 genotyping	VASP phosphorylation measurements at multiple timepoints (continuous)	VASP PRI assay with flow cytometry	Samples were collected at baseline, 2 h and 24 h post-loading dose; also at day 14 ±3 and day 29 ±3, both before that day's maintenance dose	Extensive metabolizers = *17/*17, *1A/*17, *1A/*1A	N = 37	Only reported in graph [VASP PRI, means from a linear model]	Only reported in graph	Linear model with covariate for EM vs. RM	Only reported in graph	Only reported in graph	P<0.05 comparing EM vs. RM in the clopidogrel arm at 24 h, 14 d and 29 d	Yes [the linear model include body weight as a covariate]	NO (some attempt was made to limit multiple testing)	Figures 2 and 3
						Reduced metabolizers = *1A/*2A, *1A/*8, *2A/*2A	N = 9	Only reported in graph [VASP PRI, means from a linear model]	Only reported in graph		Only reported in graph	Only reported in graph				Figures 2 and 3

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Frere, 2008{Frere, 2008 176 /id} 18394438 France NONE	600 mg loading dose of clopidogrel + 250 mg aspirin	CYP2C19 *2 genotyping	VASP phosphorylation assay	Measurement of VASP phosphorylation	At the catheterization laboratory (≥12h after the loading dose)	CYP2C19 *2/*2 (rs4244285)	NR for this assay (455 patients received this assay)	69.1 [mean of %PRI VASP]	SEM = 5.7	General linear model with genotype as the explanatory variable	NR	NR	0.0001 [across 3 groups] 0.0001 [across 3 groups] <0.007 [recessive general linear model] <0.0001 [codominant general linear model across groups]	Unadjusted Adjusted [age, sex] Unadjusted Unadjusted	NO	Additional data in Figure 1 (however reported statistics are adequate)
						CYP2C19 *2/*1 (rs4244285)	NR for this assay (455 patients received this assay)	59.1 [mean of %PRI VASP]	SEM = 2.1							
						CYP2C19 *1/*1 (rs4244285)	NR for this assay (455 patients received this assay)	50.9 [mean of %PRI VASP]	SEM = 1.3							
	600 mg loading dose of clopidogrel + 250 mg aspirin	CYP2C19 *2 genotyping	ADP-induced aggregation by LTA	Measurement of ADP-stimulated aggregation	At the catheterization laboratory (≥12h after the loading dose)	CYP2C19 *2/*2 (rs4244285)	23	66.1 [% change in light transmittance from baseline]	SEM = 4	General linear model with genotype as the explanatory variable	NR	NR	0.039 [across 3 groups] 0.05 [across 3 groups] <0.01 [recessive general linear model] <0.08 [codominant general linear model across groups]	Unadjusted Adjusted [age, sex] Unadjusted Unadjusted	NO	Additional data in Figure 1 (however reported statistics are adequate)

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						CYP2C19 *2/*1 (rs4244285)	143	56.1 [% change in light transmittance from baseline]	SEM = 1.6							
						CYP2C19 *1/*1 (rs4244285)	435	55.7 [% change in light transmittance from baseline]	SEM = 0.9							
	600 mg loading dose of clopidogrel + 250 mg aspirin	CYP2C19 *2 genotyping	ADP-induced P-selectin expression	Measurement of P-selecting expression	At the catheterization laboratory (≥12h after the loading dose)	CYP2C19 *2/*2 (rs4244285)	NR for this assay (455 patients received this assay)	0.43 [arbitrary units of fluorescence]	SEM = 0.04	General linear model with genotype as the explanatory variable	NR	NR	0.035 [across 3 groups] 0.030 [across 3 groups] <0.06 [recessive general linear model] <0.009 [codominant general linear model across groups]	Unadjusted Adjusted [age, sex] Unadjusted Unadjusted	NO	Additional data in Figure 1 (however reported statistics are adequate)
						CYP2C19 *2/*1 (rs4244285)	NR for this assay (455 patients received this assay)	0.39 [arbitrary units of fluorescence]	SEM = 0.01							
						CYP2C19 *1/*1 (rs4244285)	NR for this assay (455 patients received this assay)	0.35 [arbitrary units of fluorescence]	SEM = 0.01							
Frere, 2009{Frere, 2009 117 /id} 19496924 France Part of larger observational study	600 mg clopidogrel loading dose	CYP2C19 *4	Both VASP and ADP-induced aggregation	Measurement of PRI-VASP and ADP-induced aggregation	After clopidogrel loading dose (exact timing NR)	NR	*4/*4=0 *4/*1=8 *1/*1=589	NR	NR	Recessive and co-dominant models; analysis method NR	NR	NR	Non-significant	NR	NO	Only a text comment saying that these polymorphisms did not impact the reactivity measures

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
		CYP2C19 *5	Both VASP and ADP-induced aggregation	Measurement of PRI-VASP and ADP-induced aggregation	After clopidogrel loading dose (exact timing NR)	NR	*5/*5=0 *5/*1=8 *1/*1=589	NR	NR	Recessive and co-dominant models; analysis method NR	NR	NR	Non-significant	NR	NO	Only a text comment saying that these polymorphisms did not impact the reactivity measures
		CYP2C19 *6	Both VASP and ADP-induced aggregation	Measurement of PRI-VASP and ADP-induced aggregation	After clopidogrel loading dose (exact timing NR)	NR	*6/*6=0 *6/*1=8 *1/*1=589	NR	NR	Recessive and co-dominant models; analysis method NR	NR	NR	Non-significant	NR	NO	Only a text comment saying that these polymorphisms did not impact the reactivity measures
		CYP2C19 *17	VASP phosphorylation assay	Measurement of PRI-VASP	After clopidogrel loading dose (exact timing NR)	*17/*17	25	45.79 [mean of % PRI VASP]	SD=17.71	NR	NR	NR	0.0206 ["chi square"]	NO	NO	P=0.19 for the interaction with CYP2C19 *2 [analysis method NR]
						*17/*1	189	50.11 [mean of % PRI VASP]	SD=24.3						NO	
						*1/*1	382	55.9 [mean of % PRI VASP]	SD=22.80						NO	
		CYP2C19 *17	VASP phosphorylation assay	Measurement of PRI-VASP	After clopidogrel loading dose (exact timing NR)	*17/*17 and *17/*1 (carriers vs. non-carriers)	214	49.72 [mean of % PRI VASP]	SD=23.80	NR		NR	0.0073 ["chi-square"] 0.0005 ["chi square"]	NO	NO	P=0.08 for the interaction with CYP2C19 *2 [analysis method NR]
						*1/*1	382	55.9 [mean of % PRI VASP]	SD=22.80						NO	
		CYP2C19 *17	ADP-induced aggregation (assay NR)	Measurement of ADP-induced aggregation	After clopidogrel loading dose (exact timing NR)	*17/*17	25	50.8 [Mean of % aggregation]	SD=27.30	NR	NR	NR	0.2813 ["chi square"]	NO	NO	None

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*17/*1	189	55.5 [Mean of % aggregation]	SD=19.00						NO	
						*1/*1	382	57.03 [Mean of % aggregation]	SD=18.50						NO	
		CYP2C19 *17	ADP-induced aggregation (assay NR)	Measurement of ADP-induced aggregation	After clopidogrel loading dose (exact timing NR)	*17/*17 and *17/*1 (carriers vs. non-carriers)	214	54.96 [Mean of % aggregation]	SD=20.10	NR	NR	NR	0.2062 ["chi square"]	NO	NO	None
						*1/*1	382	57.03 [Mean of % aggregation]	SD=18.50						NO	
Harmsze 2010{Harmsze, 2010 102 /id} 19934793 Netherlands NR	clopidogrel maintenance 75 mg/day	CYP2C19*2	On-clopidogrel platelet reactivity	Maximal platelet aggregation achieved in any time during the run of 10 min with ADP 5 µmol/L	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	NR	NR	NR	Linear regression	6.7	3.6,9.8	P<0.001 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	NO	NR	
						Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	NR	NR	NR	Linear regression	6.9	3.7,10	P<0.001 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca^+ channel blockers, PPI, SSRIs, and NSAIDs.		
			On-clopidogrel platelet reactivity	Maximal platelet aggregation achieved in any time during the run of 10 min with ADP 20 µmol/L	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	NR	NR	NR	Linear regression	6.3	3.4,9.3	P<0.001 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	NO	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
										Linear regression	7	4,10	P<0.001 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca^{+} channel blockers, PPI, SSRIs, and NSAIDs.		
			On-clopidogrel platelet reactivity	on-clopidogrel platelet reactivity expressed as P2Y12 reaction units (PRU)	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	NR	NR	NR	Linear regression	35.1	17.2,53	P<0.001 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	NO	NR	
										Linear regression	34.8	16.8,52.8	P<0.001 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca^{+} channel blockers, PPI, SSRIs, and NSAIDs.		
Harmsze 2010{Harmsze, 2010 102 /id} 19934793 Netherlands	300 mg clopidogrel loading dose	CYP2C19*2	On-clopidogrel platelet reactivity	Maximal platelet aggregation achieved in any time during the run of 10 min with ADP 5 µmol/L	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	NR	NR	NR	Linear regression	7.8	3.9,12.6	P=0.002 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	NO	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	NR	NR	NR	Linear regression	5.7	0.6,10.8	P=0.028 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca+ channel blockers, PPI, SSRIs, and NSAIDs.		
			On-clopidogrel platelet reactivity	Maximal platelet aggregation achieved in any time during the run of 10 min with ADP 20 µmol/L	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	NR	NR	NR	Linear regression	7.4	3.3,11.6	P=0.001 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	NO	NR	
										Linear regression	7	2.6,11.5	P=0.002 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca+ channel blockers, PPI, SSRIs, and NSAIDs.		
			On-clopidogrel platelet reactivity	on-clopidogrel platelet reactivity expressed as P2Y12 reaction units (PRU)	NR (Before stenting)	Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)	NR	NR	NR	Linear regression	37.5	16.5,58.5	P=0.001 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	NO	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
										Linear regression	28.5	7.1,549.6	P=0.009 [Carriers (*1/*2 or *2/*2) vs Noncarriers (*1/*1)]	YES; adjusted for gender, age, BMI, DM, previous MI, days of clopidogrel administration before intervention, CYP3A4-metabolized statins, Ca^{+} channel blockers, PPI, SSRIs, and NSAIDs.		
Tantry 2010{Tantry, 2010 39 /id} 21079055 Multicountry - North America and Europe Genetic substudy of ONSET/OFFSET and RESPOND	Clopidogrel	TaqMan	5 mcg ADP-induced platelet aggregation (%)	NR	8 hr after loading dose	UM	28	To be filled in	To be filled in	Kruskal-Wallis (K-W) test	NR	NR	0.289 for this and next 3 rows [K-W]	NO	NO	Get data from Fig. 3A
						EM	31									Get data from Fig. 3A
						IM	20									Get data from Fig. 3A
						PM	3									Get data from Fig. 3A
					8 hr after last maintenance dose	UM	28						0.33 for this and next 3 rows [K-W]			Get data from Fig. 3B
						EM	31									Get data from Fig. 3B
						IM	20									Get data from Fig. 3B

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						PM	3									Get data from Fig. 3B
			20 mcg ADP-induced platelet aggregation (%)		8 hr after loading dose	UM	28						0.307 for this and next 3 rows [K-W]			Get data from Fig. 4A
						EM	31									Get data from Fig. 4A
						IM	20									Get data from Fig. 4A
						PM	3									Get data from Fig. 4A
					8 hr after last maintenance dose	UM	28						0.056 for this and next 3 rows [K-W]			Get data from Fig. 4B
						EM	31									Get data from Fig. 4B
						IM	20									Get data from Fig. 4B
						PM	3									Get data from Fig. 4B
			VerifyNow P2Y12 reaction units		8 hr after loading dose	UM	28						0.019 for this and next 3 rows [K-W]			Get data from Fig. 5A
						EM	31									Get data from Fig. 5A
						IM	20									Get data from Fig. 5A
						PM	3									Get data from Fig. 5A

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
					8 hr after last maintenance dose	UM	28						0.006 for this and next 3 rows [K-W]			Get data from Fig. 5B
						EM	31									Get data from Fig. 5B
						IM	20									Get data from Fig. 5B
						PM	3									Get data from Fig. 5B
			VASP platelet reactiveity index (%)		8 hr after loading dose	UM	28						0.153 for this and next 3 rows [K-W]			Get data from Fig. 6A
						EM	31									Get data from Fig. 6A
						IM	20									Get data from Fig. 6A
						PM	3									Get data from Fig. 6A
					8 hr after last maintenance dose	UM	28						0.069 for this and next 3 rows [K-W]			Get data from Fig. 6B
						EM	31									Get data from Fig. 6B
						IM	20									Get data from Fig. 6B
						PM	3									Get data from Fig. 6B
			5 mcg ADP-induced platelet aggregation (%)		8 hr after loading dose	LOF allele carrier	23						0.078 vs. next row [K-W]			Get data from Fig. 3A

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						LOF allele noncarrier	59									Get data from Fig. 3A
					8 hr after last maintenance dose	LOF allele carrier	23						0.097vs. next row [K-W]			Get data from Fig. 3B
						LOF allele noncarrier	59									Get data from Fig. 3B
			20 mcg ADP-induced platelet aggregation (%)		8 hr after loading dose	LOF allele carrier	23						0.080 vs. next row [K-W]			Get data from Fig. 4A
						LOF allele noncarrier	59									Get data from Fig. 4A
					8 hr after last maintenance dose	LOF allele carrier	23						0.049vs. next row [K-W]			Get data from Fig. 4B
						LOF allele noncarrier	59									Get data from Fig. 4B
			VerifyNow P2Y12 reaction units		8 hr after loading dose	LOF allele carrier	23						0.010 vs. next row [K-W]			Get data from Fig. 5A
						LOF allele noncarrier	59									Get data from Fig. 5A
					8 hr after last maintenance dose	LOF allele carrier	23						0.002 vs. next row [K-W]			Get data from Fig. 5B
						LOF allele noncarrier	59									Get data from Fig. 5B
			VASP platelet reactiveity index (%)		8 hr after loading dose	LOF allele carrier	23						0.036 vs. next row [K-W]			Get data from Fig. 6A
						LOF allele noncarrier	59									Get data from Fig. 6A

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
					8 hr after last maintenance dose	LOF allele carrier	23						0.010 vs. next row [K-W]			Get data from Fig. 6B
						LOF allele noncarrier	59									Get data from Fig. 6B
			5 mcg ADP-induced platelet aggregation (%)		8 hr after loading dose	GOF allele carrier	28						0.0168 for this row and correspondign LOF carrier and EM above [K-W]			Get data from Fig. 3A
					8 hr after last maintenance dose	GOF allele carrier	28						0.231 for this row and correspondign LOF carrier and EM above [K-W]			Get data from Fig. 3B
			20 mcg ADP-induced platelet aggregation (%)		8 hr after loading dose	GOF allele carrier	28						0.165 for this row and correspondign LOF carrier and EM above [K-W]			Get data from Fig. 4A
					8 hr after last maintenance dose	GOF allele carrier	28						0.080 for this row and correspondign LOF carrier and EM above [K-W]			Get data from Fig. 4B
			VerifyNow P2Y12 reaction units		8 hr after loading dose	GOF allele carrier	28						0.028 for this row and correspondign LOF carrier and EM above [K-W]			Get data from Fig. 5A
					8 hr after last maintenance dose	GOF allele carrier	28						0.007 for this row and correspondign LOF carrier and EM above [K-W]			Get data from Fig. 5B

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			VASP platelet reactiveity index (%)		8 hr after loading dose	GOF allele carrier	28						0.109 for this row and correspondign LOF carrier and EM above [K-W]			Get data from Fig. 6A
					8 hr after last maintenance dose	GOF allele carrier	28						0.034 for this row and correspondign LOF carrier and EM above [K-W]			Get data from Fig. 6B
			5 mcg ADP-induced platelet aggregation (%)		8 hr after last maintenance dose	*1/*1	31						NR			Get data from Fig. 7A
						*1/*2	13									Get data from Fig. 7A
						*1/*3	1									Get data from Fig. 7A
						*1/*17	28									Get data from Fig. 7A
						*2/*2	3									Get data from Fig. 7A
						*2/*17	6									Get data from Fig. 7A
			20 mcg ADP-induced platelet aggregation (%)		8 hr after last maintenance dose	*1/*1	31									Get data from Fig. 7B
						*1/*2	13									Get data from Fig. 7B
						*1/*3	1									Get data from Fig. 7B

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*1/*17	28									Get data from Fig. 7B
						*2/*2	3									Get data from Fig. 7B
						*2/*17	6						0.0995 for this and 5 previous rows [K-W]			Get data from Fig. 7B
			VerifyNow P2Y12 reaction units		8 hr after last maintenance dose	*1/*1	31									Get data from Fig. 7C
						*1/*2	13									Get data from Fig. 7C
						*1/*3	1									Get data from Fig. 7C
						*1/*17	28									Get data from Fig. 7C
						*2/*2	3									Get data from Fig. 7C
						*2/*17	6						≤0.006 for this and 5 previous rows [K-W]			Get data from Fig. 7C
			VASP platelet reactiveity index (%)		8 hr after last maintenance dose	*1/*1	31									Get data from Fig. 7D
						*1/*2	13									Get data from Fig. 7D
						*1/*3	1									Get data from Fig. 7D
						*1/*17	28									Get data from Fig. 7D

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2/*2	3									Get data from Fig. 7D
						*2/*17	6						0.0996 for this and 5 previous rows [K-W]			Get data from Fig. 7D
Jeong 2010{Jeong, 2010 70 /id} 20650435 Korea NR	clopidogrel	CYP2C19	Platelet reactivity (max)	LTA, 5uM ADP	2-4 hours	*1/*1	46	30.3	12.6	t-test	NR	NR	<0.001 comparing the following row	NR	NR	
						RMs	40.7	16.8								
			Platelet reactivity (late)	LTA, 5uM ADP	2-4 hours	*1/*1	46	17.5	12.6	t-test	NR	NR	0.001 comparing the following row	NR	NR	
						RMs		28.8	19.6							
			Platelet reactivity (max)	LTA, 20uM ADP	2-4 hours	*1/*1	46	40.5	15.8	t-test	NR	NR	<0.001 comparing the following row	NR	NR	
						RMs		54.2	16.2							
			Platelet reactivity (late)	LTA, 20uM ADP	2-4 hours	*1/*1	46	24.3	17.7	t-test	NR	NR	0.001 comparing the following row	NR	NR	
						RMs		42	21.7							
			VerifyNow P2Y12 assay(PRU)	ADP	2-4 hours	*1/*1	46	149.3	74.5	t-test	NR	NR	0.001 comparing the following row	NR	NR	
						RMs		197.7	78.1							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			VerifyNow P2Y12 assay(PRU), % inhibition	ADP	2-4 hours	*1/*1	46	55.7	20.4	t-test	NR	NR	0.001 comparing the following row	NR	NR	
						RMs		37.6	22.4							
Barker, 2010{Barker, 2010 52 /id} 20965456 USA NR	clopidogrel 150 mg/day for 7 days	CYP2C19	OTR	P2Y12 reaction units (PRU)	after 7 days	Lof allele		292	40	t-test	NR	NR	0.5	no	no	
						Vs Non-carriers		281	54							
	clopidogrel 150 mg/day for 7 days	CYP2C19	OTR	P2Y12 reaction units (PRU)	after 7 days	Lof allele		52	66	t-test	NR	NR	0.25	no	no	
						Vs Non-carriers		77	72		NR	NR				
			OTR	P2Y12 reaction units (PRU)	after 7 days	CYP2C19		61	75	ANOVA	NR	NR	0.5	no	no	
			OTR	P2Y12 reaction units (PRU)	after 7 days	CYP2C19		84	72		NR	NR				
			OTR	P2Y12 reaction units (PRU)	after 7 days	CYP2C19		56	71		NR	NR				
			OTR	P2Y12 reaction units (PRU)	after 7 days	CYP2C19		28	31		NR	NR				
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	All patients received oral LDs of 250 mg aspirin and 600 mg clopidogrel at least 6 h before the first VASP index measurement	CYP2C19	VASP index	Median fluorescence intensity (MFI)	12 h	Carrier of 1 mutant allele	411	61.7	18.4%	t-test	NR	NR	<0.001 compared with the second row	NR	NR	
			VASP index	Median fluorescence intensity (MFI)	12h	Wild-type allele homozygotes	411	49.2	24.2%	t-test	NR	NR		NR	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			VASP index	Median fluorescence intensity (MFI)	First dose	Carrier of at least one CYP2C19 *2 allele	103	69.7	10.1%	t-test	NR	NR	<0.0001 compare with the lower row	NR	NR	
			VASP index	Median fluorescence intensity (MFI)	Second dose	Carrier of at least one CYP2C19 *2 allele	103	50.6	17.6%	t-test	NR	NR		NR	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Hwang 2011{Hwang, 2011 35 /id} 21075428 South Korea NR	Clopidogrel	CYP2C19*2	Platelet measures	5 umol/L ADP-MPA,%	12h	Codominant	GG 93	43.6	15.2	ANOVA	NR	NR	0.003 comparing with the following 2 groups	NR	Yes	
				5 umol/L ADP-MPA,%	12h	Codominant	GA 79	50.6	15.1		NR	NR		NR	Yes	
				5 umol/L ADP-MPA,%	12h	Codominant	AA 18	53.0	14.7		NR	NR		NR	Yes	
				5 umol/L ADP-MPA,%	12h	dominant	GG 93	43.6	15.2	t- test	NR	NR	0.001 comparing with the following group	NR	Yes	
				5 umol/L ADP-MPA,%	12h	dominant	GA/AA 97	51.1	14.9		NR	NR		NR	Yes	
				5 umol/L ADP-MPA,%	12h	recessive	GG/GA 172	46.8	15.5	t- test	NR	NR	0.107 comparing with the following group	NR	Yes	
				5 umol/L ADP-MPA,%	12h	recessive	AA 18	53	14.7		NR	NR		NR	Yes	
		CYP2C19*3	Platelet measures	5 umol/L ADP-MPA,%	12h	Codominant	GG 165	46.3	15.5	ANOVA	NR	NR	0.008 comparing with the following 2 groups	NR	Yes	
				5 umol/L ADP-MPA,%	12h	Codominant	GA 25	55.1	13.7		NR	NR		NR	Yes	
				5 umol/L ADP-MPA,%	12h	Codominant	AA 0	-	-		NR	NR		NR	Yes	
				5 umol/L ADP-MPA,%	12h	dominant	GG 165	46.3	15.5	t- test	NR	NR	0.008 comparing with the following group	NR	Yes	
				5 umol/L ADP-MPA,%	12h	dominant	GA/AA 25	55.1	13.7		NR	NR		NR	Yes	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
				5 umol/L ADP-MPA,%	12h	recessive	GG/GA 190	47.4	15.5		NR	NR		NR	Yes	
				5 umol/L ADP-MPA,%	12h	recessive	AA 0	-	-		NR	NR		NR	Yes	
		CYP2C19*2	Platelet measures	20 umol/L ADP-MPA,%	12h	Codominant	GG 93	56.7	15.4	ANOVA	NR	NR	<0.001 comparing with the following 2 group	NR	Yes	
				20 umol/L ADP-MPA,%	12h	Codominant	GA 79	63.8	12		NR	NR		NR	Yes	
				20 umol/L ADP-MPA,%	12h	Codominant	AA 18	67.5	10.5		NR	NR		NR	Yes	
				20 umol/L ADP-MPA,%	12h	dominant	GG 93	56.7	15.4	t- test	NR	NR	<0.001 comparing with the following group	NR	Yes	
				20 umol/L ADP-MPA,%	12h	dominant	GA/AA 97	64.5	11.8		NR	NR		NR	Yes	
				20 umol/L ADP-MPA,%	12h	recessive	GG/GA 172	59.9	14.3	t- test	NR	NR	0.03 comparing with the following group	NR	Yes	
				20 umol/L ADP-MPA,%	12h	recessive	AA 18	67.5	10.5		NR	NR		NR	Yes	
		CYP2C19*3	Platelet measures	20 umol/L ADP-MPA,%	12h	Codominant	GG 165	59.7	14.4	ANOVA	NR	NR	0.008 comparing with the following 2 groups	NR	Yes	
				20 umol/L ADP-MPA,%	12h	Codominant	GA 25	67.2	10.3		NR	NR		NR	Yes	
				20 umol/L ADP-MPA,%	12h	Codominant	AA 0	-	-		NR	NR		NR	Yes	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
				20 umol/L ADP-MPA,%	12h	dominant	GG 165	59.7	14.4	t- test	NR	NR	0.008 comparing with the following group	NR	Yes	
				20 umol/L ADP-MPA,%	12h	dominant	GA/AA 25	67.2	10.3		NR	NR		NR	Yes	
				20 umol/L ADP-MPA,%	12h	recessive	GG/GA 190	60.7	14.2		NR	NR		NR	Yes	
				20 umol/L ADP-MPA,%	12h	recessive	AA 0	-	-		NR	NR		NR	Yes	
	Clopidogrel	CYP2C19*2	Platelet measures	P2Y12 reaction unit	12h	Codominant	GG 93	256.5	77.7	ANOVA	NR	NR	0.081 Comparing with the following 2 groups	NR	Yes	
				P2Y12 reaction unit	12h	Codominant	GA 79	270.9	71.9		NR	NR		NR	Yes	
				P2Y12 reaction unit	12h	Codominant	AA 18	297.6	68.3		NR	NR		NR	Yes	
				P2Y12 reaction unit	12h	dominant	GG 93	256.5	77.7	t- test	NR	NR	0.075 Comparing with the following group	NR	Yes	
				P2Y12 reaction unit	12h	dominant	GA/AA 97	275.9	71.7		NR	NR		NR	Yes	
				P2Y12 reaction unit	12h	recessive	GG/GA 172	263.1	75.2	t- test	NR	NR	0.064 Comparing with the following group	NR	Yes	
				P2Y12 reaction unit	12h	recessive	AA 18	297.6	68.3		NR	NR		NR	Yes	
		CYP2C19*3	Platelet measures	P2Y12 reaction unit	12h	Codominant	GG 165	264	76.9	ANOVA	NR	NR	0.258 Comparing with the following 2 groups	NR	Yes	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
				P2Y12 reaction unit	12h	Codominant	GA 25	282.2	60.5		NR	NR		NR	Yes	
				P2Y12 reaction unit	12h	Codominant	AA 0	-	-		NR	NR		NR	Yes	
				P2Y12 reaction unit	12h	dominant	GG 165	264	76.9	t- test	NR	NR	0.258 Comparing with the following group	NR	Yes	
				P2Y12 reaction unit	12h	dominant	GA/AA 25	282.2	60.5		NR	NR		NR	Yes	
				P2Y12 reaction unit	12h	recessive	GG/GA 190	266.4	75.1		NR	NR	-	NR	Yes	
				P2Y12 reaction unit	12h	recessive	AA 0	-	-		NR	NR		NR	Yes	
Kang, 2010{Kang, 2010 40 /id} 20724801 Korea NR	clopidogrel	CYP2C19	5 umol/L ADP PRmax	Maximal platelet reactivity	NR	mutant allele	104	51.6	16.4	t-test	NR	NR	0.008 (mutant allele Vs no carrier)	NR	NR	
						No mutant carrier	72	44.7	17.4							
		CYP2C19	20 umol/L ADP PRmax	Maximal platelet reactivity	NR	mutant allele	104	64.6	13.9	t-test	NR	NR	0.007	NR	NR	
						No mutant carrier	72	58.2	17.4							
Liu 2010{Liu, 2010 38 /id} 21163112 China NR	Clopidogrel	SNP rs4244285	Platelet aggregation	maximal percent change in LTA from the baseline value	At baseline	G/G,	426	62.8	6.6	t-test	NR	NR	P=0.756	NR	NR	
				maximal percent change in LTA from the baseline value	At baseline	G/A or A/A	296	62.7	7.1		NR	NR		NR	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
				maximal percent change in LTA from the baseline value	After loading	G/G,	426	36.3	11.5	t-test	NR	NR	P=0.039	NR	NR	
				maximal percent change in LTA from the baseline value	After loading	G/A or A/A	296	38.1	11.6		NR	NR		NR	NR	
				maximal percent change in LTA from the baseline value	Reduction	G/G,	426	26.9	12.3	t-test	NR	NR	P=0.038	NR	NR	
				maximal percent change in LTA from the baseline value	Reduction	G/A or A/A	296	24.5	12.8		NR	NR		NR	NR	
		Smoking	Platelet aggregation	maximal percent change in LTA from the baseline value	At baseline	smoking	312	63.8±6.8	63.8±6.8	t-test	NR	NR	P<0.001	NR	NR	
		Non-smoking	Platelet aggregation	maximal percent change in LTA from the baseline value	At baseline	Non-smoking	410	62.0±6.8	62.0±6.8		NR	NR		NR	NR	
		Smoking	Platelet aggregation	maximal percent change in LTA from the baseline value	After loading	smoking	312	36.0±12.3	36.0±12.3	t-test	NR	NR	P=0.041	NR	NR	
		Non-smoking	Platelet aggregation	maximal percent change in LTA from the baseline value	After loading	Non-smoking	410	37.8±10.9	37.8±10.9		NR	NR		NR	NR	
		Smoking	Platelet aggregation	maximal percent change in LTA from the baseline value	Reduction	smoking	312	27.8±13.2	27.8±13.2	t-test	NR	NR	P<0.001	NR	NR	
		Non-smoking	Platelet aggregation	maximal percent change in LTA from the baseline value	Reduction	Non-smoking	410	24.2±11.8	24.2±11.8		NR	NR		NR	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Maeda, 2010{Maeda, 2011 30 /id} 21178986 Japan NR	(i) aspirin (100 mg, q.d.), (ii) aspirin (100 mg, q.d.) plus clopidogrel (75 mg, q.d. or (iii) aspirin (100 mg, q.d.) plus ticlopidine (100 mg, b.i.d.;															Figure 2 a, box plot based on genotype, gigure 3 a, box plot based on genotype
Yamamoto 2011{Yamamoto, 2011 25 /id} 21168310 Japan NR	300mg loading dose and 75mg/day clopidogrel maintenance dose plus 100mg aspirin	CYP2C19*1/*1	Platelet reactivity	Aggregation units (AU) Min	NR	*1/*1	EM 47	3194	1570 Au min	Mann-Whitney U test	NR	NR	EM vs IM P<0.05	NR	NR	
		CYP2C19*1/*2, *1/*3	Platelet reactivity	Aggregation units (AU) Min	NR	*1/*2, *1/*3	IM 51	4184	1400 Au min		NR	NR		NR	NR	
		CYP2C19*2/*2, *2/*3, *3/*3	Platelet reactivity	Aggregation units (AU) Min	NR	*2/*2, *2/*3, *3/*3	PM 25	5088	1080 Au min	Mann-Whitney U test	NR	NR	IM vs PM P<0.05	NR	NR	
		CYP2C19*1/*1	Platelet reactivity	Aggregation units (AU) Min	<7 days	*1/*1	EM 25	3186	1595 Au min	Mann-Whitney U test	NR	NR	EM vs IM P<0.05	NR	NR	
		CYP2C19*1/*2, *1/*3	Platelet reactivity	Aggregation units (AU) Min	<7 days	*1/*2, *1/*3	IM 32	3007	1541 Au min	Mann-Whitney U test	NR	NR		NR	NR	
		CYP2C19*2/*2, *2/*3, *3/*3	Platelet reactivity	Aggregation units (AU) Min	<7 days	*2/*2, *2/*3, *3/*3	PM 12	4655	1380 Au min	Mann-Whitney U test	NR	NR	IM vs PM P<0.05	NR	NR	
		CYP2C19*1/*1	Platelet reactivity	Aggregation units (AU) Min	≥7 days	*1/*1	EM 22	3186	1595 Au min	Mann-Whitney U test	NR	NR	EM vs IM NS	NR	NR	
		CYP2C19*1/*2, *1/*3	Platelet reactivity	Aggregation units (AU) Min	≥7 days	*1/*2, *1/*3	IM 19	3007	1541 Au min	Mann-Whitney U test	NR	NR		NR	NR	
		CYP2C19*2/*2, *2/*3, *3/*3	Platelet reactivity	Aggregation units (AU) Min	≥7 days	*2/*2, *2/*3, *3/*3	PM 13	4655	1380 Au min	Mann-Whitney U test	NR	NR	IM vs PM P<0.05	NR	NR	

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing, 2010{Sibbing, 2010 48 /id} 20492469 Germany	Aspirin and clopidogrel (75 mg/day)	CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *2 (wt/wt)	738	212	NR	Kruskal-Wallis test	NR	141-351	P=0.0001 for *2/*2 vs wt/wt	No	NR	Figure 2a and b, bootstrap results
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *2 (wt/*2)	229	305				162-482	P=0.01 for *2/*2 vs wt/*2 patients			
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *2 (*2/*2)	19	475				387-575				
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *17 (wt/wt)	608	243		Kruskal-Wallis test		151-416	P=0.007 for *17/*17 vs wt/wt	No	NR	
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *17 (wt/*17)	335	217				141-375	P=0.06 for *17/*17 vs wt/*17 patients			

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *17 (*17/*17)	43	164				120-273				
		Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., EM) – ONE ROW PER GENOTYPE GROUP	No. with given genotype	Platelet reactivity measurement for the genotype group [metric] Median	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *17+/*2-	319	207	NR	Kruskal-Wallis test	NR	132-332	P<0.001 for CYP2C19 *17+/*2- Vs CYP2C19 *17-/*2+	NR	NR	
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *17+/*2-	419	NR	NR	Kruskal-Wallis test	NR		No	NR	NR	
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *17+/*2+	59	NR	NR	Kruskal-Wallis test	NR		No	NR		

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
		CYP2C19	Platelet aggregation	Aggregation measured with MEA is quantified as aggregation units(AU) and area under the curve(AUC) of aggregation units (AU*min).	NR	CYP2C19 *17-/*2+	189	309	NR	Kruskal-Wallis test	NR	172-490	No	NR		
Bouman 2011{Bouman, 2011 9 /id} 21628721 Netherlands Genetic substudy of the Popular study	Clopidogrel	CYP2C19 genetic test (real-time PCR)	On-treatment platelet reactivity	5 mcmol/l ADP-induced LTA	Within 2 hr after blood sampling	CYP2C19 *2 heterozygotes	260	44% aggregation	SD 14%	ANOVA) followed by the least significant difference post-hoc test	NR	NR	NR	YES (age, sex, BMI, current smoking, systolic BP >140 mm Hg or diastolic BP >90 mm Hg, diabetes mellitus, LVEF <45%, renal failure (creatinine level >1.36 mg/dl), platelet count, mean platelet volume, clopidogrel regimen, PPI use, and amlodipine use)	NR	
				20 mcmol/l ADP-induced LTA				63% aggregation	SD 13%							
				Plateletworks assay				72% aggregation	SD 27%							
				VerifyNow P2Y12				230 platelet reactivity units (PRU)	SD 27 PRU							
				5 mcmol/l ADP-induced LTA		CYP2C19 *2 homozygotes	27	52% aggregation	SD 14%							
				20 mcmol/l ADP-induced LTA				70% aggregation	SD 9%							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
				Plateletworks assay				90% aggregation	SD 21%							
				VerifyNow P2Y12				257 platelet reactivity units (PRU)	SD 60 PRU							
				5 mcmol/l ADP-induced LTA		CYP2C19 *2 noncarrier	737	38% aggregation	SD 14%							
				20 mcmol/l ADP-induced LTA				56% aggregation	SD 15%							
				Plateletworks assay				61% aggregation	SD 30%							
				VerifyNow P2Y12				202 platelet reactivity units (PRU)	SD 76 PRU							
Campo 2011{Campo, 2011 13 /id} 21679849 Italy NR	Clopidogrel	TaqMan	Platelet reactivity	VerifyNow values	Baseline (before PCI)	*2 noncarriers	219	Mean 181 PRU	SD 97 PRU	t test and 1-way analysis of variance	NR	NR	Unclear	linear mixed model	baseline, genetic, and procedural characteristics	Data are from Table 2. Some P values there are not yet reported here because I can't tell what comparison they're for
						*2 heterozygote	76	Mean 216 PRU	SD 92 PRU				<0.05 vs noncarrier			
						*2 homozygote	5	Mean 236 PRU	SD 112 PRU				<0.05 vs noncarrier			
						*2 carrier	81	Mean 216 PRU	SD 91 PRU							
					1 mo after PCI	*2 noncarriers	219	Mean 133 PRU	SD 81 PRU							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2 heterozygote	76	Mean 182 PRU	SD 88 PRU				<0.05 vs noncarrier			
						*2 homozygote	5	Mean 221 PRU	SD 105 PRU				<0.05 vs noncarrier			
						*2 carrier	81	Mean 185 PRU	SD 90 PRU							
					6 mo after PCI	*2 noncarriers	204	Mean 132 PRU	SD 81 PRU							Ns are less at 6 mo because data for this time point only available for 281 pts
						*2 heterozygote	73	Mean 180 PRU	SD 85 PRU				<0.05 vs noncarrier			
						*2 homozygote	4	Mean 218 PRU	SD 95 PRU				<0.05 vs noncarrier			
						*2 carrier	77	Mean 183 PRU	SD 87 PRU							
					Baseline (before PCI)	*17 noncarriers	198	Mean 203 PRU	SD 92 PRU	t test and 1-way analysis of variance	NR	NR	Unclear			Data are from Table 2. Some P values there are not yet reported here because I can't tell what comparison they're for
						*17 heterozygote	85	Mean 171 PRU	SD 100 PRU				<0.05 vs noncarrier			
						*17 homozygote	17	Mean 139 PRU	SD 100 PRU				<0.05 vs noncarrier			

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*17 carrier	102	Mean 165 PRU	SD 101 PRU							
					1 mo after PCI	*17 noncarriers	198	Mean 163 PRU	SD 83 PRU							
						*17 heterozygote	85	Mean 122 PRU	SD 79 PRU				<0.05 vs noncarrier			
						*17 homozygote	17	Mean 88 PRU	SD 88 PRU				<0.05 vs noncarrier			
						*17 carrier	102	Mean 117 PRU	SD 81 PRU							
					6 mo after PCI	*17 noncarriers	185	Mean 163 PRU	SD 81 PRU							Ns are less at 6 mo because data for this time point only available for 281 pts
						*17 heterozygote	79	Mean 119 PRU	SD 83 PRU				<0.05 vs noncarrier			
						*17 homozygote	17	Mean 88 PRU	SD 93 PRU				<0.05 vs noncarrier			
						*17 carrier	96	Mean 113 PRU	SD 85 PRU							
Fernando 2011{Fernando, 2011 233 /id} 21696537 Australia NR	Clopidogrel	GenesFx (PCR)	Mean change in platelet reactivity from baseline	VASP data (PRI units)	After treatment (first or second) or washout, but otherwise NR	Poor/intermediate metabolizers	6	Mean	SEM	Two-way ANOVA			<0.01 vs. row below [Two-way ANOVA]	NR	NR	Get data from Fig 4—either report data for esomeprazole and placebo treatment separately or average?

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Extensive metabolizers	23									
				Aggregometry data (AUC units)		Poor/intermediate metabolizers	6						<0.01 vs. row below [Two-way ANOVA]			
						Extensive metabolizers	23									
				VerifyNow (PRU) data		Poor/intermediate metabolizers	6						<0.01 vs. row below [Two-way ANOVA]			
						Extensive metabolizers	23									
Geisler 2008 18781853 Germany NR	Clopidogrel	MassARRAY for *2	Residual platelet aggregation (RPA)	From turbidometry	Post-clopidogrel loading dose	*2/*2	10	Median RPA 54%	NR	NR	NR	NR	NR	NR	NR	NO
						*1/*2	52	Median RPA, 46%								
						*1/*1	175	Median RPA, 30%								
						*17/*17	21	Median RPA 37%					NS for this and next two rows			
						*1/*17	79	Median RPA, 30%								
						*1/*1	137	Median RPA, 36%								
Gladding 2008{Gladding, 2008 149 /id} 19463375 New Zealand PRINC (Plavix Response in Coronary Intervention) Trial	Clopidogrel	TaqMan PCR	Platelet inhibition (% of baseline)	VerifyNow data	At 2 hr	CYP2C19 *1*1 homozygotes	24	Median (range) 23 (0% to 66%)	NR	NR	NR	NR	0.0295 (vs. row below) [Mann-Whitney U test]	NO	NO	Raw data in Fig 3

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						CYP2C19 *2 or *4 carriers	19	Median (range) 10% (0% to 56%)								
						CYP2C19 *17 carriers	17	Median (range) 9% (0% to 98%)					0.0262 (vs. 2 rows above) [Mann-Whitney U test]			
					At 4 hr	CYP2C19 *1*1 homozygotes receiving 1200 mg total	15	Median (range) 43% (13% to 97%)	NR	NR	NR	NR	0.3 (vs. row below) [Mann-Whitney U test]	NO	NO	Raw data in Fig 4
						CYP2C19 *1*1 homozygotes receiving 600 mg total	9	Median (range) 35% (0% to 65%)								
					At 7 hr	CYP2C19 *1*1 homozygotes receiving 1200 mg total	15	Median (range) 63% (15% to 98%)	NR	NR	NR	NR	0.05(vs. row below) [Mann-Whitney U test]	NO	NO	Raw data in Fig 4
						CYP2C19 *1*1 homozygotes receiving 600 mg total	9	Median (range) 29% (0% to 75%)								
					At 7 days	CYP2C19 *1*1 homozygotes receiving 150 mg daily	12	Median (range) 46% (18% to 97%)	NR	NR	NR	NR	0.2 (vs. row below) [Mann-Whitney U test]	NO	NO	Raw data in Fig 4
						CYP2C19 *1*1 homozygotes receiving 75 mg daily	6	Median (range) 32% (24% to 64%)								

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
					At 4 hours	CYP2C19 *2 or *4 carriers receiving 1200 mg total	11	Median (range) 37% (8% to 87%)					0.002 (vs. row below) [Mann-Whitney U test]			Raw data in Fig 5
						CYP2C19 *2 or *4 carriers receiving 600 mg total	8	Median (range) 14% (0% to 22%)								
					At 7 hours	CYP2C19 *2 or *4 carriers receiving 1200 mg total	11	Median (range) 42% (7% to 94%)					0.09 (vs. row below) [Mann-Whitney U test]			Raw data in Fig 5
						CYP2C19 *2 or *4 carriers receiving 600 mg total	8	Median (range) 22% (0% to 51%)								
					At 7 days	CYP2C19 *2 or *4 carriers receiving 150 mg daily	5	Median (range) 51% (15% to 86%)					0.042 (vs. row below) [Mann-Whitney U test]			Raw data in Fig 5
						CYP2C19 *2 or *4 carriers receiving 75 mg daily	9	Median (range) 14% (0% to 67%)								
					At 7 hours	CYP2C9* 1/*3 heterozygotes receiving 600 mg total	NR but something's wrong—"None of the patients carried the CYP2C19*3 allele."	Median (range) 9% (8% to 11%)					0.045 (vs. row below) [Mann-Whitney U test]			
						CYP2C9* 1/*1 homozygotes receiving 600 mg total	9	Median (range) 31% (0% to 96%)								

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Gurbel 2010{Gurbel, 2010 91 /id} 19817997 USA NR	75 mg clopidogrel daily	TaqMan	5 mcM ADP-induced platelet aggregation (%)	NR	Pre-elinogrel	CYP2C19 *2 carrier	17	52 ± 13% Mean±SD	NR	NR	NR	NR	0.001 vs. row below [one-way ANOVA]	NR	NR	
						CYP2C19 *2 noncarrier	19	36 ± 14% Mean±SD								
			20 mcM ADP-induced platelet aggregation (%)		Pre-elinogrel	CYP2C19 *2 carrier	17	61 ± 12% Mean±SD					0.03 vs. row below [one-way ANOVA]			
						CYP2C19 *2 noncarrier	19	50 ± 13% Mean±SD								
			VASP assay platelet reactivity index		Pre-elinogrel	CYP2C19 *2 carrier	17	72 ± 12 PRI Mean±SD					0.05 vs. row below [one-way ANOVA]			
						CYP2C19 *2 noncarrier	19	58 ± 20 PRI Mean±SD								
			VerifyNow P2Y12 assay-platelet reactivity units		Pre-elinogrel	CYP2C19 *2 carrier	17	259 ± 68 PRU Mean±SD					0.14 vs. row below [one-way ANOVA]			
						CYP2C19 *2 noncarrier	19	214 ± 82 PRU Mean±SD								
			VerifyNow P2Y12 assay-percent inhibition		Pre-elinogrel	CYP2C19 *2 carrier	17	19 ± 19% Mean±SD					0.07 vs. row below [one-way ANOVA]			
						CYP2C19 *2 noncarrier	19	35 ± 24% Mean±SD								
			TEG-ADP-induced platelet-fibrin clot strength (mm)		Pre-elinogrel	CYP2C19 *2 carrier	17	57 ± 8 mm Mean±SD					0.18 vs. row below [one-way ANOVA]			
						CYP2C19 *2 noncarrier	19	49 ± 12 mm Mean±SD								
			TEG-percent inhibition		Pre-elinogrel	CYP2C19 *2 carrier	17	23 ± 9% Mean±SD					0.07 vs. row below [one-way ANOVA]			

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						CYP2C19 *2 noncarrier	19	36 ± 20% Mean±SD								
			Change in 5 mcM ADP-induced platelet aggregation (%)	Change in % aggregration between baseline and 4 hours in the 17 patients with HPR at baseline	Pre vs post-elinogrel	CYP2C19 *2 carrier	14						0.0001 vs. row below[one-way ANOVA]			Need to digitize data from Fig 12? Data are per patient, not means
						CYP2C19 *2 noncarrier	3									
			5 mcM ADP-induced platelet aggregation (%)		Pre-elinogrel	CYP2C19 *17 noncarrier	15	41 ± 19% Mean±SD								
						CYP2C19 *17 noncarrier	21	45 ± 14% Mean±SD					0.30 vs. row above [one-way ANOVA]			
			20 mcM ADP-induced platelet aggregation (%)		Pre-elinogrel	CYP2C19 *17 noncarrier	15	51 ± 14% Mean±SD								
						CYP2C19 *17 noncarrier	21	58 ± 13% Mean±SD								
			VASP assay-platelet reactivity index		Pre-elinogrel	CYP2C19 *17 noncarrier	15	60 ± 23 PRI Mean±SD								
						CYP2C19 *17 noncarrier	21	67 ± 15 PRI Mean±SD					0.35 vs. row above [one-way ANOVA]			
			VerifyNow P2Y12 assay-platelet reactivity units		Pre-elinogrel	CYP2C19 *17 noncarrier	15	206 ± 91 PRU Mean±SD								
						CYP2C19 *17 noncarrier	21	251 ± 65 PRU Mean±SD					0.13 vs. row above [one-way ANOVA]			
			VerifyNow P2Y12 assay-per cent inhibition		Pre-elinogrel	CYP2C19 *17 noncarrier	15	35 ± 28% Mean±SD								

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						CYP2C19 *17 noncarrier	21	24 ± 18% Mean±SD					0.24 vs. row above [one-way ANOVA]			
			TEG-ADP-induced platelet-fibrin clot strength (mm)		Pre-elinogrel	CYP2C19 *17 noncarrier	15	51 ± 12 mm Mean±SD								
						CYP2C19 *17 noncarrier	21	53 ± 11 mm Mean±SD					0.83 vs. row above [one-way ANOVA]			
			TEG-percent inhibition		Pre-elinogrel	CYP2C19 *17 noncarrier	15	35 ± 28% Mean±SD								
						CYP2C19 *17 noncarrier	21	24 ± 18% Mean±SD					0.17 vs. row above [one-way ANOVA]			
Kim 2011{Kim, 2011 18 /id} 21511217 South Korea CCELAMI2C19	High-dose clopidogrel	PCR and SNaPshot assay kit	LTA maximal platelet aggregation	20 mcmol/l ADP	Pre-discharge	*2 or *3 noncarrier	24	Mean 54.1%	SD 16.1%	Student unpaired t or Mann-Whitney U test?	NR	NR	0.293 vs. corresponding cilostazol row below	NO	NO	NONE
						*2 or *3 carrier	38	Mean 60.0%	SD 15.2%				0.802 vs. corresponding cilostazol row below			
					At 30 days	*2 or *3 noncarrier	24	Mean 38.6%	SD 12.0%				0.752 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 52.3%	SD 17.5%				<0.001 vs. corresponding cilostazol row below			
				Absolute change between baseline and 30 days	?	*2 or *3 noncarrier	24	Mean 15.5%	SD 15.1%				0.197 vs. corresponding cilostazol row below			Data are also in Fig. 2
						*2 or *3 carrier	38	Mean 7.7%	SD 15.5%				<0.001 vs. corresponding cilostazol row below			
	Standar-dose clopidogrel + cilostazol	PCR and SNaPshot assay kit	LTA maximal platelet aggregation	20 mcmol/l ADP	Pre-discharge	*2 or *3 noncarrier	25	Mean 58.4%	SD 11.9%							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2 or *3 carrier	39	Mean 59.2%	SD 14.4%							
					At 30 days	*2 or *3 noncarrier	25	Mean 37.5%	SD 13.2%							
						*2 or *3 carrier	39	Mean 35.0%	SD 19.3%							
				Absolute change between baseline and 30 days		*2 or *3 noncarrier	25	Mean 20.9%	SD 13.9%							Data are also in Fig. 2
						*2 or *3 carrier	39	Mean 24.2%	SD 17.2%							
	High-dose clopidogrel	PCR and SNaPshot assay kit	LTA maximal platelet aggregation	5 mcmol/l ADP	Pre-discharge	*2 or *3 noncarrier	24	Mean 42.4%	SD 15.7%				0.256 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 46.6%	SD 16.7%				0.995 vs. corresponding cilostazol row below			
					At 30 days	*2 or *3 noncarrier	24	Mean 30.1%	SD 10.1%				0.547 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 37.6%	SD 16.0%				<0.001 vs. corresponding cilostazol row below			
				Absolute change between baseline and 30 days		*2 or *3 noncarrier	24	Mean 12.3%	SD 13.8%				0.094 vs. corresponding cilostazol row below			Data are also in Fig. 2
						*2 or *3 carrier	38	Mean 9.0%	SD 13.3%				<0.001 vs. corresponding cilostazol row below			
	Standar-dose clopidogrel + cilostazol	PCR and SNaPshot assay kit	LTA maximal platelet aggregation	5 mcmol/l ADP	Pre-discharge	*2 or *3 noncarrier	25	Mean 46.9%	SD 11.8%							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2 or *3 carrier	39	Mean 46.6%	SD 15.6%							
					At 30 days	*2 or *3 noncarrier	25	Mean 28.2%	SD 11.5%							
						*2 or *3 carrier	39	Mean 24.9%	SD 14.3%							
				Absolute change between baseline and 30 days		*2 or *3 noncarrier	25	Mean 18.8%	SD 12.5%							
						*2 or *3 carrier	39									
	High-dose clopidogrel	PCR and SNaPshot assay kit	LTA late platelet aggregation	20 mcmol/l ADP	Pre-discharge	*2 or *3 noncarrier	24	Mean 44.4%	SD 22.7%				0.379 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 50.9%	SD 21.7%				0.878 vs. corresponding cilostazol row below			
					At 30 days	*2 or *3 noncarrier	24	Mean 21.8%	SD 40.6%				0.649 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 40.6%	SD 22.2%				0.001 vs. corresponding cilostazol row below			
				Absolute change between baseline and 30 days		*2 or *3 noncarrier	24	Mean 22.6%	SD 19.6%				0.211 vs. corresponding cilostazol row below			Data are also in Fig. 3
						*2 or *3 carrier	38	Mean 10.3%	SD 20.9%				<0.001 vs. corresponding cilostazol row below			
	Standar-dose clopidogrel + cilostazol	PCR and SNaPshot assay kit	LTA late platelet aggregation	20 mcmol/l ADP	Pre-discharge	*2 or *3 noncarrier	25	Mean 49.4%	SD 15.7%							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2 or *3 carrier	39	Mean 51,.6%	SD 17.7%							
					At 30 days	*2 or *3 noncarrier	25	Mean 19.7%	SD 16.8%							
						*2 or *3 carrier	39	Mean 23.5%	SD 19.2%							
				Absolute change between baseline and 30 days	At 30 days	*2 or *3 noncarrier	25	Mean 29.6%	SD 19.3%							
						*2 or *3 carrier	39	Mean 28.1%	SD 19.4%							
	High-dose clopidogrel	PCR and SNaPshot assay kit	LTA late platelet aggregation	5 mcmol/l ADP	Pre-discharge	*2 or *3 noncarrier	24	Mean 32.5%	SD 18.2%				0.397 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 38.4%	SD 20.7%				0.749 vs. corresponding cilostazol row below			
					At 30 days	*2 or *3 noncarrier	24	Mean 16.4%	SD 9.2%				0.347 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 26.7%	SD 16.5%				<0.001 vs. corresponding cilostazol row below			
				Absolute change between baseline and 30 days	At 30 days	*2 or *3 noncarrier	24	Mean 16.0%	SD 16.2%				0.144 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 11.7%	SD 15.2%				<0.001 vs. corresponding cilostazol row below			
	Standar-dose clopidogrel + cilostazol	PCR and SNaPshot assay kit	LTA late platelet aggregation	5 mcmol/l ADP	Pre-discharge	*2 or *3 noncarrier	25	Mean 36.4%	SD 13.5%							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2 or *3 carrier	39	Mean 39.8%	SD 17.4%							
					At 30 days	*2 or *3 noncarrier	25	Mean 13.6%	SD 11.7%							
						*2 or *3 carrier	39	Mean 15.2%	SD 12.4%							
				Absolute change between baseline and 30 days	At 30 days	*2 or *3 noncarrier	25	Mean 22.8%	SD 15.6%							
						*2 or *3 carrier	39	Mean 24.6%	SD 15.4%							
	High-dose clopidogrel	PCR and SNaPshot assay kit	VerifyNow platelet reactivity	At 30 days	Pre-discharge	*2 or *3 noncarrier	24	Mean 245.0 PRU	SD 91.6 PRU				0.959 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 241.6 PRU	SD 79.3 PRU				0.220 vs. corresponding cilostazol row below			
					At 30 days	*2 or *3 noncarrier	24	Mean 152.2 PRU	SD 70.4 PRU				0.441 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 184.2 PRU	SD 80.6 PRU				0..518 vs. corresponding cilostazol row below			
				Absolute change between baseline and 30 days	Change between pre-discharge and 30 days after discharge	*2 or *3 noncarrier	24	Mean 92.8 PRU	SD 60.7 PRU				0..347 vs. corresponding cilostazol row below			Data are also in Fig. 5
						*2 or *3 carrier	38	Mean 57.3 PRU	SD 69.4 PRU				0.060 vs. corresponding cilostazol row below			
	Standar-dose clopidogrel + cilostazol	PCR and SNaPshot assay kit	VerifyNow platelet reactivity		Pre-discharge	*2 or *3 noncarrier	25	Mean 246.2 PRU	SD 76.3 PRU							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2 or *3 carrier	39	Mean 263.0 PRU	SD 72.5 PRU							
					At 30 days	*2 or *3 noncarrier	25	Mean 136.6 PRU	SD 70.0 PRU							
						*2 or *3 carrier	39	Mean 171.9 PRU	SD 86.3 PRU							
				Absolute change between baseline and 30 days		*2 or *3 noncarrier	25	Mean 109.6 PRU	SD 63.1 PRU							
						*2 or *3 carrier	39	Mean 91.1 PRU	SD 85.0 PRU							
	High-dose clopidogrel	PCR and SNaPshot assay kit	VerifyNow % inhiibition		Pre-discharge	*2 or *3 noncarrier	24	Mean 26.2%	SD 25.0%				0..672 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 22.0%	SD 19.2%				0.825 vs. corresponding cilostazol row below			
					At 30 days	*2 or *3 noncarrier	24	Mean 54.7%	SD 22.3%				0.783 vs. corresponding cilostazol row below			
						*2 or *3 carrier	38	Mean 40.3%	SD 23.5%				0.157 vs. corresponding cilostazol row below			
	Standar-dose clopidogrel + cilostazol	PCR and SNaPshot assay kit	VerifyNow % inhibition		Pre-discharge	*2 or *3 noncarrier	25	Mean 23.5%	SD 18.9%							
						*2 or *3 carrier	39	Mean 21.1%	SD 16.8%							
					At 30 days	*2 or *3 noncarrier	25	Mean 56.4%	SD 20.7%							

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						*2 or *3 carrier	39	Mean 48.0%	SD 24.0%							
Lee 2011{Lee, 2011 4 /id} 21786436 South Korea NR	Clopidogrel	Seeplex CYP2C19 ACE Genotyping system	VerifyNow P2Y12 reactivity units (clopidogrel resistance)	NR	NR	Extensive CYP2C19 metabolizers	68	195.0 PRU mean	84.9 PRU SD	analysis of variance (ANOVA) test and post hoc analysis	NR	NR	*p*<0.001 among this and next two rows [ANOVA]	NR	NR	Post hoc analysis using the Bonferroni test showed significant differences between all subgroups
						Intermediate metabolizers	74	237.9 PRU mean	88.0 PRU SD							
						Poor metabolizers	24	302.2 PRU mean	58.9 PRU SD							
			percent inhibition			Extensive CYP2C19 metabolizers	68	44.6% mean	21.8% SD				*p*<0.001 among this and next two rows [ANOVA]			Post hoc analysis using the Bonferroni test showed significant differences between all subgroups
						Intermediate metabolizers	74	30.5%mean	21.5% SD							
						Poor metabolizers	24	14.0 mean	13.4% SD							
Malek 2008{Malek, 2008 167 /id} 18577829 Poland NR	Clopidogrel and aspirin	PFA-100	Median CADP-CT value	NR	Median 6 days after starting clopidogrel	Group 1	7	95 s (IQR 59–124 s)	NR	NR	NR	NR	0.002 vs. controls (Wilcoxon rank-sum test)	NR	NR	NR

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Group 2	14	210 s (IQR 115–300 s)					0.01 vs. Group 1 (Wilcoxon rank-sum test), NS vs. controls and group 3			
						Group 3	17	286 s (IQR 108–300 s)					0.01 vs. Group 1 (Wilcoxon rank-sum test), NS vs. controls and group 2			
						Controls	67	289 s (IQR 182–300 s)					NA			
Pettersen 2011{Petterse n, 2011 228 /id} 21426546 Norway Aspirin and Clopidogrel non-responsivenes s clinical Endpoint Trial (ASCET)	Clopidogrel	TaqMan Drug Metabolism Assay	Platelet reactivity	VASP	NR	CYP2C19 *2 carrier	64	51% Mean platelet reactivity index value	NR	NR	NR	NR	< 0.001 vs. row below (either Student 's unpaired t-test or Mann-Whitney U-test)	NO	NO	NONE
						*2 noncarrier	104	38% Mean platelet reactivity index value								
				VerifyNow		*2 carrier	64	162 Mean platelet reactivity units					< 0.001 vs. row below (either Student 's unpaired t-test or Mann-Whitney U-test)			
						*2 noncarrier	104	121 Mean platelet reactivity units								

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing 2011{Sibbing, 2011 2 /id} 21527445 Germany NR	Clopidogrel	TaqMan assay	Platelet aggregation value	ADP-induced	NR	*2 carrier (*1/*2 or *2/*2)	377	Median (range) 286 (186 – 460) AU × min	NR	NR	NR	NR	0.0001 vs. row below [Kruskal – Wallis test]	NR	NR	Data in this table are for PCI cohort (n=5124)
						*2 noncarrier	1147	Median (range) 208 (134 – 329) AU × min								
						*1/*1	32	Median (range) 208 (134– 329) AU × min					0.001 for this and next three rows [multivariable linear regression]	YES [all baseline variables]		10th, 25th, 75th, and 90th percentiles are in Fig 2
						*1/*2	345	Median (range) 267 (175 – 428) AU × min								
						*2/*2	1147	Median (range) 494 (341 – 732) AU × min								
Hwang 2010{Hwang, 2010 55 /id} 20823393 Korea ACCEL	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	maximal platelet aggregation	5 umol/L ADP LTA	procedural	wild type homozygote	22	mean 47.7	16.4	t-test	NR	NR	0.600 comparing the following group	NR	NR	figure 2-5 are bar graphs.
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 50.2	15.8		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	maximal platelet aggregation	5 umol/L ADP LTA	30 days	wild type homozygote	22	mean 31.1	12.9	t-test	NR	NR	0.304 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 26.7	15.2		NR	NR				

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	maximal platelet aggregation	5 umol/L ADP LTA	procedural	mutant-type homozygote	43	mean 54	15.1	t-test	NR	NR	0.949 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 42.9	18.1		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	maximal platelet aggregation	5 umol/L ADP LTA	30 days	mutant type homozygote	43	mean 42.9	18.1	t-test	NR	NR	<0.001 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 28.4	13.9		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	maximal platelet aggregation	20 umol/L ADP LTA	procedural	wild type homozygote	22	mean 60.5	15.1	t-test	NR	NR	0.661 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 62.4	13.8		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	maximal platelet aggregation	20umol/L ADP LTA	30 days	wild type homozygote	22	mean 41.9	16.4	t-test	NR	NR	0.276 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 36.0	19.2		NR	NR				

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	maximal platelet aggregation	5 umol/L ADP LTA	procedural	mutant-type homozygote	43	mean 66.8	11.3	t-test	NR	NR	0.99 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 66.8	12.2		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	maximal platelet aggregation	5 umol/L ADP LTA	30 days	mutant type homozygote	43	mean 55.4	15.9	t-test	NR	NR	<0.001 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 40.5	16.7		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	late platelet aggregation	5 umol/L ADP LTA	procedural	wild type homozygote	22	mean 40.3	20.3	t-test	NR	NR	0.913 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 41.0	17.9		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	late platelet aggregation	5 umol/L ADP LTA	30 days	wild type homozygote	22	mean 19.0	13.4	t-test	NR	NR	0.318 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 14.9	13.4		NR	NR				

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	late platelet aggregation	5 umol/L ADP LTA	procedural	mutant-type homozygote	43	mean 47.1	20.1	t-test	NR	NR	0.742 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 45.8	16.8		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	late platelet aggregation	5 umol/L ADP LTA	30 days	mutant type homozygote	43	mean 30.7	22.2	t-test	NR	NR	<0.001 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 16.7	11.5		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	late platelet aggregation	20 umol/L ADP LTA	procedural	wild type homozygote	22	mean 52.2	21.1	t-test	NR	NR	0.734 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 54.2	18.4		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	late platelet aggregation	20umol/L ADP LTA	30 days	wild type homozygote	22	mean 26.9	18.8	t-test	NR	NR	0.321 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 21.2	19.0		NR	NR				

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	late platelet aggregation	5 umol/L ADP LTA	procedural	mutant-type homozygote	43	mean 61.0	16.8	t-test	NR	NR	0.986 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 60.9	16.0		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	late platelet aggregation	5 umol/L ADP LTA	30 days	mutant type homozygote	43	mean 43.2	22.0	t-test	NR	NR	<0.001 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 26.4	17.4		NR	NR				
	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., EM) – ONE ROW PER GENOTYPE GROUP	No. with given genotype	Platelet reactivity measurement for the genotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	VerifyNow PRU	P2Y12 reaction unit	procedural	wild type homozygote	22	mean 272.5	75.5	t-test	NR	NR	0.42 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 253.8	76.7		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	VerifyNow PRU	P2Y12 reaction unit	30 days	wild type homozygote	22	mean 149.7	65.4	t-test	NR	NR	0.348 comparing the following group	NR	NR	no

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 129.4	76.4		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	VerifyNow PRU	P2Y12 reaction unit	procedural	mutant-type homozygote	43	mean 278.3	69.7	t-test	NR	NR	0.167 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 296.5	53.2		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	VerifyNow PRU	P2Y12 reaction unit	30 days	mutant type homozygote	43	mean 214.1	68.5	t-test	NR	NR	0.153 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 191.6	78.4		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	VerifyNow PRU	P2Y12 reaction unit	procedural	wild type homozygote	22	mean 20.2	18.7	t-test	NR	NR	0.733 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 22.4	22.9		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	VerifyNow PRU	P2Y12 reaction unit	30 days	wild type homozygote	22	mean 65.2	12.8	t-test	NR	NR	0.317comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						22	mean 70.5	7.6		NR	NR				

Author, year UID Country Study name	Treatment	Genetic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	VerifyNow PRU	P2Y12 reaction unit	procedural	mutant-type homozygote	43	mean 14.0	16.2	t-test	NR	NR	0.319comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 11.1	10.8		NR	NR				
	clopidogrel therapy (75 mg +aspirin, 200 mg daily	CYP2C19*2 (rs4244285.c.681G>A) CYP2C19*3 (rs4986893,c.636G>A)	VerifyNow PRU	P2Y12 reaction unit	30 days	mutant type homozygote	43	mean 33.5	19.2	t-test	NR	NR	0.005 comparing the following group	NR	NR	no
	clopidogrel therapy (75 mg +aspirin, 200 mg daily +cilostazol						47	mean 45.8	21.2		NR	NR				

Appendix Table D14: Methods for Platelet Reactivity Ascertainment (When Used as an Outcome)

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Fontana, 2008{Fontana, 2008 182 /id} 17681590 Switzerland	VASP assay (platelet reactivity index)	VASP phosphorylation after ADP stimulation measured by flow cytometry	Platelet VASP/ P2Y12 assay using FACStrack flow cytometer	Assay: Biocytex, Marseille, France; flow cytometer: Becton Dickinson, Meylan, France	Samples were obtained 15 days after discharge (hospitalization for PCI)	Citrated blood	ADP	15 days post discharge (i.e. post-PCI hospitalization)	NR
Giusti, 2007{Giusti, 2007 190 /id} 18004210 Italy NR	Turbidimetric aggrometry to determine platelet aggregation	Light transmission aggregometry (turbidimetric method)	APACT 4	Labor Biomedical Technologies GmbH, Ahrensburg, Germany	Venous blood samples were collected 24 h after PCI intervention; for patients receiving both clopidogrel and IIb/IIIa inhibitors samples were obtained after 6 d	Citrated blood	ADP 2 µmol/L and	Samples were obtained 24 h after PCI intervention; for patients receiving both clopidogrel and IIb/IIIa inhibitors samples were obtained after 6 d	NR
							ADP 10 µmol/L		

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Platelet aggregation	Turbidimetric aggregometry	APACT4 (4 channel aggregometer)	Helena Laboratories (Milan, Italy)	Venous blood was obtained	Citrated blood	ADP (10 µM)	Venous blood was obtained 12-18 h from clopidogrel loading; for patients administered IIb/IIIa inhibitors blood was obtained 6 d after catheterization	NR
Gladding, 2009{Gladding, 2009 248 /id} 19926050 New Zealand NR	VerifyNow	Agglutination plus light transmittance	point-of-care rapid platelet function analyzer (RPFA) and its P2Y12 cartridge	Accumetrics Ltd., San Diego, California	Venous blood; collection tubes were inverted 4 times to mix the anticoagulant and left for 10 min at ambient temperature (24°C) before testing	3.2% citrate	ADP, 20 mmol/l	Platelet function was tested at baseline and at 7 days	10 min
Jinnai, 2009{Jinnai, 2009 120 /id} 19531897 Japan Partly industry funded	Inhibition of platelet aggregation (IPA)	Optical aggregometry	NR	NR	Platelet-rich plasma was obtained at different timepoints	NR	ADP 2 µmol/L	obtained at baseline, 4h, 24h, 48h and the 14th and 28th post-treatment days	NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Shuldiner, 2009{Shuldiner, 2009 116 /id} 19706858 USA Sinai Hospital of Baltimore Study	ADP-stimulated reactivity	Light-transmission aggregometry (lumi-aggregometry)	Chronolog Lumi-Aggregometer (Model 490-4D)	Chronolog; Havertown, PA	Samples were obtained at baseline (for 143 patients not receiving clopidogrel) and post-clopidogrel (188 patients)	Citrated blood	ADP 20 µmol/L or arachidonic acid 2 mmol/L	Platelet function was measured on the day of discharge for patients not receiving eptifibatide and 5 d or more after discharge for patients receiving eptifibatide	NR
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	Multiplate analyzer	Whole-blood electrode platelet aggregometry	Multiplate analyzer (no model information)	Dynabyte, Munich, Germany	Arterial blood samples were collected "directly before PCI"	lepirudin	ADP (6.4 µmol/L)	All patients received a clopidogrel loading dose with a recommended pre-treatment interval of 2h; blood was sampled directly before PCI. The median clopidogrel loading interval was 3.5h for *1/*1; 3.5 h for *17/*1; and 5.3 h for *17/*17.	NR
Varenhorst, 2009{Varenhorst, 2009 122 /id} 19429918 Sweden Genetic sub-study	VASP PRI assay with flow cytometry	VASP assay with flow cytometry	Platelet VASP kit	Biocytex, Marseille, France	NR	Citrated blood	ADP ± PGE1, concentration not reported	Samples were collected at baseline, 2 h and 24 h post-loading dose; also at day 14 ±3 and day 29 ±3, both before that day's maintenance dose	NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
	VerifyNow P2Y12 assay	Whole blood LTA, point-of-care test	VerifyNow VN-P2Y12 assay	Accumetrics, San Diego, CA	Whole-blood, point-of-care assay	NR	ADP (with fibrinogen-coated beads), concentration not reported	The assay was performed on day 1 at baseline (pre-dose), 2, and 24±4 h post-loading dose; also on day 14 ±3 and day 29 ±3, both before that day's maintenance dose	NR
Frere, 2008{Frere, 2008 176 /id} 18394438 France NONE	VASP phosphorylation assay	Flow cytometry with and without ADP stimulation (along with PGE1 for all measurements)	Platelet VASP assay with flow cytometry (EPICS XL-MCL flow cytometer)	For the VASP assay = Diagnostica Stago [Biocytex], Asnieres, France For the flow cytometer =	Blood was drawn in the catheterization laboratory, before coronary angiography	Citrated blood	ADP 10 µmol/L	Patients received 600 mg loading dose of clopidogrel and 250 mg aspirin ≥12 hours before coronary angiography	Samples were sent "immediately" to the hemostasis laboratory
	ADP-induced aggregation	Light-transmission aggregometry	PAP4 Aggregometer	Biodata Corporation, Wellcome, Paris, France	Blood was drawn in the catheterization laboratory, before coronary angiography	Citrated blood	ADP 10 µmol/L	Patients received 600 mg loading dose of clopidogrel and 250 mg aspirin ≥12 hours before coronary angiography	Samples were sent "immediately" to the hemostasis laboratory

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
	ADP-induced P-selectin expression	P-selectin expression using flow cytometry with or without ADP	EPICS XL-MCL flow cytometer	For the flow cytometer = Biodata Corporation, Wellcome, Paris, France	Blood was drawn in the catheterization laboratory, before coronary angiography	Citrated blood	ADP 10 µmol/L final concentration	Patients received 600 mg loading dose of clopidogrel and 250 mg aspirin ≥12 hours before coronary angiography	Samples were sent "immediately" to the hemostasis laboratory
Frere, 2009{Frere, 2009 117 /id} 19496924 France Part of larger observational study	VASP phosphorylation assay	VASP phosphorylation assay by flow cytometry	NR	NR	Samples for platelet aggregation testing were obtained after the administration of 600 mg clopidogrel loading dose.	NR	NR (presumably ADP as in other publications from the same group)	NR	NR
	ADP-induced platelet aggregation	NR	NR	NR	Samples for platelet aggregation testing were obtained after the administration of 600 mg clopidogrel loading dose.	NR	ADP 10 µM	NR	NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Bonello-Palot{Bonello-Palot, 2009 107 /id} 2009 19932784 France NR	VASP phosphorylation	VASP phosphorylation	platelet VASP kits	Diagnostica Stago, Asnières, France	VASP analysis done within 24 hours of blood collection	3.8% trisodium citrate	prostaglandin E1, and ADP is adenosine diphosphate	>0.25 to <0.5 days (>6 to < 12 hours); Clopidogrel came first	<1 day
Harmsze 2010{Harmsze, 2010 102 /id} 19934793 Netherlands NR	LTA	light transmission aggregometry	APACT 4004 four-channel light transmission aggregometer	LABiTec, Ahrensburg, Germany	Before the coronary stent implantation procedure & heparinization	3.2% citrate	5 and 20 µmol/l ADP	1 day; clopidogrel came first	0.083 days (2 hours)
	VerifyNow	light transmission aggregometry	VerifyNow P2Y12 test cartridge system	Accumetrics, San Diego, CA, USA (company name obtained from Ref 21)	Before the coronary stent implantation procedure & heparinization	3.2% citrate	ADP and PGE1	1 day; clopidogrel came first	0.083 days (2 hours)

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Trenk 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	4-channel Bio/ Data PAP4 aggregometer	light transmission aggregometry	4-channel Bio/ Data PAP4 aggregometer	Mölab, Langenfeld, Germany,	At baseline beforeclopidogrel and at cardiac catheterization	3.8% sodium-citrate	ADP at final concentrations of 5 and 20 µmol/l.	1 day and clopidogrel came first	1 hour

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Tantry 2010{Tantry, 2010 39 /id} 21079055 Multicountry - North America and Europe Genetic substtudy of ONSET/OFFSET and RESPOND	NR	light transmittance aggregometry	Chronolog Optical Aggregometer (Model 490-4D)	NR	Blood was collected from the antecubital vein. After discarding the first 2 to 3 mL of free-flowing blood, the tubes were filled to capacity and gently inverted 3 to 5 times to ensure complete mixing of the anticoagulant.	3.2% trisodium citrate	5 and 20 mcmol/L ADP	platelet function measurements performed at predose, 8 hours after the loading dose on day 1, and 8 hours after the last maintenance dose	NR
	NR	VASP	VASP-FCM kit	Biocytex, Inc; Marseille, France		3.2% trisodium citrate	NR		NR
	VerifyNow	NR	NR	NR		3.2% sodium citrate	NR		NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Hochholzer, 2010{Hochholzer, 2010 76 /id} 20510210 Germany EXCELSIOR	Platelet function assay	Light transmission aggregometry	4-channel Bio/Data PAP4 aggregometer	Mölab, Langenfeld, Germany	Blood samples for platelet function testing were drawn before discharge at day 1 after loading with clopidogrel, 2 to 4 h after intake of the first maintenance dose (in the vast majority of patients between 16 and 24 h after loading dose).	Samples were drawn into tubes containing 3.8% sodium-citrate (Sarstedt, Nuembrecht, Germany)	ADP	Blood samples for platelet function testing were drawn before discharge at day 1 after loading with clopidogrel, 2 to 4 h after intake of the first maintenance dose (in the vast majority of patients between 16 and 24 h after loading dose).	Within 1 hour

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Jeong 2010{Jeong, 2010 70 /id} 20650435 Korea ACCEL-DOUBLE	Platelet function assays	Light transmittance aggregometry	an AggRAM aggregometer	Helena Laboratories Corporation, Beaumont, Texas	Within 2 to 4 h after the last intake of regimen, blood samples were collected using the double syringe technique, and the first 2 to 4 ml of blood was discarded to avoid the bias of spontaneous platelet activation. Platelet reactivity was simultaneously measured <1 h after venipuncture by light transmittance aggregometry and the VerifyNow P2Y12 assay	containing 0.5 ml of 3.2% sodium citrate	ADP	With 2-4 hours	<60 mins

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
	Platelet function assays	VerifyNow P2Y12 assay	Ultegra rapid platelet function assay,	Accumetrics Inc., San Diego, California	Blood was drawn into a Greiner Bio-One Vacuette tube	3.2% citrate	ADP	With 2-4 hours	NR
Barker, 2010{Barker, 2010 52 /id} 20965456 USA NR	Platelet function measurement	Verify-Now P2Y12 assay	Verify-Now P2Y12 assay	Accumetrics, Inc., San Diego, California	NR	NR	NR	NR	NR
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	VASP index	Platelet VASP kits (Diagnostica Stago, Asnières, France)	Analyses were performed on an EPICS XL-MCL flow cytometer	Beckman Coultronics, Margency, France	Blood samples for VASP index analysis were drawn by atraumatic venipuncture of the antecubital vein between 6 and 12 h after each clopidogrel LD.	blood was collected into a Vacutainer containing 3.8% trisodium citrate and filled to capacity. .	ADP 10 umol/l	Blood samples for VASP index analysis were drawn by atraumatic venipuncture of the antecubital vein between 6 and 12 h after each clopidogrel LD.	VASP index phosphorylation analysis was performed within 24 h of blood collection.

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Gurbel 2011{Gurbel, 2011 24 /id} 21392617 USA NR	Platelet aggregation	Aggregation was assessed using a Chronolog Lumi-Aggregometer	Chronolog Lumi-Aggregometer (Model 490-4D) with the AGGRO/LINK control software	Chronolog, Havertown, PA	Blood samples were collected by venipuncture in vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ)	3.8% trisodium citrate.	ADP 5 and 20 uM	NR	Within 2 hours
Hwang 2011{Hwang, 2011 35 /id} 21075428 South Korea NR	LTA	light transmittance aggregometry (LTA)	AggRAM aggregometer	Helena Laboratories Corp., Beaumont, Texas, USA	blood samples were drawn into Vacutainer tubes (Becton-Dickinson, San Jose, CA, USA)	containing 0.5 mL of sodium citrate 3.2%	ADP 5 and 20 um	All patients received a 300-mg loading dose (LD) of clopidogrel and aspirin at least 12 hours before PCI, followed by 200 mg/day maintenance dose of aspirin and 75 mg/day of clopidogrel thereafter. Immediately after insertion of the arterial sheath in the catheterization laboratory, blood samples were obtained.	Within 60 minutes

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
		VerifyNow P2Y12 assay	Ultegra rapid platelet function assay; Accumetrics Inc.,	San Diego, CA, USA	whole-blood was drawn into vacutainer tube (Greiner Bio-One, Frickenhausen, Germany).	a Greiner Bio-One 3.2% citrate vacutainer tube	ADP 20um		NR
Kang, 2010{Kang, 2010 40 /id} 20724801 Korea NR	Light transmittance aggregometry (LTA)	Light transmittance aggregometry (LTA)	AggRAM aggregometer	(Helena Laboratories Corp., Beaumont, Texas, USA)	Blood samples were drawn into Vacutainer tubes. Blood samples were obtained Immediately after insertion of the arterial sheath in the catheterization lab.	with 0.5ml sodium citrate 3.2%	5 or 20 um ADP	A 300-mg LD of clopidogrel and aspirin was administrated 12 to 24 hours before scheduled PCI, followed by 200 mg maintenance dose of aspirin and 75 mg/day clopidogrel thereafter. Blood samples were obtained Immediately after insertion of the arterial sheath in the catheterization lab.	Within 2 hours
	Verifynow P2Y12 assay	NR	VerifyNow P2Y12 assay (Ultegrarapid platelet function assay, Accumetrics Inc., San Diego, CA, USA)	NR	NR	NR	20um ADP	NR	NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Liu 2010{Liu, 2010 38 /id} 21163112 China NR	Light transmittance aggregometry	Chrono-Log Lume-Aggregometer (model 700) and the Aggro/Link software package	Chrono-Log Lume-Aggregometer (model 700)	Chrono-Log Corporation, Havertown, Pennsylvania, USA	Blood samples were collected in evacuated container tubes which were filled to capacity and then inverted 3 to 5 times for gentle mixing.	3.8% sodium citrate	5 umol/L ADP	Blood sample were collected before clopidogrel administration, and at least 24 hours after the first 300 mg clopidogrel dose to make sure maximum platelet inhibition has been achieved.	NR
Maeda, 2010{Maeda, 2011 30 /id} 21178986 Japan NR	Residual platelet aggregation	a light-transmittance aggregometer	multichannel platelet-aggregation analyzer model PAT-2M	Mebanix, Tokyo, Japan	Venous blood samples were collected from each participant between 12:00 and 15:00	3.13% sodium citrate	5 or 20 umol/l ADP	NR	NR
Yamamoto 2011{Yamamoto, 2011 25 /id} 21168310 Japan NR	Platelet aggregation	Light transmission aggregometer	MCM HEMA TRACER 313; PAM12C	LMS inc., Japan	platelet aggregation test was done in 69 patients at <7 days and 54 patients at >7 days.	0.38% sodium citrate	20 uMol/L ADP	Test was performed at least 24 h after clopidogrel loading.	NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Park 2011{Park, 2011 21 /id} 21345843 Korea CILON-T	VerifyNow assay	The VerifyNow assay	The VerifyNow assay	Accumetrics, Inc., San Diego, California, USA	NR	NR	ADP	NR	NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Sibbing, 2010{Sibbing, 2010 48 /id} 20492469 Germany XX	Multiple electrode platelet aggregometry (MEA)	Multiplate analyzer	NR	(Dynabyte)	For all patients, peripheral venous blood samples were drawn directly at hospital admission, after the daily dose of 75 mg of clopidogrel had been taken and before any in-hospital drug administration, with a loose tourniquet through a short venous catheter inserted into a forearm vein.	EDTA	ADP	peripheral venous blood samples were drawn directly at hospital admission, after the daily dose of 75 mg of clopidogrel had been taken and before any in-hospital drug administration.	NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Bouman 2011{Bouman, 2011 9 /id} 21628721 Netherlands Genetic substudy of the Popular study	NR	LTA	IMPACT-R	Matis Medical Inc, Beersel, Belgium	Whole blood samples were drawn from the femoral or radial artery sheath	3.2% citrate	5 and 20 mcmol/l ADP (n = 1005 and n=1006, respectively)	NR	2 hours after blood collection.
	NR	NR	PlateletWorks assay	Helena Laboratories, Beaumont, Texas		K3-EDTA or diphenyl alanyl-L-prolyl-L-arginine chloromethyl ketone (PPACK [50 µmol/L])	N=511		
	NR	NR	VerifyNow P2Y12 assay	Accumetrics, San Diego, CA		Greiner tubes	N=1010		
Campo 2011{Campo, 2011 13 /id} 21679849 Italy NR	VerifyNow P2Y12	NR	NR	Accumetrics, San Diego CA	NR	NR	NR	Blood samples were drawn at baseline (just before PCI and administration of interventional therapy) and at 1 and 6 months after PCI. Clopidogrel dosing came first (at least 12 hours before PCI)	NR

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Fernando 2011{Fernando, 2011 233 /id} 21696537 Australia NR	NR	Light transmittance aggregometry (LTA)	AggRAM light transmittance aggregometer	Helena laboratories, Melbourne, Australia	Platelet-rich and platelet-poor plasma were obtained by centrifuging whole blood	3 .8% citrate	20 mcg ADP over 10 min	NR except noted to be at baseline, after treatment (first or second period), and after washout	Within 30 min
	VerifyNow	Light transmittance	VerifyNow P2Y12 cartridge	Accumetrics , San Diego, CA	Whole blood	3.8% citrate	ADP	NR except noted to be at baseline, after treatment (first or second period), and after washout	Between 10 and 30 min after
Geisler 2008{Geisler, 2008 161 /id} 18781853 Germany NR	NR	Turbidometry	Chronolog Lumi aggregometer with Aggro-link software	NR	Blood samples were centrifuged at 1000 rpm for 10 min to obtain platelet-rich plasma and for another 10 minutes to recover platelet-poor plasma	3.8% citrate	20 mcmol/literADP	Platelet aggregation measured after first 600-mg dose of clopidogrel (at least 6 hours after)	RPA was measured at 5 min after ADP added (median, 21 hours; IQR, 5.1-285.0)

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Gladding 2008{Gladding, 2008 149 /id} 19463375 New Zealand PRINC (Plavix Response in Coronary Intervention) Trial	VerifyNow	Agglutination plus light transmittance	point-of-care rapid platelet function analyzer (RPFA) and its P2Y12 cartridge	Accumetrics Ltd., San Diego, California	Arterial blood was sampled through a 6-F femoral sheath and transferred immediately; collection tubes were inverted 4 times to mix the anticoagulant and left at ambient temperature (24°C)	3.2% citrate	ADP, 20 mmol/l	Platelet function was tested at baseline, 2, 4, and 7 h from the first clopidogrel loading dose; and at 7 days.	10 min

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Gurbel 2010{Gurbel, 2010 91 /id} 19817997 USA NR	NR	LTA	Chronolog Optical Aggregometer (Model 490-4D) with Aggrolink software ( )	Chronolog, Havertown, PA	Blood was collected from the antecubital vein with an 18-gauge needle.	3.2% trisodium citrate	5 and 20 mcM ADP, proprietary anticoag ulant CT 921- 78 (f actor Xa Inhibitor), or 10 mcM ADP and 4 mcg/ml collagen	At screening (before dosing) and at 12–16 h after the previous day's clopidogrel dose; then at 4 h , 6 h, 24 h, and 7 –10 days after dosing with elinogrel	NR
	NR	VASP	Platelet VASP; Diagnostica Stago	Biocytex, Asnieres, France		NR	NR		
	TEG PlateletMapping	Thrombelastography	TEG Hemostasis Analyzer with PlateletMapping assay	Haemoscope Corporation, Niles, IL		Lithium heparin	ADP		
	VerifyNow	Turbidimetric-based optical detection	NR	NR		.2% sodium citrate	NR		

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Kim 2011{Kim, 2011 18 /id} 21511217 South Korea CCELAMI2C19	NR	Light transmittance aggregometry	AggRAM Aggregometer	Helena Laboratories Corp., Beaumont, Texas	Blood samples were collected using the double-syringe technique, in which the first 2 to 4 ml of blood were discarded to avoid spontaneous platelet activation.	0.5 ml of 3.2% sodium citrate	5 and 20 mcmol/l ADP	Platelet reactivity measured pre-discharge (either at least 3 days after PCI in patients not treated with tirofiban or at least 5 days after procedure in patients treated with tirofiban) and at 30 day followup (At 30-day follow-up, peripheral venous blood was drawn from an antecubital vein within 2 to 4 h after the last intake of clopidogrel dose.)	within 2 h
	VerifyNow P2Y12 assay	VerifyNow P2Y12 assay	NR	Accumetrics Inc, San Diego, CA	SAME AS ABOVE	3.2% citrate	20 mcmol/l ADP	SAME AS ABOVE	SAME AS ABOVE
Lee 2011{Lee, 2011 4 /id} 21786436 South Korea NR	VerifyNow P2Y12 assay	VerifyNow P2Y12 assay	P2Y12 assay	Accumetrics, San Diego, CA	Venous whole blood	NR	NR		within 10 to 15 min

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Malek 2008{Malek, 2008 167 /id} 18577829 Poland NR	NR	Closure time (CADP-CT)	PFA-100	Dade Behring, German	blood from the peripheral vein. Results are reported as the closure time (CADP-CT) in seconds. The test stops automatically after 300 s, which is considered a maximal response to the agonist	3.2% buffered citrate	Collagen, ADP	after a median of 6 days of antiplatelet treatment (interquartile range (IQR) 5–7)	analyzed within 2 h of sampling
Pettersen 2011{Pettersen, 2011 228 /id} 21426546 Norway Aspirin and Clopidogrel non-responsiveness clinical Endpoint Trial (ASCET)	NR	VASP	PLT VASP/P2Y12 assay	Biocytex, France	Blood samples drawn between 8 and 10:30 am in a fasting condition	Citrated blood (0.129 mM in dilution 1:10)	NR	1 month after randomization, 24 hours after the last intake of medication	within 48 hours

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
	VerifyNow	LTA	NR	Accumetrics, San Diego, CA		Vacuette tubes (Grüner Bio-One, Austria, 0.109 mM in dilution 1: 10)	ADP		

Author Year PMID Country Study name	Test name	Device category (e.g., light transmission aggregometry, turbidoaggregometry)	Device name and model information	Manufacture, location	Sample collection and procurement	Anticoagulant used	Agonist used*	Interval between clopidogrel dose and blood sampling [in days] and which came first	Interval between sampling and testing [in days]
Sibbing 2011{Sibbing, 2011 2 /id} 21527445 Germany NR	NR	Multiple electrode aggregometry (MEA)	Multiplate analyzer	NR	Blood for genomic DNA extraction and genotyping was taken from the arterial sheath of all patients directly prior to PCI. Whole blood was obtained from the arterial sheath of all patients directly before PCI and prior to the administration of any anticoagulant/antithrombotic treatment in the cath lab.	lepirudin (25 mg/mL, Refludan, Dynabyte, Munich, Germany)	ADP (6.4 mcM)	NR	NR

Appendix Table D15: Risk of Bias of Individual Studies

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Collet, 2009 19108880 France AFIJI (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) registry	YES (explicitly states consecutive patients were enrolled)	YES	NO [the study included person time during which patients were not exposed to clopidogrel – and the drug was started a subsequent hospitalization; 16%]	LOW	LOW (all patients younger than 45 yrs)	NR	NO (no rationale for the grouping of genotypes)	HIGH	LOW	YES	YES (events adjudicate by 2 cardiologists blind to the genetic analysis)	LOW	LOW	YES (mean FU = 2.84 yr)	YES	YES	YES	LOW
Fontana, 2008{Fontana, 2008 182 /id} 17681590 Switzerland NR	YES	YES	YES	LOW	LOW	YES (genotype technician was blind to phenotypic status)	NO (based on observed sample size)	HIGH	HIGH (PCR-RFLP assay home-brew)	NO (laboratory measurements only)	NO	HIGH	YES	NO (median = 19 d)	YES	YES	YES	LOW
Giusti, 2007{Giusti, 2007 190 /id} 18004210 Italy	YES	YES	YES	LOW	LOW	NR	NO (multiple genetic models	HIGH	HIGH	NO (lab measurements	NR	HIGH	HIGH	NO (24 h; 6 d for patients receiving	YES	YES	YES	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
NR							tested)			only)				IIb/IIIa inhibitors)				
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	YES	YES	YES	LOW	LOW	NR	NO	HIGH	HIGH	YES	YES (states that event adjudication was blind to laboratory results)	LOW	LOW	NO (6 mo)	YES	YES	YES	LOW
Gladding, 2009{Gladding, 2009 248 /id} 19926050 New Zealand NR	NR	YES	YES	LOW	LOW	NO	NO	HIGH	LOW	NO	NR	UNCLEAR	HIGH	NO	YES	YES	YES	LOW
Jinnai, 2009{Jinnai, 2009 120 /id} 19531897 Japan Partly industry funded	NO	YES	NO	HIGH	LOW	NR	NO	HIGH	LOW	YES (for stent thrombosis)	NR	UNCLEAR	UNCLEAR (because the ascertainment method for stent thromboses was not reported)	NO	YES	YES	YES (2/25 = 8%)	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Mega, 2009{Mega, 2009 141 /id} 19106084 Multinational Genetics substudy of TRITON-TIMI 38 [Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction]	NO (sample selected from those participating in a trial)	YES	YES	LOW	LOW	NR	YES (literature based)	UNCLEAR	LOW	YES	NR (blinding was to treatment assignment, not genotype status)	UNCLEAR	LOW	YES (upto 15 mo)	YES	YES	YES	LOW
Shuldiner, 2009{Shuldiner, 2009 116 /id} 19706858 USA Sinai Hospital of Baltimore Study	NR	YES	YES	LOW	LOW	NR	No	HIGH	LOW	YES	YES	LOW	LOW (composite outcome only)	YES (12 month for time-to-event analyses)	YES	YES	YES	LOW
Sibbing, 2009{Sibbing, 2009 133 /id} 19193675 Germany NR	NO	YES	NO [convenience sample of 46% of the	HIGH	LOW	NR	YES	UNCLEAR	LOW	YES	YES (explicitly states blinding of outcome	LOW	LOW	NO (30d)	YES	YES	YES	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
			patients in 4 ISAR trials + genotyping material not available from all]								assessor to genotype data)							
Sibbing, 2010{Sibbing, 2010 95 /id} 20083681 Germany Part of a prospective study of the Multiplate analyzer	YES	YES	YES	LOW	LOW	YES (blind genotyping)	NO (analyses performed with multiple genetic models)	HIGH	LOW	YES (several clinical endpoints)	YES (blind outcome adjudication)	LOW	LOW	NO (all outcome ascertained at 30 d)	YES	YES	YES	LOW
Varenhorst, 2009{Varenhorst, 2009 122 /id} 19429918 Sweden Genetic sub-study	NO	YES	NO (11% of eligible patients refused to provide Consec o)	HIGH	LOW	NR (unclear when genetic testing was performed)	YES (grouping was based on literature)	UNCLEAR	LOW	NO	NR (unclear if blinding was used for the test results)	HIGH	HIGH	NO [max followup was 29 d]	YES	YES	YES [1 patients was classified as "uncertain functional status"]	LOW
Frere, 2008{Frere, 2008 176 /id} 18394438 France NONE	YES	YES	YES	LOW	LOW	NR	NO	HIGH	HIGH	NO	NR	YES	HIGH	NO	NO [not for all assays; i.e. there was incomplete	YES [there was no differential verification]	NO [at least for some of the assays]	HIGH

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
															verification]			
Frere, 2009{Frere, 2009 117 /id} 19496924 France Part of larger observational study	NO	YES	NR (appears that patients were selected from a previous study but criteria NR)	UNCLEAR	UNCLEAR	NR	NO	HIGH	UNCLEAR (genotyping assay not reported)	NO (only lab measurements)	NR	HIGH	HIGH	NO (details about timing poorly reported)	YES	YES	YES	LOW
Bonello-Palot{Bonello-Palot, 2009 107 /id} 2009 19932784 France NR	NO	YES	YES	LOW	LOW	NR	YES	UNCLEAR	LOW	NO	NR	HIGH	HIGH	NO	YES	YES	YES	LOW
Harmsze 2010{Harmsze, 2010 102 /id} 19934793 Netherlands NR	YES	YES	YES	LOW	LOW	NR	YES	UNCLEAR	LOW	NO	NR	HIGH	HIGH	NO	YES	YES	YES	LOW
Trenk 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel - Induced Platelet Inhibition	NO (included all patients in the prospective EXCELSIOR cohort that had genoty	YES	NO	HIGH	LOW	YES	YES	LOW	LOW	YES	YES	LOW	LOW	YES; 12 months	YES	YES	YES	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
During Elective Stent Implantation on Clinical Event Rate)	pic information)																	
Tantry 2010{Tantry, 2010 39 /id} 21079055 Multicountry - North America and Europe Genetic substudy of ONSET/OFFSET and RESPOND	NO [but patients are volunteers from 2 RCTs]	YES	YES	LOW	LOW	NR	NO [not explicitly based on independent information]	HIGH	LOW	NO [lab measurements]	NR	HIGH	HIGH	NO [2-6 weeks]	YES	YES	YES	LOW
Wallentin, 2010{Wallentin, 2010 56 /id} 20801498 Multiple countries (43 countries in North America, South America, Europe, Asia, Australia) PLATO	NO [substudy, voluntary provision of samples]	YES	YES	LOW	LOW	NR [study was "double-blind, double-dummy" but genetic testing done only in substudy and NR	NO	HIGH	LOW	YES	NR [study was "double-blind, double-dummy" but genetic testing done only in substudy and NR there]	UNCLEAR	LOW	YES [12months]	YES	YES	YES	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
						there]												
Hochholzer, 2010{Hochholzer, 2010 76 /id} 20510210 Germany EXCELSIOR	NO	YES	YES	LOW	LOW	NR	YES	UNCLEAR	LOW	NO	NR	HIGH	HIGH	NO [6months]	YES	YES	YES	LOW
Jeong 2010{Jeong, 2010 70 /id} 20650435 Korea NR	NO	YES	YES	LOW	LOW	NR	NO	HIGH	HIGH	NO	NR	HIGH	HIGH	NO [1 month]	YES	YES	YES	LOW
Barker, 2010{Barker, 2010 52 /id} 20965456 USA NR	NO	YES	NO	UNCLEAR	LOW	NR	YES	UNCLEAR	LOW	NO	NR	HIGH	HIGH	NO	YES	YES	YES	LOW
Bonello, 2010{Bonello, 2010 45 /id} 20708365 France NR	NR	YES	YES	LOW	LOW	NR	NO	UNCLEAR	HIGH	YES	NR	UNCLEAR	LOW	NO	YES	YES	YES	LOW
Gurbel 2011{Gurbel, 2011 24 /id} 21392617 USA NR	YES	YES	No [1 patient with CYP2C19*3 excluded]	LOW	LOW	NR	YES	UNCLEAR	LOW	NO	NR	HIGH	HIGH	NR	YES	YES	YES	LOW
Hwang 2011{Hwang, 2011 35 /id} 21075428	YES	YES	NR	LOW	LOW	NR	YES	UNCLEAR	LOW	NO	NR	HIGH	HIGH	NO	YES	YES	YES	HIGH

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Souh Korea NR																		
Kang, 2010{Kang, 2010 40 /id} 20724801 Korea NR	YES	YES	No[19.1% excluded]	LOW	LOW	NR	YES	UNCLEAR	LOW	NO	NR	HIGH	HIGH	No [1 month]	YES	YES	NO [176 of 215 included;19.1% excluded]	HIGH
Liu 2010{Liu, 2010 38 /id} 21163112 China NR	YES	YES	NR	LOW	LOW	NR	NR	NR	HIGH	NO	NR	HIGH	HIGH	YES [12 months]	YES	YES	YES	LOW
Maeda, 2010{Maeda, 2011 30 /id} 21178986 Japan NR	NR	YES	YES	LOW	LOW	NR	NR	UNCLEAR	LOW	NO	NR	HIGH	HIGH	NO	YES	YES	YES	LOW
Malek, 2010{Malek, 2010 43 /id} 20924183 Poland NR	YES	YES	YES	LOW	LOW	NR	NR	UNCLEAR	LOW	YES	NR	UNCLEAR	LOW	YES [4 years]	YES	YES	YES	LOW
Simon 2011{Simon, 2011 27 /id} 21262992 France NR	NO	YES	YES	LOW	LOW	NR	NR	NR	NR	YES	NR	NR	LOW	NR	YES	YES	NO	NR
Yamamoto 2011{Yamamoto, 2011 25 /id} 21168310 Japan NR	YES	YES	YES	LOW	LOW	NR	YES	UNCLEAR	HIGH	YES	NR	UNCLEAR	LOW	YES [1 year]	YES	YES	NO [20%]	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Park 2011{Park, 2011 21 /id} 21345843 Korea CILON-T	YES	YES	YES	LOW	LOW	NR	YES	UNCLEAR	LOW	NO	NR	HIGH	HIGH	NO [6 months]	YES	YES	YES	LOW
Tiroch, 2010{Tiroch, 2010 62 /id} 20826260 Germany NR	YES	YES	YES	LOW	LOW	NR	NR	UNCLEAR	LOW	YES	NR	UNCLEAR	LOW	YES [1 year]	YES	YES	YES	LOW
Sorich, 2010{Sorich, 2010 49 /id} 20492467 707 sites in 30 countries Substudy of TRITON-TIMI 38	YES	YES	YES	LOW	LOW	NR	NR	UNCLEAR	LOW	YES	NR	UNCLEAR	LOW	YES [15 months]	YES	YES	YES	LOW
Sibbing, 2010{Sibbing, 2010 48 /id} 20492469 Germany	YES	YES	YES	LOW	LOW	YES	NO	HIGH	LOW	NO	YES	HIGH	HIGH	NO	YES	YES	YES	LOW
Sawada, 2010{Sawada, 2010 36 /id} 21099121 Japan NR	NR	YES	NR [367 patients at start, end up 100]	UNCLEAR	LOW	NR	NR	UNCLEAR	LOW	YES	NR	UNCLEAR	LOW	NO	YES	YES	YES	LOW
Pare, 2010{Pare, 2010 46 /id} 20979470 Multiple countries CURE and ACTIVE	YES	YES	YES	LOW	LOW	NR	NR	UNCLEAR	UNCLEAR	YES	NR	UNCLEAR	LOW	Yes/no[3-12 months for CURE; 3.6 years for ACTIVE]	YES	YES	YES	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Mega, 2010{Mega, 2010 57 /id} 20801494 707 sites in 30 countries TRITON-TIMI 38	YES	YES	YES	LOW	LOW	NR	NR	UNCLEAR	LOW	YES	NR	UNCLEAR	LOW	YES [15 months]	YES	YES	YES	LOW
Bouman 2011{Bouman, 2011 9 /id} 21628721 Netherlands Genetic substudy of the Popular study	yes	Yes	NO [but 45 (4%) of patients without DNA samples were excluded	Low	Low	NR	NA (no grouping used)	Unclear	UNCLEAR [manufacturer not reported]	NO [lab measurements]	NR	High	High	NR	Yes	Yes	NO	UNCLEAR
Campo 2011{Campo, 2011 185 /id} 21679849 Italy NR	Yes	Yes	Yes	Low	Low	NR	Yes	Low	Low	Yes	NR	Unclear	Low	Yes 12 mo	Yes	Yes	Yes	LOW
Fernando 2011{Fernando, 2011 233 /id} 21696537 Australia NR	NO [but study is a randomized crossover trial]	Yes	Yes	Low	Low	NR	NO	High	Low	No	NR	High	High	No	Yes	Yes	Yes 2/31<10%	Low
Geisler 2008{Geisler, 2008 161 /id} 18781853 Germany NR	Yes	Yes	Yes	Low	Low	Yes	No	High	Low	No	NR	High	High	No max 285 hours	Yes	Yes	Yes	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Gladding 2008{Gladding, 2008 149 /id} 19463375 New Zealand PRINC (Plavix Response in Coronary Intervention) Trial	Yes	Yes	Yes	Low	Low	NR	Yes	Unclear	Low	No	NR	High	Low	No 7 days	Yes	Yes	Yes	LOW
Gurbel 2010{Gurbel, 2010 91 /id} 19817997 USA NR	No	Yes	Yes	Low	Low	NR	Yes	Unclear	Low	No	NR	High	High	No 97-10 days)	Yes	Yes	Yes	LOW
Harmsze 2010{Harmsze, 2010 6 /id} 20833683 Netherlands NR	Yes	No	YES	LOW	LOW	NR	NA	Unclear	UNCLEAR [manufacturer not named]	Yes	NR	Unclear	Low	Yes	Yes	Yes	Yes	LOW
Kim 2011{Kim, 2011 18 /id} 21511217 South korea CCELAMI2C19	Yes	Yes	Yes	LOW	LOW	NR	NO	High	Low	No	NR	High	High	No (30 days)	Yes	Yes	NO [14 patients (11.4 %) excluded for lack of DNA sample or poor compliance]	HIGH

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Lee 2011{Lee, 2011 4 /id} 21786436 South Korea NR	No	Yes	Yes	LOW	LOW	NR	No	High	Low	No	NR	High	High	No	YES	YES	YES	LOW
Malek 2008{Malek, 2008 167 /id} 18577829 Poland NR	NR	Yes	Yes	LOW	LOW	NR	No	High	Low	Yes	NR	Unclear	Low	Yes (12 mo)	YES	YES	YES	LOW
Pettersen 2011{Pettersen, 2011 228 /id} 21426546 Norway Aspirin and Clopidogrel non-responsiveness clinical Endpoint Trial (ASCET)	Yes	Yes	Yes	LOW	LOW	NR	Yes	Unclear	Low	No	NR	High	High	NR	Yes	Yes	Yes	LOW
Sibbing 2011{Sibbing, 2011 2 /id} 21527445 Germany NR	NO [but from larger consecutive samples]	NO [it was in one group—the main, PCI cohort, but not in the second part of the study]	Yes	High	LOW	NR	NA	UNCLEAR	Low	YES	NR	Low	Low	NR	YES	YES	YES	LOW

Author, year UID Country Study name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Simon 2009{Simon, 2009 142 /id} 19106083 France FAST-MI	yes	yes	YES [but only 66% of FAST-MI patients had genetic data]	low	LOW	NR	No	high	low	YES	YES	low	low	YES	YES	YES	YES	LOW
Hwang 2010{Hwang, 2010 55 /id} 20823393 Korea ACCEL	no	yes	no	high	low	yes	yes	low	low	no	NR	high	high	no	yes	yes	no	unclear

RISK OF BIAS AND APPLICABILITY ASSESSMENT KEY

1. Consecutive or random sample of patients enrolled.
2. Case-control design avoided
3. Study avoided inappropriate exclusions

Risk of bias: could the selection of patients have introduced bias (if ≥2 of the above 3 questions are YES, give LOW here; if ≥2 are NO give HIGH; otherwise, give UNCLEAR)
Applicability: Concerns that the included patients do not match the review question?

4. Index test results interpreted without knowledge of results of reference standard?
5. If a threshold used, was it prespecified?

Risk of bias: Could the conduct or interpretation of the index test have introduced bias? (if both of the above questions are YES, give LOW here; if one or both are NO, give HIGH; otherwise, give UNCLEAR)
Applicability: Concerns that the index test, its conduct, or its interpretation differ from the review question?

6. Reference standard likely to correctly classify the target condition?
7. Reference standard results interpreted without knowledge of index test results?

Risk of bias: Could the reference standard, its conduct, or its interpretation have introduced bias? (If both of the above questions are YES, give LOW here; if one or both are NO, give HIGH; otherwise, give UNCLEAR)
Applicability: Are there concerns that the target condition as defined by the reference standard does not match the review question?

8. Appropriate interval between index test and reference standard?
9. All patients received a reference standard?
10. All patients received the same reference standard?
11. Were all patients included in the analysis?

Risk of bias: Could the patient flow have introduced bias? (If ≥3 of the above 4 questions are YES, give LOW here; if ≥2 are NO give HIGH; otherwise, give UNCLEAR)

Appendix E. Appendix Figures and Tables for Key Question 2

Key Question 2a - Figures

Appendix Figure E1: Study Quality and Completeness of Reporting for Studies on the Analytic Validity of Assays for Measuring Platelet Reactivity

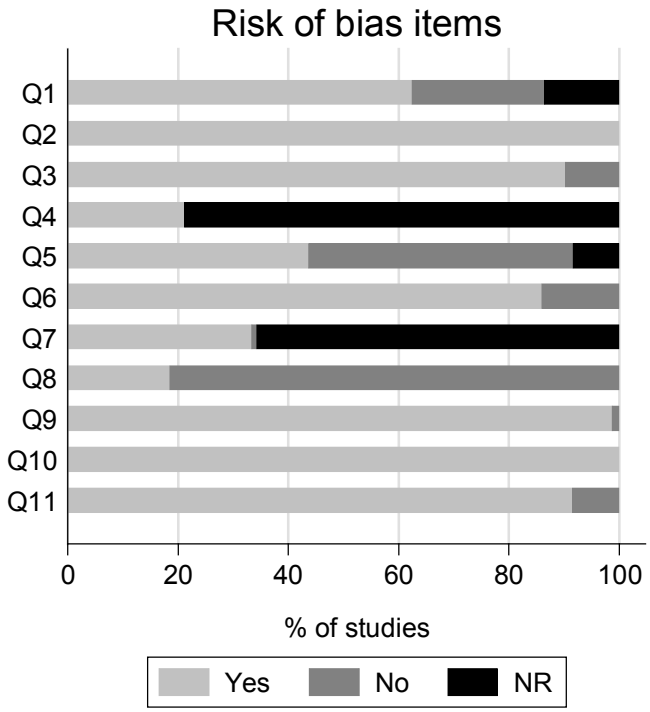
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Mobley, 2004 [14969622]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Van Werkum, 2006 [16938130]	YES	NR	NA	NR	NR	NA	NO	NO	NO	NO	NO
Frere, 2007 [17938809]	YES	NR	NA	NR	NR	NO	NO	NO	NR	NO	NO
Marcucci, 2007 [17938810]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Paniccia, 2007 [17723123]	YES	NR	NA	NR	NR	YES	NO	NO	YES	NO	NO
Collet, 2008 [18765393]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Jeong, 2008 [18617479]	NO	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Lordkipanidze, 2008 [18520610]	YES	NR	NA	NR	NR	NA	NO	NO	NO	NO	NO
Lordkipanidze, 2008 [18826988]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Schafer, 2008 [18841284]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Shenkman, 2008 [18155752]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Sibbing, 2008 [18217143]	YES	YES	NR	NR	NR	NO	NO	NO	YES	NO	NO
Godino, 2009 [19419580]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Gremmel, 2009 [19190818]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Lordkipanidze, 2009 [19840560]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Lordkipanidze, 2009 [19419755]	YES	NR	NA	NR	NR	NO	NO	NO	YES	NO	NO
Lordkipanidze, 2009 [19250657]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Michelson, 2009 [19435740]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	YES
Oestreich, 2009 [19318928]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Paniccia, 2009 [19461090]	YES	NR	NA	NR	NR	YES	NO	NO	YES	NO	NO
Smit, 2009 [19200163]	YES	NR	NA	NR	NR	NO	NO	NO	YES	NO	NO
Varenhorst, 2009 [19249429]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Aradi, 2010 [20642320]	YES	NR	YES	NR	NR	YES	NO	NO	NO	NO	NO
Cuisset, 2010 [20142119]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Kim, 2010 [20449634]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Madsen, 2010 [20224050]	YES	NR	NA	NR	NR	YES	NO	NO	YES	NO	NO
Paniccia, 2010 [20458439]	YES	NR	NA	NR	NR	YES	NO	NO	YES	NO	NO
Siller-Matula, 2010 [19943879]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Von Beckerath, 2010 [19823079]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Woo, 2010 [20890076]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Ko, 2011 [21315223]	YES	NR	NA	NR	NR	NA	NO	NO	NO	NO	NO
Koessler, 2011 [20873965]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Paniccia, 2011 [21192314]	YES	NR	NA	NR	NR	YES	NO	NO	YES	NO	NO
Pettersen, 2011 [21426546]	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO
Ren, 2011 [21518592]	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO

Each row corresponds to a study (listed with first author surname, publication year [PMID]). Each column refers to a question (Q) about quality and reporting (see list below for the complete questions and **Appendix Table E6** for

additional study-level information). “YES,” “NO,” and “NR”/“NA” (green, red, and yellow circles, respectively) refer to whether the question was addressed and the salient information reported in the study.
Q1=Was the execution of the assay described in sufficient detail to permit replication?
Q2=Were both positive and negative control samples tested?
Q3=Were negative control materials from the same type of tissue, and collected, stored, and processed in the same way that sample materials used clinically for testing will be?
Q4=Were the tests performed with positive or negative control samples being blinded to the testers?
Q5=Were the testing results interpreted with positive or negative control samples being blinded to the interpreters?
Q6=Were criteria for determining a testing result as positive, negative, indeterminate, or uninterpretable set a priori?
Q7=Was the limit of detection of the test reported?
Q8=Was the assay linearity range reported?
Q9=Was the reproducibility of the test when performed multiple times on a single specimen established?
Q10=Was the reproducibility of the test adequately established (across operators, instruments, reagent lots, different days of the week, different laboratories)?
Q11=Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?

Key Question 2b - Figures

Appendix Figure E2: Risk of Bias Assessment for Studies Contributing Data to Key Question 2b



Each row corresponds to risk of bias item (Q). The horizontal axis represents the percentage of studies adequately addressing a risk of bias item ("Yes"), inadequately addressing it ("No"), or not reporting information to allow assessment ("NR").

Q1=Was a consecutive or random sample of patients enrolled?
Q2=Was a case–control design avoided?
Q3=Did the study avoid inappropriate exclusions?
Q4=Was the index test interpreted without knowledge of the results of the reference standard test?
Q5=Was the cutoff for defining reactivity prespecified or based on external information?
Q6=Was the reference standard likely to correctly classify the target condition (was it a clinical outcome)?
Q7=Was the reference standard interpreted without knowledge of the index test results?
Q8=Was the interval between index test and reference standard application appropriate (followup >12 months)?
Q9=Did all patients receive a reference standard?
Q10=Did all patients received the same reference standard?
Q11=Were all patients included in the analysis?

Key Question 2a - Tables

Appendix Table E1: Descriptive characteristics of studies reporting analytic validity information

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Treatment preceding testing	Study design for the assessment of analytic validity	Sample size (measurements performed and included in analyses)	Results
Michelson 2009{Michelson, 2009 121 /id} USA 19435740	Patients with ACS scheduled for PCI in the TRITON-TIMI 38 trial. Patients who had received abciximab within 30 d, or tirofiban or eptifibatide within 7 d of testing, were excluded from the LTA component of the study.	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [BioCytex, Marseilles, France]; using flow cytometry [FACSCalibur, Becton Dickinson, San Jose, California] LTA (ADP 5 µmol/L and 20 µmol/L) [not reported]	Samples were collected at 3 timepoints: at baseline (pre-PCI, pre-study drug); 1-2 h post PCI(at least 1 h after dosing); and at 30 d post-PCI.	A loading dose of the study medication (1:1 randomization; prasugrel 60 mg or clopidogrel 300 mg) was administered between randomization and 1 h after leaving the catheterization laboratory. Pretreatment with the study drug was permitted for up to 24 h pre-PCI. Adjunctive medication was left at the discretion of the treating physician. After PCI patients received maintenance doses of prasugrel (10 mg) or clopidogrel (75 mg). Aspirin use was required (recommended 325-500 mg loading dose; 75-162 mg maintenance dose).	All 13 participating sites sent samples for the VASP phosphorylation assay; 3 pre-selected sites performed LTA on site.	125 using the VASP assay; of these 31 were also evaluated with LTA (both ADP concentrations). Measurements at baseline, 1-2 h post PCI, and 30 days (clopidogrel and prasugrel treated subjects) were analyzed together and observations were treated as independent.	Relative risk for identifying responders between VASP assay and MPA (20 µmol/L) = 5.25 (95% CI 2.34, 11.75)
Paniccia 2009{Paniccia, 2009 127 /id} Italy 19461090	Patients admitted to the coronary care of a single center unit for ACS; all patients underwent coronary angiography and PCI	Impedance aggregometry (ADP, 10 µmol/L and collagen, 2 g/mL) [Multiplate analyzer, Dynabyte, Munich, Germany] LTA (ADP, 10 µmol/L and collagen, 2 g/mL) [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany] High shear platelet function (collagen/ADP and collagen/epinephrine cartridges) [PFA-100, Dade-Behring, Marburg, Germany]	Samples were collected 24-48 h after PCI.	A loading dose of aspirin (500 mg IV) and oral clopidogrel (600 mg), followed by daily aspirin (325 mg) and clopidogrel (75 mg). During the procedure patients received UFH.	Measurements of samples with 3 techniques and different agonists; ROC analysis to identify optimal cut-offs for the Multiplate analyzer and PFA-100, using LTA as the reference method; 50 datapoints (10 measurements in each of 5 patient samples) for LTA	Multiplate analyzer and LTA (ADP as agonist): 297 Multiplate analyzer and LTA (collagen as agonist): 297 Multiplate analyzer and PFA-100 (ADP as agonist): 111 PFA-100 and LTA (collagen as agonist): 111	Agreement for residual platelet reactivity between the Multiplate analyzer and LTA (ADP as agonist): kappa = 0.74 (95% CI 0.64, 0.84); P<0.001 Agreement for residual platelet reactivity between the Multiplate analyzer and LTA (collagen as agonist): kappa = 0.68 (95% CI 0.58, 0.78); P<0.001 Agreement for residual platelet reactivity between the Multiplate analyzer and PFA-100 (ADP as agonist): kappa = 0.19; P = NS Agreement for residual platelet reactivity between the PFA-100 and LTA (collagen as agonist): kappa = 0.82 (95% CI 0.71, 0.93); P<0.001 Multiplate analyzer analytic test performance (using LTA as the reference test, ADP as the agonist): sensitivity = 0.78 (95% CI 0.68, 0.89); specificity = 0.95 (95% CI 0.92, 0.98); accuracy = 0.92 (95% CI NR); PPV = 0.80 (95% CI 0.69, 0.90); NPV = 0.95 (95% CI 0.92, 0.97) Multiplate analyzer analytic test performance (using LTA as the reference test, collagen as the agonist): sensitivity = 0.70 (95% CI 0.59, 0.81); specificity = 0.95 (95% CI 0.92, 0.98); accuracy = 0.89 (95% CI NR); PPV = 0.81 (95% CI 0.71, 0.90); NPV = 0.91 (95% CI 0.87, 0.94) ROC analysis for the Multiplate analyzer for detecting residual platelet reactivity on LTA (ADP as agonist): AUC = 0.93 (95% CI 0.89,

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Treatment preceding testing	Study design for the assessment of analytic validity	Sample size (measurements performed and included in analyses)	Results
							0.96); P<0.001 ROC analysis for the Multiplate analyzer for detecting residual platelet reactivity on LTA (collagen as agonist): AUC = 0.90 (95% CI 0.86, 0.94); P<0.001
Oestreich 2009{Oestreich, 2009 132 /id} USA 19318928	Patients with CAD from a single center outpatient cardiology clinic on dual antiplatelet therapy	LTA (ADP, 5 and 20 µM) [570VS aggregometer, Chrono-Log, Havertown, Pennsylvania] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, additional details NR]	At baseline; days 30 and 60 after enrollment	At baseline patients were receiving daily clopidogrel (75 mg) and aspirin (81-325 mg); clopidogrel was then increased to 150 mg for 30 d; after that, clopidogrel dosing at 75 mg was resumed for another 30 d (total duration of the study = 60 d)	Agreement between assays and different agonists, using predefined cut-offs for poor response	20 subjects measured 3 times (different timepoints)	Agreement between PRU and MPA (LTA, ADP 5 µM): kappa = 0.85 Agreement between PRU and MPA (LTA, ADP 20 µM): kappa = 0.46 Agreement between PRU and RPA (LTA, ADP 5 µM): kappa = 1.00 Agreement between PRU and RPA (LTA, ADP 20 µM): kappa = 0.30 Agreement between MPA (LTA, ADP 5 µM) and MPA (LTA, 20 µM): kappa = 0.62 Agreement between MPA (LTA, ADP 5 µM) and RPA (LTA, 5 µM): kappa = 0.85 Agreement between MPA (LTA, ADP 5 µM) and RPA (LTA, 20 µM): kappa = 0.43 Agreement between MPA (LTA, ADP 20 µM) and RPA (LTA, 5 µM): kappa = 0.46 Agreement between MPA (LTA, ADP 20 µM) and RPA (LTA, 20 µM): kappa = 0.33 Agreement between RPA (LTA, ADP 5 µM) and RPA (LTA, 20 µM): kappa = 0.30
Marcucci 2007{Marcucci, 2007 192 /id} Italy 17938810	Consecutive patients with STE MI admitted to a single center coronary care unit	LTA (ADP, 2 and 10 µM) [APACT 4 aggregometer, Helena Laboratories Italia s.p.a., Milan, Italy]	12-15 h after PCI for patients receiving aspirin + clopidogrel; 24 h after the infusion of abciximab for patients receiving aspirin + clopidogrel + IIb/IIIa inhibitor	All patients underwent angiography and primary PCI; 200 patients received aspirin (500 mg loading dose; 100 mg maintenance) + clopidogrel (300 mg loading dose; 75 mg maintenance) and 167 received aspirin (500 mg loading dose; 100 mg maintenance) + clopidogrel (300 mg loading dose; 75 mg maintenance) + IIb/IIIa inhibitor (abciximab bolus 0.25 mg/kg of body weight, followed by continuous infusion 0.125 µg/kg/minute for 12 hours). All patients received UFH.	Agreement between LTA using alternative ADP concentrations	367 subjects measured with two agonist concentrations	Agreement between LTA with ADP 2µM and ADP 10 µM: out of 367 measurements, 17 were positive by both tests; 279 were negative by both tests; 71 were positive with ADP 10 µM but not ADP 2 µM; none were positive with ADP 2 µM but not ADP 10 µM.
Frere 2007{Frere, 2007 193 /id} France 17938809	Consecutive patients with NSTE ACS admitted to the department of cardiology in a single center, following successful coronary	LTA (ADP 10 µmol/L) [PAP4, Biodata Corporation, Wellcome, Paris, France] VASP phosphorylation assay (PGE1 ± ADP, concentration not	Before the PCI, at least 12 h after the loading dose of clopidogrel and aspirin; before the administration of tirofiban (if needed)	Clopidogrel (600 mg loading; 75 mg maintenance) + aspirin (250 mg loading; 75 mg maintenance); LMWH or UFH was used for anticoagulation	Agreement between LTA and VASP for determining low clopidogrel response	195 patients measured with both tests	Weighted kappa for agreement between methods = 0.32

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Treatment preceding testing	Study design for the assessment of analytic validity	Sample size (measurements performed and included in analyses)	Results
	stenting.	reported) [Platelet VASP, Diagnostica Stago (BioCytex), Asnieres, France]; using flow cytometry [EPICS XL-MCL, Beckman Coultronics, Margency, France]					
Paniccia 2007{Paniccia, 2007 198 /id} Italy 17723123	Consecutive adult patients admitted to the coronary care units of a single center for ACS (STE MI, NSTE MI, UA), who underwent coronary angiography and PCI	LTA (ADP, 2 µmol/L and 10 µmol/L) [APACT-4 aggregometer, LABiTec, Ahrensburg, Germany] High shear platelet function (collagen/ADP and collagen/epinephrine cartridges) [PFA-100, Dade-Behring, Marburg, Germany] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	24-48 h after PCI; assays performed within 2 h of blood sampling	Acetylsalicylic acid (500 mg loading; 100-325 mg maintenance) + clopidogrel orally (300 mg loading; 75 mg maintenance). UFH was used as the anticoagulant. Patients receiving IIb/IIIa inhibitors were excluded.	Measurements of samples from the same patient with multiple methods to assess agreement	For analyses of agreement, 626 to 1267 samples measured with the tests of interest (specific sample sizes reported by specific comparisons)	USING CUT-OFFS DERIVED FROM STUDY DATA Agreement between LTA (ADP 2µml/L) and PFA-100 (collage/ADP cartridge) for residual platelet reactivity: out of 626 measurements, 22 were positive by both tests; 393 were negative by both tests; 80 were positive with LTA (ADP 2µml/L) but not PFA-100 (collage/ADP cartridge); 131 were positive with PFA-100 (collage/ADP cartridge) but not LTA (ADP 2µml/L). *NOTE:* discrepant numbers are reported in the text of the paper for the same comparison: out of 626 measurements, 41 were positive by both tests; 335 were negative by both tests; 138 were positive with LTA (ADP 2µml/L) but not PFA-100 (collage/ADP cartridge); 112 were positive with PFA-100 (collage/ADP cartridge) but not LTA (ADP 2µml/L). Agreement between LTA (ADP 2µmol/L) with PFA-100 (collagen/ADP cartridge) for residual platelet reactivity: kappa = -0.02; P = NS. Agreement between LTA (ADP 10µml/L) and PFA-100 (collage/ADP cartridge) for residual platelet reactivity: out of 626 measurements, 35 were positive by both tests; 345 were negative by both tests; 128 were positive with LTA (ADP 10µml/L) but not PFA-100 (collage/ADP cartridge); 118 were positive with PFA-100 (collage/ADP cartridge) but not LTA (ADP 10µml/L). Agreement between LTA (ADP 10µmol/L) with PFA-100 (collagen/ADP cartridge) for residual platelet reactivity: kappa = -0.04; P = NS Agreement between LTA (ADP 2µml/L) and VerifyNow (P2Y12 assay) for residual platelet reactivity: out of 1267 measurements, 159 were positive by both tests; 795 were negative by both tests; 159 were positive with LTA (ADP 2µml/L) but not VerifyNow (P2Y12 assay); 154 were positive with VerifyNow (P2Y12 assay) but not LTA (ADP 2µml/L). Agreement between LTA

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Treatment preceding testing	Study design for the assessment of analytic validity	Sample size (measurements performed and included in analyses)	Results
							(ADP 2µmol/L) with VerifyNow (ADP assay) for residual platelet reactivity: kappa = 0.34; 95% CI 0.29, 0.35; P<0.001. Agreement between LTA (ADP 10µml/L) and VerifyNow (P2Y12 assay) for residual platelet reactivity: out of 1267 measurements, 171 were positive by both tests; 831 were negative by both tests; 123 were positive with LTA (ADP 10µml/L) but not VerifyNow (P2Y12 assay); 142 were positive with VerifyNow (P2Y12 assay) but not LTA (ADP 10µml/L). Agreement between LTA (ADP 10µmol/L) with VerifyNow (ADP assay) for residual platelet reactivity: kappa = 0.43; 95% CI 0.36, 0.42; P<0.001. Agreement between VerifyNow (P2Y12 assay) and PFA-100 (collage/ADP cartridge) for residual platelet reactivity: out of 626 measurements, 53 were positive by both tests; 315 were negative by both tests; 158 were positive with VerifyNow (P2Y12 assay) but not PFA-100 (collage/ADP cartridge); 100 were positive with PFA-100 (collage/ADP cartridge) but not VerifyNow (P2Y12 assay). Agreement between PFA-100 (collage/ADP cartridge) with VerifyNow (ADP assay) for residual platelet reactivity: kappa = -0.01; P=NS. Analytic performance of VerifyNow, using LTA (ADP 2 µml/L) as the reference standard (cut-off based on study data): sensitivity = 50.0%; specificity = 83.8 %; PPV = 50.8%; NPV = 83.3%. Analytic performance of VerifyNow, using LTA (ADP 10 µml/L) as the reference standard (cut-off based on study data): sensitivity = 58.2%; specificity = 85.4 %; PPV = 54.6%; NPV = 87.1%. USING CUT-OFFS DERIVED FROM PRIOR LITERATURE Agreement between LTA (ADP 10 µml/L) and VerifyNow (P2Y12 assay) for residual platelet reactivity: out of 1267 measurements, 142 were positive by both tests; 858 were negative by both tests; 96 were positive with LTA (ADP 10µml/L) but not VerifyNow (P2Y12 assay); 171 were positive with VerifyNow (P2Y12 assay) but not LTA (ADP 10µml/L). Agreement between

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							LTA (ADP 10µmol/L) with VerifyNow (ADP assay) for residual platelet reactivity: kappa = 0.38; 95% CI 0.33, 0.39; P<0.001. Analytic performance of VerifyNow, using LTA (ADP 10 µml/L) as the reference standard (70% cut-off, based on prior literature): sensitivity = 59.7%; specificity = 83.4%; PPV = 45.5%; NPV = 89.9%.
Van Werkum 2006{van Werkum, 2006 209 /id} Netherlands 16938130	Consecutive patients undergoing elective PCI with stenting referred to a single center	LTA (ADP, 20 µmol/L) [NR] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Variable (based on patient referral patterns)	Clopidogrel pre-treatment varied by center (maintenance therapy of 75mg for >5 d, n = 116; loading dose 300mg at least 24 h before PCI, n = 75; loading dose 600 mg at least 4 h before PCI, n = 20). All patients were on aspirin ≥80mg of aspirin for at least 7 days.	Assessment of agreement between measurements using both assays	211 patients	Bland-Altman analysis "did not show proportional or systematic bias, with minimal clustering of values" for the following pairs of measurements: "Peak aggregation" with LTA versus VerifyNow PRU units, and "Late aggregation" with LTA versus VerifyNow PRU units
Mobley 2004{Mobley, 2004 221 /id} USA 14969622	Patients scheduled for cardiac catheterization at a single center	Optical platelet aggregometry (ADP, 1 µM) [Dual Channel Aggregometer; Chrono-Log Corp., Havertown, PA] TEG (ADP, 1 µM) [Thromboelastograph assay, Hemoscope, additional details NR] PlateletWorks (ADP, 1 µM) [PlateletWorks assay, Ichor, additional detaisl NR]	"After a variable number of days on therapy"	300 mg loading doses administered at the clinicians discretion; orally 75 mg maintenance; samples drawn to monitor platelet inhibition were obtained before treatment with additional anticoagulants or antiplatelet agents	Assessment of agreement between measurements with different assays	50 patients	Agreement between was 89% for optical platelet aggregation; 91% for TEG; 76% for PlateletWorks; agreement was judged against an average of % change from baseline across all analyzers.
Ren 2011{Ren, 2011 17 /id} China 21518592	Patients with high-risk ACS undergoing elective PCI	TEG (ADP, 2 µmol/L) [Thromboelastograph mapping assay in TEG5000, Hemoscope Corp., USA]	Blood samples were obtained after 5 days of using omeprazole.	Clopidogrel (600 mg loading dose; 75 mg daily maintenance) + aspirin (300 mg loading dose; 100 mg daily maintenance); no patients received IIb/IIIA inhibitors. At the beginning of elective PCI patients were randomized to omeprazole (20 mg) or placebo for 30 days.	Not reported (for analytic validity assessment)	Not reported (for analytic validity assessment)	Analytic sensitivity for the ADP pathway = 80% Analytic specificity for the ADP pathway = 86%
Godino 2009{Godino, 2009 231 /id} Italy 19419580	Consecutive patients with evidence of stable coronary artery disease undergoing elective PCI	ADP-stimulated IIb/IIIa receptor AND P-selectin expression (considered jointly as the reference standard) (ADP, 20 µM and collagen, 5 µg/mL) Using flow cytometry [FC500; Beckman Coulter, S.p.A., Cassina De' Pecchi, Milan, Italy] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Patients had to have been under treatment for 7 or d prior to testing; 2 samples were obtained within 1 hour; analyzed at least 10 min and within 2 h of sampling	Clopidogrel (75 mg) and aspirin (100 mg), daily, foe at least 7 days prior to testing. Patients who had received heparin, abciximab, tirofiban, or eptifibatide in the previous week were excluded from the study.	Samples from patients measured with 2 assays; flow cytometry used as the reference standard to determine analytic sensitivity and specificity for identifying non-responders using cut-offs determined by measurements in control	52 patients measured with both tests	Using % inhibition and a cut-off of ≤15% inhibition, derived from ROC analysis (AUC = 0.94; 95% CI 0.84, 0.98; P<0.0001): Analytic sensitivity of VerifyNow, using ADP-stimulated IIb/IIIa receptor and P-selectin expression as the reference standard = 100% Analytic specificity, using ADP-stimulated IIb/IIIa receptor and P-selectin expression as the reference standard = 89.1% Using absolute PRU values and a cut-off of

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					individuals		>213 units of inhibition, derived from ROC analysis (AUC = 0.85; 95% CI 0.72, 0.93; P<0.005): Analytic sensitivity of VerifyNow, using ADP-stimulated IIb/IIIa receptor and P-selectin expression as the reference standard = 83.3% Analytic specificity, using ADP-stimulated IIb/IIIa receptor and P-selectin expression as the reference standard = 84.4% Agreement between ADP-stimulated IIb/IIIa receptor and P-selectin expression: out of 52 measurements, 6 were positive by both tests; 23 were negative by both tests; 2 were positive based on P-selectin expression but not IIb/IIIa receptor expression; 21 were positive based on IIb/IIIa receptor expression but not P-selectin expression.
Paniccia 2011{Paniccia, 2011 31 /id} Italy 21192314	Patients with CAD admitted to a single center's coronary care unit for ACS. All patients underwent coronary angiography and PCI.	LTA (ADP, 2 µmol/L, 5 µmol/L, 10 µmol/L, and 20 µmol/L) [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Samples were collected 24 or 48 h after the end of PCI; all assays were performed within 2 h of blood sampling.	Acetylsalicylic acid (500 mg IV) followed by aspirin (maintenance dose 100-325 mg) + clopidogrel (300 mg loading dose; followed by maintenance dosing at 75 mg daily). Patients receiving IIb/IIIa receptor inhibitors were excluded.	Measurements of samples with 2 assays (and different agonist concentrations for LTA) for the assessment of agreement and the derivation of limits of agreement; for the assessment of reliability, repeat measurements on samples from smaller groups of patients were performed (only for LTA)	Samples from 466 patients for assessment of agreement	Agreement between LTA (ADP 2 µmol/L) and LTA (ADP 5 µmol/L): kappa = 0.69 (95% CI 0.59, 0.79); P < 0.0001; percentage agreement = 93.1% Agreement between LTA (ADP 2 µmol/L) and LTA (ADP 10 µmol/L): kappa = 0.63 (95% CI 0.53, 0.73); P < 0.0001; percentage agreement = 90.3% Agreement between LTA (ADP 2 µmol/L) and LTA (ADP 20 µmol/L): kappa = 0.61 (95% CI 0.51, 0.71); P < 0.0001; percentage agreement = 89.2% Agreement between LTA (ADP 5 µmol/L) and LTA (ADP 10 µmol/L): kappa = 0.68 (95% CI 0.59, 0.77); P < 0.0001; percentage agreement = 91.6% Agreement between LTA (ADP 5 µmol/L) and LTA (ADP 20 µmol/L): kappa = 0.65 (95% CI 0.56, 0.74); P < 0.0001; percentage agreement = 90.6% Agreement between LTA (ADP 10 µmol/L) and LTA (ADP 20 µmol/L): kappa = 0.86 (95% CI 0.80, 0.92); P < 0.0001; percentage agreement = 95.9% Agreement between VerifyNow and LTA (ADP 10 µmol/L): kappa = 0.51 (95% CI 0.43, 0.60); P

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							< 0.0001; percentage agreement = 82.4% Agreement between VerifyNow and LTA (ADP 20 µmol/L): kappa = 0.44 (95% CI 0.35, 0.53); P < 0.0001; percentage agreement = 79.6% Bland-Altman limits of agreement comparing LTA with ADP 10 µmol/L and 20 µmol/L: mean difference = -0.70% ±4.6% (CI, -9.7%, 8.3%). The difference in platelet reactivity between assays using these ADP concentrations was >20% in 3 samples (out of 466)
Koessler 2011{Koessler, 2011 32 /id} Germany 20873965	Patients with stable coronary artery disease under dual antiplatelet therapy who underwent PCI	High shear platelet function (collagen/ADP and collagen/epinephrine cartridges) [PFA-100 P2Y* and PFA collagen/ADP cartridges, Dade Behring (now Siemens), Marburg, Germany] VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP/P2Y12, BioCytex, Marseille, France]; using flow cytometry [FACScan, Becton Dickinson, Heidelberg, Germany]	The intended timing of measurements was not reported for the patient group; in the total population (n=50) samples were obtained on average 1.4 days post PCI	Patients were on dual antiplatelet treatment (aspirin + clopidogrel).	Agreement between the PFA-100 assay (at different thresholds) and VASP phosphorylation assay; analytic sensitivity and specificity of PFA-100 against VASP phosphorylation assay	50 patients measured with both tests; alternative cut-offs applied to the PFA-100 measurements	Analytic sensitivity of PFA-100 (cut-off 106 sec) against VASP (cut-off of PRI 50%) = 100% (among 31 responders) Analytic specificity of PFA-100 (cut-off 106 sec) against VASP (cut-off of PRI 50%) = 42% (among 19 non-responders) Highest agreement between PFA-100 and VASP assay was achieved using a cut-off of 200 sec for the former and 55% for the latter (Cohen's kappa = 0.66). Using these cut-offs the analytic sensitivity of PFA-100 is 97% and specificity = 65%. Results at additional thresholds (where agreement was lower) are presented in Figure 5 of the paper.
Paniccia 2010{Paniccia, 2010 69 /id} Italy 20458439	Adult patients referred to a single vascular disease center enrolled in a registry of ACS; patients underwent PCI with stent implantation	LTA (ADP, 10 µM) [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany] Impedance aggregometry (ADP, 10 µM final concentration) [Multiplate analyzer, Dynabyte, Munich, Germany] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Samples were collected 24 or 48 h after the end of PCI; PCI was performed 3-6 h after the ACS. All assays were performed within 2 h of blood sampling.	Acetylsalicylic acid (500 mg IV) followed by aspirin (maintenance 100-325 mg) + clopidogrel (300-600 mg loading dose) followed by maintenance dosing (75 mg daily). None of the investigated patients received other platelet function inhibitors (including IIb/IIIa receptor inhibitors).	Measurement of samples with 3 assays for assessment of agreement; cut-offs for residual platelet reactivity were based on prior literature. For the assessment of reliability, repeat measurements on samples from smaller groups of patients were performed (adequate information for the assessment of reliability was provided for LTA only)	801 samples for the assessment of agreement; 5 samples from each of 10 patients of the assessment of reliability	Agreement between Multiplate analyzer and LTA: out of a total of 801 samples, 102 samples were positive with both tests; 609 samples were negative with both tests; 27 samples were positive by LTA but not the Multiplate analyzer; 63 samples were positive by the Multiplate analyzer but not LTA. Agreement kappa = 0.63 (95% CI 0.56, 0.70); P < 0.0001. Agreement between Multiplate analyzer and VerifyNow: out of a total of 801 samples, 132 samples were bositive by both tests; 521 samples were negative by both tests; 33 samples were positive by Multiplate analyzer but negative by VerifyNow; 115 samples were positive by VerifyNow but not Multiplate analyzer. Agreement kappa = 0.52 (95% CI 0.46, 0.58); P < 0.0001. Agreement between VerifyNow and LTA: out of a total of 801 samples, 105 samples were

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							positive by both tests; 635 samples were negative by both tests; 24 samples were positive by LTA but not VerifyNow; 142 samples were positive by VerifyNow but not LTA. Agreement kappa = 0.44 (95% CI 0.38, 0.50); P < 0.0001
Ko 2011{Ko, 2011 26 /id} Korea 21315223	Consecutive CAD patients undergoing PCI in two university hospitals; all patients received drug eluting stents	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, additional details not reported] Impedance aggregometry (ADP, concentration not reported) [Multiplate analyzer, Dynabyte, additional details not reported]	Samples were obtained in the catheterization room through the femoral catheter, before the administration of heparin	Patients were pre-treated with aspirin (100 mg/d) and clopidogrel (75 mg/d) ≥ 5 d before the procedure, or received oral loading doses of aspirin (250 mg) and clopidogrel (300 mg) 12-24 h before the procedure.	Measurement of samples using both tests to calculate limits of agreement	Data from both tests were available from 222 patients	Bland-Altman[4] limits of agreement between VerifyNow PRU and Multiplate analyzer = -17.1 (SD = 232.1) with 95% limits of agreement from -472.0 to 437.8
Aradi 2010{Aradi, 2010 60 /id} Hungary 20642320	Prospectively recruited clopidogrel-naïve stable angina patients with planned PCI	LTA (ADP, 5 µM and epinephrine, 10 µM) [CARAT TX4 aggregometer, Carat Diagnostics, Budapest, Hungary] VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP/P2Y12 kit, BioCytex, Marseille, France]; using flow cytometry [Beckman Coulter flow cytometer, no additional details reported]	Samples were obtained 12-18 h post-clopidogrel loading and at 25 ± 2 d after PCI	All patients received clopidogrel (600 mg) and aspirin (300 mg) loading doses after angiography and immediately before PCI.	Measurement of samples with both assays (and different reactivity indexes from the same assay) to obtain limits of agreement; repeat measurements were obtained after clopidogrel loading and 25 ± 2 d after PCI but were treated as independent	242 samples from 121 patients, all assessed with both assays	Bland-Altman analysis comparing maximal aggregation by LTA and PRI VASP measurements = +1.3 Bland-Altman analysis comparing late aggregation by LTA and PRI VASP measurements; bias = -10.6 Bland-Altman analysis comparing disaggregation by LTA and PRI VASP measurements; bias = -19.9 Bland-Altman analysis comparing LTA AUC of the light transmission curve and PRI VASP; bias measurements = -15.1 The authors noted the presence of substantial heteroscedasticity in the Bland-Altman plots for the last three of the four analyses listed above.[5] Analytic accuracy using PRI VASP (50% cut-off) as the reference standard: - Maximal aggregation by LTA (34.5% cut-off, based on ROC analysis): Specificity = 79.4% Sensitivity = 61.3% Concordant pairs = 71.1% Discordant pairs = 28.9% Kappa = 0.4 (P<0.001) AUC (95% CI) = 0.75 (0.68, 0.81); P<0.0001 - Late aggregation by LTA (12% cut-off, based

[4] The two tests report results in different units; thus Bland-Altman analysis is not strictly valid.

[5] The interpretation of "bias" (or limits of agreement) from the Bland-Altman test is not straightforward in the presence of heteroscedasticity.

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							on ROC analysis): Specificity = 83.2% Sensitivity = 62.2% Concordant pairs = 73.1% Discordant pairs = 26.9% Kappa = 0.45; P<0.001 AUC (95% CI) = 0.73 (0.67, 0.80) - Disaggregation by LTA (63.5% cut-off, based on ROC analysis): Specificity = 80.2% Sensitivity = 63.1% Concordant pairs = 72.7% Discordant pairs = 27.3% Kappa = 0.44; P<0.001 AUC (95% CI) = 0.71 (0.64, 0.78); P<0.0001 - AUC of LTA light transmission curve (82xmin cut-off, based on ROC analysis): Specificity = 86.7% Sensitivity = 60.8% Concordant pairs = 72.3% Discordant pairs = 27.7% Kappa = 0.44; P<0.001 AUC (95% CI) = 0.76 (0.69-0.82); P<0.0001
Woo 2010{Woo, 2010 61 /id} Korea 20890076	Patients with CAD scheduled to undergo PCI with DES placement in a single center.	LTA (ADP, 10 µM) [Chronolog impedance aggregometer Series 590, Probe and Co., Endingen Germany] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] Impedance aggregometry (ADP, 20 µM) [Multiplate analyzer, Dynabyte Medical,Munich, Germany] VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP/P2Y12 kit, BioCytex, Marseille, France]; using flow cytometry [no additional details reported]	Samples were collected "just before" PCI	All patients were administered lading doses of aspirin (300 mg), clopidogrel (300 mg), and cilostazol (200 mg) ≥ 12 h before stenting.	Measurements with 4 assays to assess agreement	66 patients	Agreement between LTA and VerifyNow, kappa = 0.25 Agreement between LTA and Multiplate analyzer, kappa = 0.21 Agreement between LTA and PRI VASP assay, kappa = 0.14
Madsen 2010{Madsen, 2010 79 /id} Canada 20224050	Patients undergoing PCI at a single center	LTA (ADP, 5 µM) [Chrono-Log Lumi Aggregometer, model 810; Chrono-Log Corporation, no additional details provided]	Before PCI and on 1 d, 1 mo, 6 mo, and 12 mo, post-treatment	"Just before" PCI patients received 600 mg of clopidogrel; during the procedure use of tirofiban or eptifibatide was permitted but their administration was to be stopped ≥ 10 h before blood was drawn; abciximab was not permitted. Aspirin (325 mg/d) and clopidogrel (75 mg/day) were administered for a year post-PCI.	Measurement of samples with all three techniques and comparison of measurements for agreement	33 patients, 26 of whom completed all study visits. Patients contributed samples at multiple timepoints and measurements were considered	Agreement between absolute maximal ADP aggregation (50% cut-off) and change in aggregation (cut-off 10%) by LTA: "low response" by both tests, 1; "normal response" by change in aggregation but not absolute aggregation, 6; "normal response" by absolute aggregation but not change in aggregation, 14.

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		Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, no additional details provided] TEG (ADP, 2 µmol/L) [TEG Hemostasis Analyzer, Haemonetics Corporation, no additional details provided]				independent. The total number of measurements for each comparison was not reported; as such data are incomplete for the assessment of agreement.	Agreement between VerifyNow and change in aggregation (cut-off 10%) by LTA: "low response" by both tests, 1; "normal response" by change in aggregation but not VerifyNow, 3; "normal response" by VerifyNow but not change in aggregation, 8. Agreement between TEG and change in aggregation (cut-off 10%) by LTA: "low response" by both tests, 1; "normal response" by change in aggregation but not TEG, 12; "normal response" by TEG but not change in aggregation, 8. Agreement between VerifyNow and absolute maximal aggregation (cut-off 50%) by LTA: "low response" by both tests, 3; "normal response" by absolute aggregation but not VerifyNow, 1; "normal response" by VerifyNow but not change in aggregation, 5. Agreement between TEG and absolute aggregation (cut-off 50%) by LTA: "low response" by both tests, 2; "normal response" by absolute aggregation but not TEG, 15; "normal response" by TEG but not change in aggregation, 4. Agreement between VerifyNow and TEG: "low response" by both tests, 1; "normal response" by TEG but not VerifyNow, 1; "normal response" by VerifyNow but not TEG, 14.
Siller-Matula 2010{Siller-Matula, 2010 89 /id} Austria 19943879	Single center prospective observational study of patients undergoing PCI with stent implantation ≥2 hours after clopidogrel loading. The majority of patients were undergoing elective PCI.	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP/P2Y12 kit, BioCytex, Marseille, France]; using flow cytometry [FACSCalibur System, BD Biosciences, Vienna, Austria] Impedance aggregometry (ADP, concentration not reported) [Multiplate analyzer, Dynabyte Medical, Munich, Germany]	Blood samples were obtained in the catheterization laboratory "directly after" PCI and at least 5 min after the IV administration of aspirin	326 patients were on chronic clopidogrel treatment; 90 patients received a clopidogrel loading dose (600mg) within 2 d before PCI, followed by a maintenance dose of 75 mg. All patients received 250 mg of IV acetylsalicylic acid directly after stent placement, followed by a daily dose of 100 mg. Patients receiving IIb/IIIa inhibitors were excluded from analyses with the Multiplate analyzer.	Measurement of samples with both assays	402 patients with results available from both assays	Agreement between Multiplate analyzer and VASP assay: "non-responders" by both tests, 54 (13%); "responders" by both tests, 138 (34%); "non-responders" by Multiplate analyzer but "responders" by VASP, 7 (2%); "responders" by Multiplate analyzer but "non-responders" by VASP assay, 203 (51%) Bland-Altman analysis for agreement between VASP assay and Multiplate analyzer[6]: average difference (bias) = 21; 95% limits of agreement, -34 to 78
Cuisset 2010{Cuisset, 2010 93 /id}	Consecutive patients admitted to a single institution for NSTE	LTA (ADP 10 µmol/L) [PAP4, Biodata Corporation,	Samples were drawn 1 mo after discharge	Patients received oral loading doses of aspiring (250 mg) and clopidogrel (600 mg) at least 12 h before stenting	Measurement of patient samples with all three	70 patients, assessed with all 3 assays	Bland-Altman analysis comparing aggregation by LTA versus PRI VASP[7]: bias = 10.6; 95% limits of agreement, -23.3, 44.4

[6] The two tests report results in different units; thus Bland-Altman analysis is not strictly valid.
[7] The two tests report results in different units; thus Bland-Altman analysis is not strictly valid.

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France 20142119	ACS	Wellcome, Paris, France] VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP-FCM kit, Diagnostic Stago (BioCytex), Asnieres, France]; using flow cytometry [no additional details reported] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]			assays to determine limits of agreement and kappa statistics		Bland-Altman analysis comparing aggregation by LTA versus VerifyNow PRU[8]: bias = -146.4; 95% limits of agreement, -331.6, 39.0 Bland-Altman analysis comparing PRI VASP versus VerifyNow PRU[9]: bias = -156.9; 95% limits of agreement, -342.1, 28.3 Agreement between LTA (cut-off 70%) and VASP PRI: kappa = 0.35 Agreement between VerifyNow PRU and LTA (cut-off 70%): kappa = 0.36 Agreement between VASP PRI and VerifyNow PRU: kappa = 0.46 Additional analysis using a different threshold: Agreement between LTA (cut-off 50%) and VASP PRI: kappa = 0.42 Agreement between VerifyNow PRU and LTA (cut-off 50%): kappa = 0.52
Smit 2009{Smit, 2009 137 /id} Netherlands 19200163	Patients participating in a multicenter trial of tirofiban vs. placebo (On-TIME 2 study) for STEMI requiring PCI	Fe-induced platelet aggregation [samples were added to tubes containing 100 mg of steel wool (Haemoscan, Groningen, Netherlands)] and a platelet counter was use to assess platelet aggregation (against a control tube no containing iron). Plateletworks (ADP, 20 μM/L) [PlateletWorks, Helena Laboratories, Beaumont, TX]	Samples were obtained before PCI, but after the patients received the study medication (tirofiban or placebo) and antiplatelets	Before testing, patients received clopidogrel (600 mg orally) and acetylsalicylic acid (500 mg IV); blood was drawn at the "start of catheterization"	Measurement of samples with three assays to assess limits of agreement	111 patients (53 randomized to tirofiban and 58 randomized to placebo)	Bland-Altman comparison between duplicate measurements using the iron-based assay: the mean was close to 0 (exact result not reported) and in ~6/111 samples were outside "limits of agreement of ±20%" (see also Figure 2 of the paper). Bland-Altman comparison of the iron-based assay versus Plateletworks (ADP as the agonist): ~4/111 samples were outside limits of agreement of ±40% (see also Figure 4 of the paper).
Gremmel 2009{Gremmel, 2009 138 /id} Austria 19190818	Patients with peripheral, coronary, or carotid artery disease after elective percutaneous intervention with endovascular stent	LTA (ADP 10 μM) [APACT 4S Plus aggregometer, LABiTec, Ahrensburg, Germany] Platelet agglutination assay (ADP cartridges)	Samples were obtained 24 h after the percutaneous intervention	Patients had received acetylsalicylic acid (100 mg/d) at least 2 w prior to the percutaneous intervention. All patients received a loading dose of clopidogrel (300 mg) 24 h prior to the intervention, followed by a maintenance dose of 75 mg/day	Measurement of samples with 5 methods; assessment of correlations between methods, agreement	80 patients assessed with 5 assays	Analytic performance, using LTA as the reference standard (20 positive samples): Analytic sensitivity -VerifyNow, 55% - VASP assay,45% -Multiplate analyzer, 35%

[8] The two tests report results in different units; thus Bland-Altman analysis is not strictly valid.
[9] The two tests report results in different units; thus Bland-Altman analysis is not strictly valid.

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Treatment preceding testing	Study design for the assessment of analytic validity	Sample size (measurements performed and included in analyses)	Results
	implantation	[VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP kit, Diagnostica Stago, BioCytex, Marseille, France]; using flow cytometry [FACSCalibur system, Becton Dickinson, BD Biosciences, Vienna, Austria] Impedance aggregometry (ADP, 6.4 µM) [Multiplate analyzer, Dynabyte Medical, Munich, Germany] Cone and plate analyzer (ADP 1.36 µM) [Impact-R test, DiaMed, Cressier, Switzerland]			between methods, and analytic sensitivity and specificity using LTA as the reference standard test (treated as a gold standard)		- Impact-R, 40% Analytic specificity -VerifyNow, 85% - VASP assay, 81.7% -Multiplate analyzer, 78.3% - Impact-R, 78.3% Analytic positive predictive value -VerifyNow, 55% - VASP assay, 45% -Multiplate analyzer, 35% - Impact-R, 38.1% Analytic negative predictive value -VerifyNow, 85% - VASP assay, 81.7% -Multiplate analyzer, 78.3% - Impact-R, 79.7% Agreement between LTA and VerifyNow: concordant positive samples = 11; concordant negative samples = 51; positive with LTA but not VerifyNow = 9; positive with VerifyNow but not LTA = 9 Agreement between LTA and VASP assay: concordant positive samples = 9; concordant negative samples = 49; positive with LTA but not VASP assay = 11; positive with VASP assay but not LTA = 11 Agreement between LTA and Multiplate analyzer: concordant positive samples = 7; concordant negative samples = 47; positive with LTA but not Multiplate analyzer = 13; positive with Multiplate analyzer but not LTA = 13 Agreement between LTA and Impact-R: concordant positive samples = 8; concordant negative samples = 47; positive with LTA but not Impact-R = 12; positive with Impact-R but not LTA = 13 Cut-offs for all assays were based on quartiles of the observed measurement distribution (most extreme reactivity quartile vs. all others).
Schafer 2008{Schafer, 2008 158 /id} Germany 18841284	Consecutive patients with CAD admitted to a single center	LTA (ADP 20 µM) [PAP-8, BioData, Horsham, PA] VASP phosphorylation assay (PGE1 ± ADP, 20 µM) [Platelet VASP Test kit, American Diagnostica, Pfungstadt, Germany];	Samples were obtained 2-4 h after drug intake	Patients had been on maintenance dose clopidogrel (75 mg/d) for ≥5 d after a loading dose of 300-600 mg (on the first day); patients not on clopidogrel were used as controls (no data extracted)	Measurement of samples using 3 assays for assessment of agreement	100 patients on clopidogrel	Agreement between VASP assay (cut-off 50%) and LTA (cut-off 50%): concordant positive results, 44%; concordant negative results, 28%; positive by VASP but not LTA, 25%; positive by LTA but not VASP assay, 3%. Subgroup analysis by diabetic status:

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Treatment preceding testing	Study design for the assessment of analytic validity	Sample size (measurements performed and included in analyses)	Results
		using flow cytometry [FACSCalibur, Becton Dickinson, Heidelberg, Germany]					Diabetic patients (n=30): agreement between VASP assay (cut-off 50%) and LTA (cut-off 50%): concordant positive results, 41%; concordant negative results, 24%; positive by VASP but not LTA, 34%; positive by LTA but not VASP assay, 0%. Non-diabetic patients (n=70): agreement between VASP assay (cut-off 50%) and LTA (cut-off 50%): concordant positive results, 44%; concordant negative results, 28%; positive by VASP but not LTA, 23%; positive by LTA but not VASP assay, 5%.
Shenkman 2008{Shenkman, 2008 166 /id} Israel 18155752	Consecutive ACS patients who underwent PCI with stent implantation	LTA (ADP, 5.5 μM) [PACKS-4 aggregometer, Helena Laboratories, Beaumont, TX] Impact-R (ADP 1.38 μM) [DiaMed, Cressier, Switzerland]	In one group of patients (n=114) blood samples were obtained before and 4 d after clopidogrel administration. In a second group (n=290) samples were obtained only 4 d after clopidogrel treatment.	All patients received aspirin 300 mg on admission and 200 mg/d thereafter. Eptifibatide was administered before PCI and for at least 12 h after the procedure. Clopidogrel was administered at a loading dose of 300 mg on completion of PCI, followed by a maintenance dose of 75 mg/d.	Measurement of samples with both assays to determine agreement and analytic sensitivity and specificity. For the later analyses LTA results were treated as a "gold standard"	114 patients contributed measurements before and after clopidogrel administration; 290 patients only contributed measurements after clopidogrel administration. Only results from the second groups of patients were used for ROC and agreement analyses.	Analytic performance using LTA as the reference standard (cut-off 70%) Optimal cut-off value for Impact_r = 2.8 Analytic sensitivity = 71% Analytic specificity = 83% Analytic positive predictive value = 72% Analytic negative predictive = 83% AUC = 0.867 Agreement between LTA and Impact-R for non-response using the cut-offs identified through ROC analysis: concordant positive results, 78; concordant negative results, 151; non-responders by LTS but responders by Impact-R, 32; non-responders by Impact-R but responders by LTA, 29.
Lordkipanidze 2008{Lordkipanidze, 2008 170 /id} Canada 18520610	Patients with CAD requiring eletive diagnostic coronary angiography with or without PCI from a single center. Patients were participants in a prospective, randomized, double-blind, placebo controlled trial	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] Comparisons were performed between a before-after assessment of the clopidogrel effect (based on two measurements using VerifyNow, pre- and post-clopidogrel administration) and a single on-clopidogrel measurement with VerifyNow where the TRAP channel of the assay is used to "approximate" the pre-clopidogrel reactivity level.	Blood was drawn "before clopidogrel initiation" (pre-clopidogrel measurement) and "just before" elective angiography	Patients were allocated randomly to 4 groups: 300 or 600 mg on the day before angiography, or 300 mg loading followed by 75 or 150 mg maintenance daily dose, started 1 w before angiography. All patients received aspirin (80 mg). Patients receiving IIb/IIIa inhibitors were excluded.	Two measurements with VerifyNow (before and after clopidogrel) to compare the before-after contrast versus as "estimated" contrast using the post-clopidogrel measurement and the TRAP channel of the same device	68 patients contributing data for both timepoints	Bland-Altman analysis: bias = 8%; limits of agreement from -49% to 65%
Lordkipanidze 2009{Lordkipanidze, 2009 108 /id} Canada 19840560	Consecutive patients with stable CAD treated with aspirin and clopidogrel selected from the	LTA (ADP 5, 10, and 20 μM) [Chrono-Log aggregometer 540 model, Chrono-Log, Havertown, PA]	Samples were obtained 2-12 h after the last aspirin and clopidogrel dose.	All patients were on aspirin (≥80 mg/d) and clopidogrel (≥75 mg/d) for ≥ 3 mo.	Measurements were obtained with both assays (and using different concentrationsof	85 patients contributed measurements with LTA, using ADP 5 and 20 μM concentrations, and VerifyNow; 77	Agreement between VerifyNow and LTA ADP 5 μM: kappa = 0.487; P<0.0001 Agreement between VerifyNow and LTA ADP 10 μM: kappa = 0.309; P=0.004

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	outpatient cardiology clinic of a single center	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]			ADP for LTA) to compare agreement	patients were also assessed with LTA using an ADP concentration of 10 µM	Agreement between VerifyNow and LTA ADP 20 µM: kappa = 0.661; P<0.0001
Lordkipanidze 2009{Lordkipanidze, 2009 110 /id} Canada 19419755	Patients presenting at a single center outpatient cardiology department with symptomatic CAD requiring diagnostic coronary angiography. Patients were participants in a prospective, randomized, double-blind, placebo controlled trial.	LTA (ADP 5 and 20 µM) [ChronoLog aggregometer 540 model, Havertown, PA]	Samples were obtained before clopidogrel initiation and "just before" elective angiography.	Patients were allocated randomly to 4 groups: 300 or 600 mg on the day before angiography, or 300 mg loading followed by 75 or 150 mg maintenance daily dose, started 1 w before angiography. All patients received aspirin (80 mg). Patients receiving IIb/IIIa inhibitors were excluded	Measurements obtained with both ADP concentrations to assess agreement	120 patients contributed measurements	Bland-Altman analysis of peak versus late aggregation using LTA ADP 5 µM: bias = 10.8%; limits of agreement from -5.8% to 27.3% Bland-Altman analysis of peak versus late aggregation using LTA ADP 20 µM: bias = 10.3%; limits of agreement from -8.5% to 29.2% Analyses of inhibition of platelet reactivity (i.e., change from baseline) Bland-Altman analysis of peak versus late absolute inhibition using LTA ADP 5 µM: bias = 3.4%; limits of agreement from -18% to 25% Bland-Altman analysis of peak versus late absolute inhibition using LTA ADP 20 µM: bias = 5.9%; limits of agreement from -18% to 30% Bland-Altman analysis of peak versus late relative inhibition using LTA ADP 5 µM: bias = -16.3%; limits of agreement from -59% to 26% Bland-Altman analysis of peak versus late relative inhibition using LTA ADP 20 µM: bias = -12.3%; limits of agreement from -49% to 23%
Collet 2008{Collet, 2008 160 /id} France 18765393	Adult patients on maintenance clopidogrel for > 7 d scheduled to undergo cardiac catheterization because of unstable CAD or stable angina. Patients were participants in a prospective trial of alternative clopidogrel loading doses.[10]	LTA (ADP 5, 10, 20, and 50 µmol/L) [Chronolog Aggregometer model 490-4D, Chrono-Log Corp., Kordia, Netherlands] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Samples were obtained before the first and second loading doses and 24 h after the first loading dose (see adjacent cell for details). Agreement was assessed using the baseline measurements only (i.e., reflective of patients' reactivity on maintenance clopidogrel)	All patients were on clopidogrel maintenance (75 mg/d) for > 7 d. They were alternately allocated to clopidogrel loading doses of 300, 600, or 900 mg (first loading dose). Depending on the initial assignment, patients then received a second loading dose, such that the total clopidogrel amount received would be 900 mg. Thereafter, all patients received maintenance clopidogrel (75 mg/d) and aspirin (≤100 mg/d). Only baseline measurements were used for the assessment of agreement.	Agreement regarding baseline on-clopidogrel non-responsiveness between assays	166 patients measured at baseline	Agreement for poor response between LTA (cut-off 50% for residual platelet reactivity) and VerifyNow (cut-off 15%): kappa = 0.20; 95% CI 0.06, 0.40

[10] The trial was described as "randomized", however it appears to have been a alternate allocation design (often called, "pseudo-randomized" or "quasi-randomized" design).

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Von Beckerath 2010{Von, 2010 98 /id} Germany 19823079	Consecutive patients without clopidogrel treatment within the last 4 week, scheduled for coronary angiography	LTA (ADP 5 µmol/L) [PAP 8 aggregometer, Molab, Berlin, Germany] Impedance aggregometry (ADP 6.4 µmol/L ± PGE1 9.4 µmol/L) [Multiplate analyzer, Dynabyte Medical, Munich, Germany] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] VASP phosphorylation assay (PGE1 ± ADP, 20 µM) [Platelet VASP, Biocytex, Marseille, France]; using flow cytometry [no additional details provided]	Samples were obtained before the administration of clopidogrel and immediately after stent placement (post-clopidogrel loading)	All patients received a single clopidogrel loading dose (600 mg), which was recommended to be given ≥ 2 h before catheterization. Patients treated with IIb/IIIa inhibitors within 28 d were excluded.	Assessment of samples with all 3 assessment and assessment of agreement for identifying "lack of response". Lack of response was defined as values in the top quintile of measurements obtained from each assay.	Samples from 60 patients measured with 4 assays (2 different agonist types were used for the Multiplate analyzer)	12 patients were in the upper quintile of the Multiplate analyzer using ADP as the agonist; of those 7 were in the upper quintile of VerifyNow (P<0.001), 6 in the upper quintile if Multiplate analyzer using ADP+ PGE1 as the agonist (P=0.004), and 3 were in the upper quintile of VASP PRI (P=0.63). P-values were from a "chi-square test"; it was unclear whether the paired nature of the measurements was accounted for in the analysis. The authors stated that "comparisons of categorical classifications (upper quintiles) yielded a poor agreement of post-clopidogrel values" [no additional statistics were reported]
Varenhorst 2009 Sweden 19249429	Patients with stable CAD participating in a parallel-group randomized trial of prasugrel versus clopidogrel, both in combination with aspirin	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] VASP phosphorylation assay (PGE1 ± ADP, concentrations NR) [Platelet VASP kit, BioCytex, Marseille, France]; using flow cytometry [samples were analyzed on different flow-cytometers in 2 participating centers: Epics XL, Beckman Coulter, Fullurton, CA; and FACScan, Becton Dickinson, Franklin Lakes, NJ]. The authors reported that "synchronization between the flow cytometers was performed". Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Samples were obtained before the loading dose, 2h and 24h post-loading, and the 14th and 29th day of clopidogrel maintenance treatment	Patients received aspirin 75mg/d for 5-21 d before randomization and were then assigned to clopidogrel (600 mg loading, 75 mg maintenance dose) or prasugrel (60 mg loading; 10 mg maintenance) groups, while continuing the same aspirin regimen	Two measurements with VerifyNow (before and after antiplatelet treatment) to compare the before-after contrast versus an "estimated" contrast using the post-clopidogrel measurement and the TRAP channel of the same device	110 patients (1:1 randomized to clopidogrel or prasugrel) measured at 5 timepoints (not clear if all measurements were available for all patients and timepoints)	Lin's concordance correlation coefficient between observed and estimated % inhibition = 0.97; P<0.0001 (the authors indicated that there is "modest underestimation by the device-reported %inhibition") Agreement for high platelet inhibition (quartile 1 vs. quartiles 2-4 for each assay), 95% CI Agreement between VASP PRI and PRU, during loading phase = 0.35 (0.20, 0.49) Agreement between VASP PRI and PRU, during maintenance phase = 0.55 (0.42, 0.68) Agreement between late reactivity by LTA and PRU, during loading phase = 0.54 (0.41, 0.67) Agreement between late reactivity by LTA and PRU, during maintenance phase = 0.52 (0.39, 0.66) Agreement for low platelet inhibition (quartile 4 vs. quartiles 1-3 for each assay), 95% CI Agreement between VASP PRI and PRU, during loading phase = 0.79 (0.69, 0.89) Agreement between VASP PRI and PRU, during maintenance phase = 0.66 (0.54, 0.78)

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							Agreement between late reactivity by LTA and PRU, during loading phase = 0.75 (0.64, 0.85) Agreement between late reactivity by LTA and PRU, during maintenance phase = 0.66 (0.54, 0.77)
Lordkipanidze 2008 Canada 18826988	Patients with suspected CAD requiring elective diagnostic coronary angiography, recruited from the pre-angiography outpatient clinic of a single center. The current study was a pre-specified analysis nested within a prospective randomized trial of alternative clopidogrel dosing regimens	LTA (ADP 5 and 20 μM) [ChronoLog 540 model, Havertown, PA] Impedance aggregometry (ADP 5 and 20 μM) [ChronoLog 560 model, Havertown, PA] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Blood was drawn at two time points: before clopidogrel initiation and "just before" coronary angiography	Patients were allocated randomly to 4 groups: 300 or 600 mg on the day before angiography, or 300 mg loading followed by 75 or 150 mg maintenance daily dose, started 1 w before angiography. All patients received aspirin (80 mg). Patients receiving IIb/IIIa inhibitors were excluded	Measurement of samples with all assays to assess agreement	116 patients contributed samples to the analyses; only 72 patients had measurements with VerifyNow	Data were extracted only for on-clopidogrel measurements. Bland-Altman analyses Agreement between LTA ADP 5 μM and 20 μM: bias = 4.5% (95% CI, 1.3%, 7.7%); P=0.006 by paired t-test; limits of agreement: -26% to 38%. Agreement between LTA ADP 20 μM and impedance aggregometry ADP 5 μM: bias = 13% (95% CI, 2.6%, 24.0%; overestimation by impedance aggregometry); P=0.01 by paired t-test; limits of agreement: -97% to 124%. Agreement between LTA ADP 20 μM and impedance aggregometry ADP 20 μM: bias = -11% (95% CI, -20.7%, -1.8%; underestimation by impedance aggregometry); P=0.02 by paired t-test; limits of agreement: -110% to 87%. Agreement between LTA ADP 20 μM and VerifyNow: bias = 6.3% (95% CI, -1.6%, 14.2%; non-significant overestimation by VerifyNow); P=0.117 by paired t-test; limits of agreement: -54.4% to 67.0%. --- Agreement using a cut-off of 50% Agreement between LTA ADP 5 μM and LTA ADP 20 μM: kappa = 0.679; P<0.05 Agreement between LTA ADP 5 μM and impedance aggregometry ADP 5 μM: kappa = -0.117; P=NS Agreement between LTA ADP 5 μM and impedance aggregometry ADP 20 μM: kappa = 0.057; P=NS Agreement between LTA ADP 5 μM and VerifyNow: kappa = 0.295; P<0.05

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Treatment preceding testing	Study design for the assessment of analytic validity	Sample size (measurements performed and included in analyses)	Results
							Agreement between LTA ADP 20 µM and impedance aggregometry ADP 5 µM: kappa = -0.187; P<0.05 Agreement between LTA ADP 20 µM and impedance aggregometry ADP 20 µM: kappa = 0.101; P=NS Agreement between LTA ADP 20 µM and VerifyNow: kappa = 0.364; P<0.05 Agreement between impedance aggregometry ADP 5µM and impedance aggregometry ADP 20 µM: kappa = 0.308; P<0.05 Agreement between impedance aggregometry ADP 5µM and VerifyNow: kappa = -0.047; P=NS Agreement between impedance aggregometry ADP 20 µM and VerifyNow: kappa = 0.132; P=NS (exact p-values were not reported)
Jeong 2008 S. Korea 18617479	Consecutive patients undergoing PCI with DES implantation at a single center	LTA (ADP 5 µM) [ChronoLog 540 model, Havertown, PA] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	"from the arterial sheath"	Unclear (on-clopidogrel)	Measurements with both assays to assess analytic performance using LTA as the reference standard	300 patients provided measurements with both assays	Optimal VerifyNow cut-off for HPR using LTA (with 50% cut-off) as the reference standard = 239 PRU; AUC = 0.794; 95% CI 0.736, 0.851; P<0.001 At this cut-off analytic sensitivity = 83.6%; analytic specificity = 68.3% The authors also reported the analytic sensitivity and specificity of LTA % inhibition as 76.2% and 83.6% respectively, presumably against LTA on-treatment reactivity. For this analysis the optimal LTA cut-off was determined to be 20% (AUC = 0.841; 95% CI 0.790, 0.891).
Kim 2010 S. Korea 20449634	Unselected patients treated with coronary stenting for symptomatic coronary artery disease, including AMI	LTA (ADP 5 and 20 µM) [AggRam aggregometer, Helena Laboratories Corp., Beaumont, TX] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	"Pre-discharge" measurement, either ≥3 d after coronary stenting in patients not treated with tirofiban or at ≥5 d post-procedure in patients treated with tirofiban	In cases of scheduled coronary stenting, clopidogrel-naive patients received clopidogrel 300-mg (loading) at least 12 h pre-PCI. In patients already on chronic clopidogrel therapy, no loading dose was used. All AMI patients received clopidogrel 600 mg loading, followed by 75 mg/d maintenance. Tirofiban was the only IIb/IIIa inhibitor allowed.	Measurements with both assays to assess agreement and analytic performance	1058 patients contributed measurements	Agreement between maximal reactivity by LTA ADP 5 µmol/L (50% cut-off) and VerifyNow (PRU 240 cut-off): kappa = 0.438; P<0.001; 29.1% concordant positives; 42.5% concordant negatives; 5.9% positive by LTA but not VerifyNow; 22.5% positive by VerifyNow but not LTA; overall concordance = 71.6% Agreement between maximal reactivity by LTA ADP 20 µmol/L (50% cut-off) and VerifyNow (PRU 240 cut-off): kappa = 0.505; P<0.001; 35.0% concordant positives; 40.2% concordant negatives; 8.2% positive by LTA but not VerifyNow; 16.6% positive by VerifyNow but not LTA; overall concordance = 75.1%

Author Year Country PMID	Patient population	Assays evaluated (agonist) [brand name, manufacturer]	Test timing	Treatment preceding testing	Study design for the assessment of analytic validity	Sample size (measurements performed and included in analyses)	Results
							Analytic performance using LTA as the reference standard test (however, with different thresholds for each analysis) Analytic performance of VerifyNow against maximal reactivity by LTA ADP 5 µmol/L (cut-off 50%): optimal cut-off for VerifyNow = 241; AUC = 0.822 (95% CI 0.797, 0.847); analytic sensitivity = 0.830; analytic specificity = 0.660 Analytic performance of VerifyNow against maximal reactivity by LTA ADP 20 µmol/L (cut-off 62%): optimal cut-off for VerifyNow = 241; AUC = 0.840 (95% CI 0.816, 0.863); analytic sensitivity = 0.807; analytic specificity = 0.714 Analytic performance of VerifyNow against maximal reactivity by LTA ADP 20 µmol/L (cut-off 50%): optimal cut-off for VerifyNow = 195; AUC = 0.851 (95% CI 0.827, 0.875); analytic sensitivity = 0.889; analytic specificity = 0.635 Analytic performance of VerifyNow against late reactivity by LTA ADP 5 µmol/L (cut-off 14%): optimal cut-off for VerifyNow = 194; AUC = 0.826 (95% CI 0.796, 0.856); analytic sensitivity = 0.829; analytic specificity = 0.683 The paper also includes a table (see Table 2 in the manuscript for additional details) reporting comparisons between LTA (both maximal and late reactivity and 5 and 20 µmol/L ADP concentration) and VerifyNow using different thresholds for each test. Kappa statistics for all combinations assessed ranged between 0.260 and 0.734; concordance rates ranged between 56.7% and 87.2%; analytic sensitivities ranged between 68.8% and 100%; analytic specificities ranged between 34.4% and 83.9%.
Lordkipanidze 2009 Canada 19250657	Patients with CAD receiving aspirin and clopidogrel[11] were recruited from a single center's pre-angiography clinic	LTA (ADP 5 and 20 µM) [ChronoLog Aggregometer, 540 model, Havertown, PA] "Platelet count drop method" using impedance platelet counting before and after exposure to the agonist (ADP 5 and 20 µM) Using a Coulter ACT Series	NR	Patients were on aspirin (80 mg/d) and clopidogrel (varying dosing schemes)	Measurements with both methods to assess agreement	91 patients on clopidogrel + aspirin	Bland-Altman analysis comparing LTA (ADP 5 µM) and platelet count drop method (ADP 5 µM): bias = 13% (overestimation by platelet count drop); limits of agreement -27% to 52%. Bland-Altman analysis comparing LTA (ADP 20 µM) and platelet count drop method (ADP 20 µM): bias = 18% (overestimation by platelet count drop); limits of agreement -30% to 65%.

[11] The paper also reported on a cohort of patients receiving aspirin alone. We only extracted data from patients on clopidogrel.

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		Analyzer, Beckman Coulter Inc., Fullerton, CA]					Agreement between LTA (ADP 5 µM) and platelet count drop method (ADP 5 µM) using a cut-off of 50% for both: kappa = 0.192; P = 0.02 Agreement between LTA (ADP 20 µM) and platelet count drop method (ADP 20 µM) using a cut-off of 50% for both: kappa = 0.281; P = 0.002 Agreement between LTA (ADP 5 µM) and platelet count drop method (ADP 5 µM) using a cut-off of 70% for both: kappa = 0.207; P = 0.001 Agreement between LTA (ADP 20 µM) and platelet count drop method (ADP 20 µM) using a cut-off of 70% for both: kappa = 0.089; P = 0.191
Pettersen 2011 Norway 21426546	Patients with symptomatic CAD randomized to the aspirin + clopidogrel arm of a randomized trial	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [PLT VASP/P2Y12 assay, Biocytex, France]; using flow cytometry [FACS Calibur System, Becton Dickinson, Plymouth, UK] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	One month post-randomization to the clopidogrel arm	Aspirin (160 mg/d) + clopidogrel (75 mg/day) treatment for ≥ 1 mo; patients on aspirin only were used to derive the cut-off for "clopidogrel resistance"	Measurements with both assays to determine agreement	219 patients were on aspirin + clopidogrel; 155 were analyzed successfully with the VASP assay and 212 with the VerifyNow assay	Agreement between VASP assay and VerifyNow: kappa = 0.379; P<0.001; concordance rate = 74.5%
Sibbing 2008 Germany 18217143	Consecutive patients scheduled for coronary angiography; patients were required to not have received clopidogrel within 4 w of enrollment	LTA (ADP 5 or 20 µM) [PAPA 8 aggregometer, Bio/Data, no additional information reported] Impedance aggregometry (ADP, 6.4 µM) [Multiplate analyzer, Dynabyte, Munich, Germany]	Samples were obtained from a subset of 60 patients at baseline (pre-clopidogrel loading) and from all participating patients (n=149) during catheterization (post-loading dose)	Patients received a loading dose of clopidogrel of 600 mg, recommended to be given ≥ 2 h before catheterization	Measurements with both methods to assess agreement	149 patients contributed on-clopidogrel measurements; 60 patients also had baseline (pre-clopidogrel) measurements available	Agreement between LTA and Multiplate analyzer for lowest quartile of inhibition (n = 60): concordant positives = 7 (12%); concordant negatives = 35 (58%); positives by LTA but not Multiplate analyzer = 8 (13%); positives by Multiplate analyzer but not LTA = 10 (17%) Agreement between LTA and Multiplate analyzer for lowest quartile of inhibition (n=149): concordant positives = 21 (14%); concordant negatives = 94 (63%); positives by LTA but not Multiplate analyzer = 17 (11%); positives by Multiplate analyzer but not LTA = 17 (11%)

ACS = acute coronary syndrome; ADP = adenosine diphosphate; CI = confidence interval; d = days; h = hour; LMWH = low molecular weight heparin; LTA = light transmittance aggregometry; MI = myocardial infarction; mo = month; MPA = maximal platelet aggregation; NPV = negative predictive value; NS = non-significant; NSTE = non-ST elevation; PCI = percutaneous coronary intervention; PGE1 = prostaglandin E1; PMID = PubMed identification number; PPV = positive predictive value; PRI = platelet reactivity index; PRU = platelet reactivity units; RPA = residual platelet aggregation; UA = unstable angina; UFH = unfractionated heparin; VASP = vasodilator-stimulated phosphoprotein. Percentages may not sum to 100% because of rounding.

Appendix Table E2: Studies reporting correlation results between alternative platelet reactivity assays

Gurbel 2009{Gurbel, 2009 103 /id} International (USA and UK) 19923168	LTA (ADP 5 µmol/L and 20 µmol/L; collagen 2 µg/mL) [Chronolog Optical Aggregometer model 490-4D, Chrono-log Corporation, Havertown, PA] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Biocytex Inc, Marseille, France]; using flow cytometry [additional details NR] ADP-stimulated surface expression of activated IIb/IIIa receptors (ADP, 5 µmol/L final concentration) Using flow cytometry [FACScan flow cytometer, Becton Dickinson] ADP-stimulated P-selectin expression (ADP, 5 µmol/L final concentration) Using flow cytometry [FACScan flow cytometer, Becton Dickinson]	104 patients on antiplatelet treatment (54 on ticagrelor; 50 on clopidogrel)	PATIENTS ON CLOPIDOGREL Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA ADP 5 µM ADP (maximum) = 0.8805; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA ADP 5 µM ADP (final) = 0.9067; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA ADP 20 µM ADP (maximum) = 0.9396; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA ADP 2 µg/mL collagen (maximum) = 0.4471; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA 2 µg/mL collagen (final) = 0.4298; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and VASP PRI (%) = 0.3973; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and Inhibition of stimulated P-selectin expression = 0.3586; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and inhibition of stimulated IIb/IIIa receptor expression = 0.2934; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and VerifyNow (% inhibition) = 0.7408; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and VerifyNow (PRU units) = -0.5921; P < 0.0001 PATIENTS ON TICAGRELOR Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA ADP 5 µM ADP (maximum) = 0.9099; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA ADP 5 µM ADP (final) = 0.9257; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA ADP 20 µM ADP (maximum) = 0.9290; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA ADP 2 µg/mL Collagen (maximum) = 0.6249; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and LTA 2 µg/mL Collagen (final) = 0.6640 <0.0001

			Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and VASP PRI (%) = 0.7463; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and Inhibition of stimulated P-selectin expression = 0.4731; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and inhibition of stimulated IIb/IIIa receptor expression = 0.3584; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and VerifyNow (% inhibition) = 0.8483; P < 0.0001 Pearson correlation between inhibition of platelet aggregation with LTA ADP 20 µM (final extent) and VerifyNow (PRU units) = -0.8631; P < 0.0001
Lordkipanidze 2009{Lordkipanidze, 2009 110 /id} Canada 19419755	LTA (ADP 5 and 20 µM) [ChronoLog aggregometer 540 model, Havertown, PA]	120 patients contributed measurements	Spearman correlation coefficient between late and peak aggregation by LTA ADP 5 µM = 0.853; P<0.0001 Spearman correlation coefficient between late and peak aggregation by LTA ADP 20 µM = 0.912; P<0.0001 Spearman correlation coefficient between absolute inhibition using late vs. peak aggregation by LTA ADP 5 µM = 0.848; P<0.0001 Spearman correlation coefficient between absolute inhibition using late vs. peak aggregation by LTA ADP 20 µM = 0.799; P<0.0001 Spearman correlation coefficient between relative inhibition using late vs. peak aggregation by LTA ADP 5 µM = 0.824; P<0.0001 Spearman correlation coefficient between relative inhibition using late vs. peak aggregation by LTA ADP 20 µM = 0.857; P<0.0001
Voisin 2011 France 21544318	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	93 patients tested at two timepoints (24-48h and 5-7 w post-PCI) to assess the correlation between different measurements produced by the same assay	Spearman correlation between PRU and %inhibition at 24-48 h post-PCI = -0.93; P < 0.0001 Spearman correlation between PRU and %inhibition at 5-7 w post-PCI = -0.86; P < 0.0001 Linear regression results (PRU ~ %inhibition) were also reported by Hb quartile: Q1: PRU = 393 – 4.16*(%inh); r^2=0.88 Q2: PRU = 352 – 3.56*(%inh); r^2=0.90 Q3: PRU = 332 – 3.41*(%inh); r^2=0.85 Q4: PRU = 314 – 3.28*(%inh); r^2=0.87
Von Beckerath 2006 Germany 16676093	LTA (ADP 5 and 20 µM) [Chrono-log lumi-aggregometer; Probe & go Labordiagnostica; Endingen, Germany] Platelet agglutination assay	Measurements were obtained in 30 patients, before and after clopidogrel administration (results were not analyzed separately) with all 3 assays; results from VerifyNow were correlated with LTA (using two different ADP concentrations)	"Correlations assessed by linear regression" between VerifyNow PRU units and LTA (ADP 5 µM) = 0.86; P < 0.0001 "Correlations assessed by linear regression" between VerifyNow PRU units and LTA (ADP 20 µM) = 0.86; P < 0.0001

	(ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]		"Correlations assessed by linear regression" between VerifyNow %inhibition units and LTA (ADP 5 µM) = -0.85 "Correlations assessed by linear regression" between VerifyNow %inhibition units and LTA (ADP 5 µM) = -0.84
Sambu 2011 UK 21231856	TEG (ADP channel, concentrations NR) [TEG Haemostasis system; Haemonetics Corp., MA, USA] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Analyses were based on "296 timepoints". In the methods section the patients included in this analyses are reported as follows: 30 on clopidogrel 600 mg × 5 timepoints = 150 measurements; 29 on clopidogrel 900 mg × 5 timepoints = 145 measurements; 20 on dual treatment (presumably at a single time point) = 20 measurements, for a total of 315 measurements. The discrepancy is not clarified in the paper. It is also unclear if a small number of healthy volunteers were included (at most they would represent 17% of the total sample size).	Pearson correlation between TEG ADP channel (AUC for the response curve at 15 minutes) and VerifyNow = 0.609; P<0.001 (R^2=0.371 from linear regression)
Freynhofer 2011 Austria 21614416	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Biocytex Inc, Marseille, France]; using flow cytometry [additional details NR] Impedance aggregometry (ADP 6.5 µM ± PGE1 9.4 µM) [Multiplate analyzer, Dynabyte Medical, Munich, Germany]	196 patients with valid measurements on both assays	Spearman correlation coefficient between Multiplate analyzer and PRI VASP = 0.587; P<0.001
Ang 2008 USA 18848137	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	157 patients provided measurements to compare two metrics reported by the same assay	Pearson correlation coefficient between % inhibition and final PRU values = -0.879; P<0.001
Varenhorst 2009 Sweden 19249429	LTA (ADP 20 µmol/L) [PAP-4 optical aggregometer, BioData, no additional information reported] VASP phosphorylation assay (PGE1 ± ADP, concentrations NR) [Platelet VASP kit, BioCytex, Marseille, France]; using flow cytometry [samples were analyzed on different flow-cytometers in 2 participating centers: Epics XL, Beckman Coulter, Fullurton, CA; and FACScan, Becton Dickinson, Franklin Lakes, NJ]. The authors reported that "synchronization between the flow cytometers was performed". Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	110 patients (1:1 randomized to clopidogrel or prasugrel) measured at 5 timepoints (not clear if all measurements were available for all patients and timepoints)	Pearson correlation coefficient between PRI VASP and VerifyNow PRU = 0.86; P<0.0001 during the loading dose phase Pearson correlation coefficient between PRI VASP and VerifyNow PRU = 0.81; P<0.0001 during the maintenance dose phase Pearson correlation coefficient between late reactivity (6 min) by LTA and VerifyNow PRU = 0.88; P<0.0001 during the loading dose phase Pearson correlation coefficient between late reactivity (6 min) by LTA and VerifyNow PRU = 0.79; P<0.0001 during the maintenance dose phase Pearson correlation coefficient between maximal reactivity by LTA and VerifyNow PRU = 0.76; P<0.0001 during the loading dose phase --- Linear regression of PRI VASP over VerifyNow PRU: (PRI VASP) = 8.418 + 0.284*(VerifyNow PRU), during the loading dose phase Linear regression of PRI VASP over VerifyNow PRU: (PRI VASP) = 16.335 + 0.192*(VerifyNow PRU), during the maintenance dose phase Linear regression of late reactivity (6 min) by LTA over VerifyNow PRU: (LTA reactivity) = 3.096 + 0.233*(VerifyNow PRU), during the loading dose phase Linear regression of late reactivity (6 min) by LTA over VerifyNow PRU: (LTA reactivity) = 9.839 + 0.177*(VerifyNow PRU), during the maintenance dose phase
Lordkipanidze	LTA	116 patients contributed samples to the analyses; only	Partial correlations (accounting for randomization group)

2008 Canada 18826988	(ADP 5 and 20 μM) [ChronoLog 540 model, Havertown, PA] Impedance aggregometry (ADP 5 and 20 μM) [ChronoLog 560 model, Havertown, PA] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA] High shear platelet function (collagen/ADP cartridges) [PFA-100, Dade Behring, Deerfield, IL]	72 patients had measurements with VerifyNow	Correlation between LTA ADP 5 μM and LTA ADP 20 μM = 0.902 (95% CI, 0.862, 0.931); P<0.05 Correlation between LTA ADP 5 μM and impedance aggregometry ADP 5 μM = 0.255 (95% CI, 0.077, 0.417); P<0.05 Correlation between LTA ADP 5 μM and impedance aggregometry ADP 20 μM = 0.307 (95% CI, 0.133, 0.463); P<0.05 Correlation between LTA ADP 5 μM and PFA-100 = -0.270 (95% CI, -0.438, -0.102); P<0.05 Correlation between LTA ADP 5 μM and VerifyNow = 0.370 (95% CI, 0.152, 0.554); P<0.05 Correlation between LTA ADP 20 μM and impedance aggregometry ADP 5 μM = 0.291 (95% CI, 0.112, 0.449); P<0.05 Correlation between LTA ADP 20 μM and impedance aggregometry ADP 20 μM = 0.382 (95% CI, 0.215, 0.527); P<0.05 Correlation between LTA ADP 20 μM and PFA-100 = -0.274 (95% CI, -0.434, -0.097); P<0.05 Correlation between LTA ADP 20 μM and VerifyNow = 0.496 (95% CI, 0.299, 0.652); P<0.05 Correlation between impedance aggregometry ADP 5μM and impedance aggregometry ADP 20 μM = 0.881 (95% CI, 0.833, 0.916); P<0.05 Correlation between impedance aggregometry ADP 5μM and PFA-100 = -0.139 (95% CI, -0.313, 0.044); P=NS Correlation between impedance aggregometry ADP 5μM and VerifyNow = 0.187 (95% CI, -0.046, 0.401); P=NS Correlation between impedance aggregometry ADP 20 μM and PFA-100 = -0.150 (95% CI,- 0.322, 0.033); P=NS Correlation between impedance aggregometry ADP 20 μM and VerifyNow = 0.293 (95% CI, 0.066, 0.491); P<0.05 Correlation between PFA-100 and VerifyNow = -0.334 (95% CI, -0.525, -0.111); P<0.05
Jeong 2008 S. Korea 18617479	LTA (ADP 5 μM) [ChronoLog 540 model, Havertown, PA] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	300 patients measured with both assays	Correlation between LTA PRU and VerifyNow = 0.641; P<0.001 Correlation between LTA % inhibition and VerifyNow = 0.679; P<0.001
Kim 2010 S. Korea 20449634	LTA (ADP 5 and 20 μM) [AggRam aggregometer, Helena Laboratories Corp., Beaumont, TX] Platelet agglutination assay	1058 patients contributed measurements	Pearson correlation between maximal reactivity by LTA ADP 5 μmol/L and VerifyNow PRU = 0.653 P<0.001 Pearson correlation between late reactivity by LTA ADP 5 μmol/L and VerifyNow PRU = 0.669 P<0.001

	(ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]		Pearson correlation between maximal reactivity by LTA ADP 20 µmol/L and VerifyNow PRU = 0.683 P<0.001 Pearson correlation between late reactivity by LTA ADP 20 µmol/L and VerifyNow PRU = 0.718 P<0.001
Malinin 2006 USA 16845449	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	131 patients with CAD contributed two measurements with VerifyNow (before and after clopidogrel) to compare the before-after contrast (using the measured values) versus an "estimated" contrast using the post-clopidogrel measurement and the TRAP channel of the same device	Pearson correlation between estimated and observed contrast = 0.971 Base on linear regression of the %inhibition using the TRAP channel versus inhibition using the observed baseline value: (estimated %inhibition) = 0.9989*(observed % inhibition) – 0.0129
Hochholzer 2007 Germany 16603231	LTA (ADP 20 µmol/L) [PAP4, Molab, Hilden, Germany] Impedance aggregometry (ADP 20 µmol/L) [Chronolog Series 590; Probe and Co, Endingen, Germany] ADP-stimulated P-selectin and activated IIb/IIIa expression (ADP 20 µmol/L final concentration) Using flow cytometry [FACSCalibur flow cytometer, Becton Dickinson, Germany] Platelet agglutination assay (ADP cartridges) [ULTEGRA rapid platelet function assay, Accumetrics, San Diego, CA]	27 patients presumably at two timepoints; on-clopidogrel samples were obtained before PCI (after loading) and 24 h post-PCI; measurements in analyses of correlations appear to have been treated as independent observations	Spearman correlation coefficient between LTA and P-selectin expression = 0.515; P<0.001 Spearman correlation coefficient between LTA and activated IIb/IIIa expression = 0.568; P<0.001 Spearman correlation coefficient between LTA and impedance aggregometry = 0.257; P=0.196 Spearman correlation coefficient between LTA and ULTEGRA assay = 0.135; P=0.504 Spearman correlation coefficient between P-selectin expression and activated IIb/IIIa expression = 0.815; P<0.001 Spearman correlation coefficient between P-selectin expression and impedance aggregometry = 0.292; P=0.139 Spearman correlation coefficient between P-selectin expression and ULTEGRA assay = 0.453; P=0.059 Spearman correlation coefficient between activated IIb/IIIa expression and impedance aggregometry = 0.471; P=0.013 Spearman correlation coefficient between activated IIb/IIIa expression and ULTEGRA assay = 0.523; P=0.026
Lordkipanidze 2009 Canada 19250657	LTA (ADP 5 and 20 µM) [ChronoLog Aggregometer, 540 model, Havertown, PA] "Platelet count drop method" using impedance platelet counting before and after exposure to the agonist (ADP 5 and 20 µM) Using a Coulter ACT Series Analyzer, Beckman Coulter Inc., Fullerton, CA]	91 patients receiving aspirin + clopidogrel	Spearman correlation coefficient between LTA (ADP 5 µM) and platelet count drop method (ADP 5 µM) = 0.374; P<0.001 Spearman correlation coefficient between LTA (ADP 20 µM) and platelet count drop method (ADP 20 µM) = 0.402; P<0.001
Pettersen 2011 Norway 21426546	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [PLT VASP/P2Y12 assay, Biocytex, France]; using flow cytometry [FACS Calibur System, Becton Dickinson, Plymouth, UK] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	219 patients were on aspirin + clopidogrel; 155 were analyzed successfully with the VASP assay and 212 with the VerifyNow assay	Spearman correlation coefficient between PRI VASP and VerifyNow PRU = 0.682; P<0.001
Sibbing 2008 Germany	LTA (ADP 5 or 20 µM) [PAPA 8 aggregometer, Bio/Data, no additional information reported]	149 patients were included in the study and contributed on-clopidogrel measurements to the analysis; baseline (pre-clopidogrel) measurements were available from 60	Correlation between LTA (ADP 5 µM) and Multiplate analyzer = 0.71; P<0.0001

18217143	Impedance aggregometry (ADP, 6.4 μM) [Multiplate analyzer, Dynabyte, Munich, Germany]	patients (data not reported separately); pre- and post-clopidogrel measurements were treated as independent observations	Correlation between LTA (ADP 20 μM) and Multiplate analyzer = 0.71; P<0.0001

NA = not applicable; NR = not reported; PMID = PubMed identification number; TEG = Thromboelastography.

Appendix Table E3: Studies reporting results on the reliability of platelet reactivity assays with unclear study designs

Author Year Country PMID	Assays evaluated (agonist) [brand name, manufacturer]	Results
Cuisset 2009{Cuisset, 2009 113 /id} France 19761935	LTA (ADP 10 µmol/L) [PAP4, Biodata Corporation, Wellcome, Paris, France]	COV of maximal intensity of aggregation (PAP4) = 6.5%
Cecchi 2009{Cecchi, 2009 114 /id} Italy 19733708	LTA (ADP 10 µmol/L) [APACT 4, Helena Laboratories, Milan, Italy]	Mean COV for ADP-induced aggregation = 6.8%
Paniccia 2009{Paniccia, 2009 127 /id} Italy 19461090	LTA (ADP, 10 µmol/L and collagen, 2 g/mL) [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany] Impedance aggregometry (ADP, 10 µmol/L and collagen, 2 g/mL) [Multiplate analyzer, Dynabyte, Munich, Germany]	Mean COV for LTA (50 measurements) = 6.8% (ADP as agonist) and 6.7% (collagen as agonist) Mean COV (5 repeat measurements in an unspecified number of patients) = 6.2% (ADP as agonist) and 6.6% (collagen as agonist)
Cuisset 2009{Cuisset, 2009 131 /id} France 18990434	LTA (ADP 10 µmol/L) [PAP4, Biodata Corporation, Wellcome, Paris, France]	COV of maximal intensity of platelet aggregation = 6.5%
Frere 2008{Frere, 2008 176 /id} France 18394438	LTA (ADP 10 µmol/L) [PAP4, Biodata Corporation, Wellcome, Paris, France]	COV of maximal intensity of platelet aggregation = 6.5%
Bonello 2008{Bonello, 2008 177 /id} France 18387444	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP kit, Diagnostica Stago, Asnieres, France]; using flow cytometry [EPICS XL cytometer, Beckman Coulter Inc., Fullerton, California]	Intra-assay COV was <5%
Mani 2008{Mani, 2008 183 /id} Germany 18223467	LTA (ADP 2µmol/L) [Behring Coagulation Timer, BCT, Dade Behring, Dudingen, Switzerland]	Within-subject variation was 3.3%
Frere 2007{Frere, 2007 193 /id} France 17938809	LTA (ADP 10 µM) [PAP4 aggregometer, Biodata Corporation, Wellcome, Paris, France]	COV of maximal intensity of platelet aggregation = 6.5%
Cuisset 2007{Cuisset, 2007 196 /id} France 17337040	LTA (ADP 10 µmol/L) [PAP4 Aggregometer, Biodata Corporation, Wellcome, Paris, France]	COV of maximal intensity of platelet aggregation = 6.5%
Bonello 2007{Bonello, 2007 199 /id} France 17488353	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP kit, Biocytex, Marseille, France]; using flow cytometry [Coulter EpicsXL cytometer, no additional information reported]	Intra-assay COV <5%.
Cuisset 2007{Cuisset, 2007 203 /id} France 17264949	LTA (ADP 10 µM) [PAP4 Aggregometer, Biodata Corporation, Wellcome, Paris, France]	COV of maximal intensity of platelet aggregation = 6.5%
Cuisset 2006{Cuisset, 2006 212 /id} France 16371119	LTA (ADP 10 µmol/L) [PAP4 Aggregometer, Biodata Corporation, Wellcome, Paris, France]	COV of maximal intensity of platelet aggregation = 6.5%
Wang 2011{Wang, 2011 16 /id} China 21538380	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP kit, Becton Dickinson, Franklin Lakes, NJ]; using flow cytometry [Coulter Epics XL cytometer, FACSCalibur, Becton Dickinson, Franklin Lakes, NJ]	Intra-assay COV < 5% Inter-assay COV < 8%
Gori 2008{Gori, 2008 151 /id}	LTA (ADP, 10 µmol/L and collagen, 2 Mg/mL) [APACT-4, Helena Laboratories, Italy]	COV for LTA (ADP) = 6.8% COV for LTA (collagen) = 5.6%

Italy 19132241	High shear platelet function (collagen/ADP and collagen/epinephrine cartridges) [PFA-100, Dade-Behring, Marburg, Germany]	COV for PFA-100 (collagen/ADP) = 9.3% COV for PFA-100 (collagen/epinephrine) = 9.9%
Neubauer 2011{Neubauer, 2011 28 /id} Germany 21226927	Impedance aggregometry (ADP 5µM) [Whole Blood Aggregometry, Model 590, Chrono-log Corporation, Havertown, PA]	"Results were reproducible with a variability <10%"
Armero 2010{Armero, 2010 59 /id} France 20670107	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [Platelet VASP kit, Diagnostica Stago, Asnieres, France]; using flow cytometry [Coulter Epics XL cytometer, Beckman Coulter, Inc., Fullerton, CA]	Intra-assay COV <5%.
Neubauer 2010{Neubauer, 2010 71 /id} Germany 20410834	Impedance aggregometry (ADP 5µmol/L) [Model 590, Chrono-log Corporation, Havertown, PA]	Results were "reproducible with a variability <10%"
Madsen 2010{Madsen, 2010 79 /id} Canada 20224050	LTA (ADP, 5 µM) [Chrono-Log Lumi Aggregometer, model 810; Chrono-Log Corporation, no additional details provided]	Duplicate measurements were performed only for LTA (other tests were assessed in the study) While patients were on clopidogrel (measurements within 1 d to 12 mo of drug initiation) the standard deviations between duplicate measurements of maximal aggregation and late aggregation were 3.0% and 3.3%, respectively.
Cuisset 2010{Cuisset, 2010 93 /id} France 20142119	LTA (ADP 10 µmol/L) [PAP4, Biodata Corporation, Wellcome, Paris, France]	COV of maximal platelet aggregation = 6.5%
Cuisset 2009{Cuisset, 2009 139 /id} France 18499233	LTA (ADP 10 µmol/L) [PAP4 Aggregometer, Biodata Corporation, Wellcome, Paris, France]	COV of maximal platelet aggregation = 6.5%
Lordkipanidze 2009{Lordkipanidze, 2009 110 /id} Canada 19419755	LTA (ADP 5 and 20 µM) [ChronoLog aggregometer 540 model, Havertown, PA]	Intra-assay variability for peak platelet aggregation ranged from 8.5% to 11.3% at baseline, and 12.1% to 12.9% post-clopidogrel Intra-assay variability for late platelet aggregation ranged from 10.5% to 17.1% at baseline, and 16.6% to 17.5% post-clopidogrel
Paniccia 2010{Paniccia, 2010 69 /id} Italy 20458439	LTA (ADP, 10 µM) [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany] Impedance aggregometry (ADP, 10 µM final concentration) [Multiplate analyzer, Dynabyte, Munich, Germany]	Mean COV for LTA = 4.8% (5 samples × 10 patients = 50 datapoints) Mean COV of Multiplate analyzer based on 5 samples obtained from each of several subjects (exact number not reported) = 5.8%
Migliorini 2009 Italy 19917884	LTA (ADP, 10 µmol/L) [APACT4 aggregometer, Helena Laboratories, Milan, Italy]	COV of maximal percentage platelet aggregation = 6.8%
Gori 2008 Italy 18718420	LTA (ADP, 10 µM and collagen, 2 µg/mL) [APACT4 aggregometer, Helena Laboratories, Milan, Italy]	COV of platelet aggregation (ADP) = 6.8% COV of platelet aggregation (ADP) = 5.6%
Wilson 2009 UK 19786240	Percentage of platelets binding fibrinogen (ADP, 10^{-5} mol/L) [using flow cytometry, Coulter Epics XL-MCL Flow Cytometer; Beckman Coulter Inc., Brea, CA]	Inter-assay COV = 5.7%
Cuisset 2006 France 17010792	LTA (ADP 10 µmol/L) [PAP4 Aggregometer, Biodata Corporation, Wellcome, Paris, France]	COV of maximal intensity of platelet aggregation = 6.5%
Huczek 2008 Poland 18301358	High shear platelet function (collagen/ADP and collagen/epinephrine cartridges) [PFA-100, Dade-Behring, Marburg, Germany]	In "duplicate analyses": COV using the collagen/ADP cartridge = 9.5% COV using the collagen/epinephrine cartridge = 11.7%;
Patti 2011 Italy 21256470	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Repeat analyses in 25 patients (number of replicate samples NR) Intra-assay variability = 2.0% ±1.1% Intra-assay COV = 6%
Lee 2011 S. Korea 21791883	Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Variability of the P2Y12 assay = 7.5% at "the authors institution"
Freynhofer 2011	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported)	Repeatability coefficient for PRI VASP = 6.6%

Austria 21614416	[Biocytex Inc, Marseille, France]; using flow cytometry [additional details NR]	
Marcucci 2007 Italy 17555759	LTA (ADP 2 and 10 µM) [APACT4 aggregometer, Helena Laboratories Italia s.p.a., Milan, Italy]	COV of LTA (ADP) = 6.8%
Pettersen 2011 Norway 21426546	VASP phosphorylation assay (PGE1 ± ADP, concentration not reported) [PLT VASP/P2Y12 assay, Biocytex, France]; using flow cytometry [FACS Calibur System, Becton Dickinson, Plymouth, UK] Platelet agglutination assay (ADP cartridges) [VerifyNow P2Y12 assay, Accumetrics, San Diego, CA]	Intra-assay COV for VASP assay = 2.3% Intra-assay COV for VerifyNow assay = 7%
Paniccia 2007{Paniccia, 2007 198 /id} Italy 17723123	LTA (ADP, 2 µmol/L and 10 µmol/L) [APACT-4 aggregometer, LABiTec, Ahrensburg, Germany]	Mean COV of LTA = 6.8% (5 measurements × 10 CAD patients (50 data-points)
Paniccia 2011{Paniccia, 2011 31 /id} Italy 21192314	LTA (ADP, 2 µmol/L, 5 µmol/L, 10 µmol/L, and 20 µmol/L) [APACT-4004 aggregometer, LABiTec, Ahrensburg, Germany]	5 samples from each of 10 patients of the assessment of reliability: Mean CoV for LTA (ADP 2 µmol/L) = 6.8% Mean CoV for LTA (ADP 2 µmol/L) = 5.2% Mean CoV for LTA (ADP 2 µmol/L) = 2.7% Mean CoV for LTA (ADP 2 µmol/L) = 3.1%

COV = coefficient of variation; NA = not applicable; NR = not reported; PMID = PubMed identification number.

Appendix Table E4: Reporting characteristics and methodological quality of studies of analytic validity

Author Year Country PMID	Was the execution of the assay described in sufficient detail to permit replication?	Were both positive and negative control samples tested?	Were negative control materials from the same type of tissue, and collected, stored, and processed in the same way that sample materials used clinically for testing will be?	Were the tests performed with positive or negative control samples being blinded to the testers?	Were the testing results interpreted with positive or negative control samples being blinded to the interpreters?	Were criteria for determining a testing result as positive, negative, indeterminate, or uninterpretable set *a priori*?	Was the limit of detection of the test reported?	Was the assay linearity range reported?	Was the reproducibility of the test when performed multiple times on a single specimen established?	Was the reproducibility of the test adequately established(across operators/ instruments/reagent lots/ different days of the week/ different laboratories)?	Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?
Michelson 2009{Michelson, 2009 121 /id} USA 19435740	YES	NR	NA	NR	NR	YES (thresholds based on prior literature; criteria for non-evaluable samples)	NO	NO	NO	NO	YES (data read locally at each of the 13 participating centers; centralized testing was done for all samples; agreement between central and local readings NR)
Paniccia 2009{Paniccia, 2009 127 /id} Italy 19461090	YES	NR	NA	NR	NR	YES (thresholds based on prior literature; alternative thresholds for analytic performance derived from ROC analysis)	NO	NO	YES	NO	NO
Oestreich 2009{Oestreich, 2009 132 /id} USA 19318928	YES	NR	NA	NR	NR	NO (thresholds for poor response were defined based on the study data: values 2 or more standard errors higher than the mean value for each assay)	NO	NO	NO	NO	NO
Marcucci 2007{Marcucci, 2007 192 /id} Italy 17938810	YES	NR	NA	NR	NR	NO (thresholds for poor response were defined based on study data on control individuals: values beyond the 90th percentile of controls were considered positive)	NO	NO	NO	NO	NO
Frere 2007{Frere, 2007 193 /id} France 17938809	YES	NR	NA	NR	NR	NO (thresholds for poor response were defined based on study data on subsequent vascular events, using ROC analysis)	NO	NO	UNCLEAR (COV reported for one of the assays but methods for calculation not reported)	NO	NO
Paniccia 2007{Paniccia, 2007 198 /id} Italy 17723123	YES	NR	NA	NR	NR	YES (for *some* of the assays cut-offs were derived from the prior literature)	NO	NO	YES (for one of the assays)	NO	NO
Van Werkum	YES	NR	NA	NR	NR	NA	NO	NO	NO	NO	NO

Author Year Country PMID	Was the execution of the assay described in sufficient detail to permit replication?	Were both positive and negative control samples tested?	Were negative control materials from the same type of tissue, and collected, stored, and processed in the same way that sample materials used clinically for testing will be?	Were the tests performed with positive or negative control samples being blinded to the testers?	Were the testing results interpreted with positive or negative control samples being blinded to the interpreters?	Were criteria for determining a testing result as positive, negative, indeterminate, or uninterpretable set *a priori*?	Was the limit of detection of the test reported?	Was the assay linearity range reported?	Was the reproducibility of the test when performed multiple times on a single specimen established?	Was the reproducibility of the test adequately established(across operators/ instruments/reagent lots/ different days of the week/ different laboratories)?	Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?
2006{van Werkum, 2006 209 /id} Netherlands 16938130						(no thresholds were employed)					
Mobley 2004{Mobley, 2004 221 /id} USA 14969622	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Ren 2011 China 21518592	YES	NR	NA	NR	NR	NO	NO	NO	NO	NO	NO
Godino 2009 Italy 19419580	YES	NR	NA	NR	NR	NO (thresholds were determined based on the observed distribution of measurements)	NO	NO	NO	NO	NO
Paniccia 2011{Paniccia, 2011 31 /id} Italy 21192314	YES	NR	NA	NR	NR	YES (cut-offs were derived based on prior literature)	NO	NO	YES	NO	NO
Koessler 2011{Koessler, 2011 32 /id} Germany 20873965	YES	NR	NA	NR	NR	YES (cut-offs in some analyses were those suggested by the manufacturer; other cut-offs were used as part of the study design)	NO	NO	NO (however, experiments were run at least in duplicate and results were averaged)	NO	NO
Paniccia 2010{Paniccia, 2010 69 /id} Italy 20458439	YES	NR	NA	NR	NR	YES (based on prior literature)	NO	NO	YES	NO	NO
Ko 2011{Ko, 2011 26 /id} Korea 21315223	YES	NR	NA	NR	NR	NA (no thresholds were used)	NO	NO	NO	NO	NO
Aradi 2010{Aradi, 2010 60 /id} Hungary 20642320	YES	NR	YES	NR	NR	YES (based on literature for PRI VASP; ROC analyses for LAT)	NO	NO	NO	NO	NO
Woo	YES	NR	NA	NR	NR	YES	NO	NO	NO	NO	NO

Author Year Country PMID	Was the execution of the assay described in sufficient detail to permit replication?	Were both positive and negative control samples tested?	Were negative control materials from the same type of tissue, and collected, stored, and processed in the same way that sample materials used clinically for testing will be?	Were the tests performed with positive or negative control samples being blinded to the testers?	Were the testing results interpreted with positive or negative control samples being blinded to the interpreters?	Were criteria for determining a testing result as positive, negative, indeterminate, or uninterpretable set *a priori*?	Was the limit of detection of the test reported?	Was the assay linearity range reported?	Was the reproducibility of the test when performed multiple times on a single specimen established?	Was the reproducibility of the test adequately established(across operators/ instruments/reagent lots/ different days of the week/ different laboratories)?	Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?
2010{Woo, 2010 61 /id} Korea 20890076						(based on prior literature for all assays)					
Madsen 2010{Madsen, 2010 79 /id} Canada 20224050	YES	NR	NA	NR	NR	YES (cut-offs based on prior literature)	NO	NO	YES (for LTA duplicate measurements were obtained and the mean used in analyses; the variance in repeat testing was also reported)	NO (repeat measurements only for one of the tests of interest; details about reproducibility assessment not reported)	NO
Siller-Matula 2010{Siller-Matula, 2010 89 /id} Austria 19943879	YES	NR	NA	NR	NR	NO (cut-offs were determined based on observed data, using ROC analysis)	NO	NO	NO (however references were provided to previous investigations, some from the same investigators)	NO	NO
Cuisset 2010{Cuisset, 2010 93 /id} France 20142119	YES	NR	NA	NR	NR	YES (main analyses used cut-offs obtained from prior literature; analyses with alternative thresholds were also presented)	NO	NO	NO (references to previous investigations on reproducibility are provided)	NO	NO
Smit 2009{Smit, 2009 137 /id} Netherlands 19200163	YES	NR	NA	NR	NR	NO (no explicit thresholds were used)	NO (however, the authors commented that the iron-based assay could obtain measurement beyond the detection limit of other assays used in the study)	NO	YES (duplicate measurements were performed in 111 samples for one of the assays)	NO	NO
Gremmel 2009{Gremmel, 2009 138 /id} Austria 19190818	YES	NR	NA	NR	NR	NO (thresholds were determined based on the empirical distribution of the	NO	NO	NO	NO	NO

Author Year Country PMID	Was the execution of the assay described in sufficient detail to permit replication?	Were both positive and negative control samples tested?	Were negative control materials from the same type of tissue, and collected, stored, and processed in the same way that sample materials used clinically for testing will be?	Were the tests performed with positive or negative control samples being blinded to the testers?	Were the testing results interpreted with positive or negative control samples being blinded to the interpreters?	Were criteria for determining a testing result as positive, negative, indeterminate, or uninterpretable set *a priori*?	Was the limit of detection of the test reported?	Was the assay linearity range reported?	Was the reproducibility of the test when performed multiple times on a single specimen established?	Was the reproducibility of the test adequately established(across operators/ instruments/reagent lots/ different days of the week/ different laboratories)?	Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?
						results in the study)					
Schafer 2008{Schafer, 2008 158 /id} Germany 18841284	YES	NR	NA	NR	NR	YES (thresholds were based on prior literature)	NO	NO	NO (measures of variability were obtained from a population not on clopidogrel treatment)	NO	NO
Shenkman 2008{Shenkman, 2008 166 /id} Israel 18155752	YES	NR	NA	NR	NR	YES (cut-offs for the reference standard test were)	NO	NO	NO	NO	NO
Lordkipanidze 2008{Lordkipanidze, 2008 170 /id} Canada 18520610	YES	NR	NA	NR	NR	NA (no explicit thresholds were used)	NO	NO	NO	NO	NO
Lordkipanidze 2009{Lordkipanidze, 2009 108 /id} Canada 19840560	YES	NR	NA	NR	NR	NO (thresholds were determined based on the observed distribution of measurements; positive tests were defined as those > mean + 2*SD)	NO	NO	NO	NO	NO
Lordkipanidze 2009{Lordkipanidze, 2009 110 /id} Canada 19419755	YES	NR	NA	NR	NR	NO (no thresholds were used in analyses relevant to analytic validity)	NO	NO	YES (analyses of intra-assay variability were reported)	NO	NO
Collet 2008{Collet, 2008 160 /id} France 18765393	YES	NR	NA	NR	NR	YES (based on prior literature)	NO	NO	NO	NO	NO
Von Beckerath 2010{Von, 2010 98 /id} Germany 19823079	YES	NR	NA	NR	NR	NO (thresholds were determined based on the observed distribution of measurements)	NO	NO	NO	NO	NO
Varenhorst 2009 Sweden 19249429	YES	NR	NA	NR	NR	NO (thresholds were determined based on the observed distribution of	NO	NO	NO	NO	NO (however, two laboratories participated in the study and the authors reported that

Author Year Country PMID	Was the execution of the assay described in sufficient detail to permit replication?	Were both positive and negative control samples tested?	Were negative control materials from the same type of tissue, and collected, stored, and processed in the same way that sample materials used clinically for testing will be?	Were the tests performed with positive or negative control samples being blinded to the testers?	Were the testing results interpreted with positive or negative control samples being blinded to the interpreters?	Were criteria for determining a testing result as positive, negative, indeterminate, or uninterpretable set *a priori*?	Was the limit of detection of the test reported?	Was the assay linearity range reported?	Was the reproducibility of the test when performed multiple times on a single specimen established?	Was the reproducibility of the test adequately established(across operators/ instruments/reagent lots/ different days of the week/ different laboratories)?	Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?
						measurements)					flow cytometers were "synchronized")
Lordkipanidze 2008 Canada 18826988	YES	NR	NA	NR	NR	YES (based on published guidelines)	NO	NO	NO	NO	NO
Jeong 2008 S. Korea 18617479	NO	NR	NA	NR	NR	NO (thresholds were determined based on the observed distribution of measurements)	NO	NO	NO	NO	NO
Kim 2010 S. Korea 20449634	YES	NR	NA	NR	NR	YES (for some analyses thresholds were determined based on prior literature; analyses with alternative thresholds were also presented)	NO	NO	NO	NO	NO
Lordkipanidze 2009 Canada 19250657	YES	NR	NA	NR	NR	YES (based on prior literature)	NO	NO	NO	NO	NO
Pettersen 2011 Norway 21426546	YES	NR	NA	NR	NR	YES (determined based on an independent group of patients receiving aspirin only)	NO	NO	NO	NO	NO
Sibbing 2008 Germany 18217143	YES	YES (mentions the use of control samples for quality control)	NR	NR	NR	NO (thresholds were determined based on the observed distribution of measurements)	NO	NO	YES (assessed assay variability)	NO	NO

NA = not applicable; NR = not reported; PMID = PubMed identification number; ROC = receiver operating characteristic.

Key Question 2b - Tables

Appendix Table E5: Baseline characteristics of patients with ischemic heart disease in studies assessing the predictive ability of LTA

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[12]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
Geisler, 2010{Geisler, 2010 54 /id} 20526607 Germany NR	1703 NR 74.8 67.5±10.9	NR NR NR NR NR NR NR NR	hyper 62.4 40.6 HTN 81.5 32	NR 100 100 NR	26 DES 25; BMS 1 NR	PCI	Patients who were naı¨ve to clopidogrel received a 600 mg loading dose and patients already receiving chronic clopidogrel therapy were treated by a 300 mg LD prior to stent implantation. A standard maintenance dose of 75 mg/day Clopidogrel and ASA 100 mg/day was prescribed for all patients.	NR
Cuisset, 2009{Cuisset, 2009 111 /id} 19801028 France NR	599 NR 465 (77.8) Median: 65	NR NR NR NR	331 (55.4) 232 (38.8) 334 (55.9) 210 (35.1)	NR NR NR NR	NR 182 (30.4) NR	Treatment of NSTE ACS	Patients received oral loading doses of 250 mg aspirin and 600 mg clopidogrel ≥12 hours before stenting.	NR

[12] Mean (standard deviation), unless otherwise stated.

		NR NR NR NR NR						
Frere, 2007{Frere, 2007 193 /id} 17938809 France NR	195 NR 158 (81) 63.4±11.1	NR NR NR NR NR NR NR NR NR	107 (54.9) 96 (49.2) 111(56.9) 68 (34.9)	NR 100 100 NR	NR NR NR	Patients had undergone successful coronary stenting	All patients received a 600 mg loading dose of clopidogrel and a 250 mg loading dose of aspirin administered at least 12 h before stenting. After PCI, patients received clopidogrel and aspirin 75 mg daily during one-month follow-up.	Anticoagulation was performed with low-molecular-weight heparin (enoxaparin), or unfractionated heparin if age over 75 years or in case of renal insufficiency (creatinin clearance < 60 ml/min).
Hoshino, 2009{Hoshino, 2009 143 /id} 19106460 Japan NR	30 ? Asian: 30 (100%) 22 (73%) 70 ± 7	1 NR Prior cerebrovascular disease: 3% PCI: 13% NR NR 7% 3% NR	hyperlipidemia: 73% Current: 33% HTN (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg): 60% 2HbA1c >6.5 %: 23%	0 NR NR 23%	NR NR NR	Patients undergoing percutaneous coronary intervention (PCI) for ischemic heart disease	Clopidogrel 300 mg LD 24 hrs before PCI + 75 mg/d MD Aspirin 81-100 mg/day	NR
Breet, 2010{Breet,	1069	NR	80.3	NR	100	coronary artery disease	clopidogrel treatment (a	unless they were receiving

2010 86 /id} 20179285 Netherlands POPULAR	NR 75 64±10.6	NR NR NR NR NR NR 54.5 NR	11.1 HTN 76.9 18.6	100 89.4 27.8	DES 63.5 NR	scheduled for elective PCI with stent	maintenance of 75 mg/d therapy for>5 days or a loading dose of 300 mg ≥24 hours before PCI or 600 mg ≥4 hours before PCI) and aspirin (80-100 mg/d ≥10 days).	long-term anticoagulation with warfarins
Gurbel, 2010{Gurbel, 2010 84 /id} 20194878 10 study sites in North America and Europe RESPOND	98 White 87 (89); Black 8 (8); Other 3 (3) 76 (78%) 65±8	1 NR NR PCI:48%;CABG:37% NR NR NR NR NR	Hyperlipidemia: 94% Current: 17% HTN: 81% 26%	NR NR 100% 22%	NR NR NR	Patients with CAD on aspirin therapy	Nonresponders and responders were randomly treated with either a 600-mg clopidogrel load followed by 14±2 days of 75-mg daily maintenance therapy or a 180-mg ticagrelor load followed by 14±2 days of 90-mg twice daily maintenance therapy (period 1). In period 2, all nonresponders switched treatment, whereas half of the responders continued the same treatment, and the other half of the responders switched to the other treatment.	
Kim, 2010{Kim, 2010 241 /id} 20449634	1058 NR	62.2±11.2 NR	19% 39.8%	NR 25.3%	NR NR	Patients treated with coronary stenting for symptomatic	scheduled coronary stenting procedures, 300-	If use of glycoprotein IIb/IIIa inhibitor (GPI) was

Korea NR	70.1 62.2±11.2	3.6% PCI 30.4% NR NR NR 20.9% NR	52% 29%	NR NR	27.6%	coronary artery disease, including acute myocardial infarction (AMI) and on chronic clopidogrel therapy	mg loading-dose (LD) of clopidogrel at least 12 h before procedure. In AMI patients, all received a 600-mg LD of clopidogrel immediately after emergency room arrival, followed by a maintenance dose of 75 mg daily.	deemed necessary, only tirofiban, which has a short half-life, was administered.
Angiolillo, 2008{Angiolillo, 2008 180 /id} 18312754 USA OPTIMUS	34 NR 22 (64.7) 64.5±9	NR NR NR CABG 6(17.6) NR NR NR 14 (41.2) NR	31 (91.2) 10 (29.4) 31 (91.2) 100	NR 100 100 NR	NR NR 27(79.4)	Patients underwent PCI and were treated with standard clopidogrel	Clopidogrel 75 mg/day, and 1 month after clopidogrel 150 mg/ day. Thereafter, all patients resumed the standard 75 mg/day maintenance dose.	None
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	99 NR 74 (74.7) 63.7±11.2	NR NR NR PCI 47 (47.5) 35 (35.4) NR NR	58 (58.6) 42 (42.4) 70 (70.1) 16 (16.2)	NR 100 100 NR	NR DES 65 (65.7); BMS 34 (34.3) NR	Patients with an elevated risk to develop ST acute MI within 48 hours undergoing emergency or elective PCI	All patients were given 75 mg clopidogrel and 100 mg aspirin once a day at least five days prior to PCI. Only in case of emergency PCI, patients received a loading dose of 600 mg before the intervention. Dual antiplatelets for 6	

		47 (47.5) 22(22.2)/29 (29.3)					months.	
Bliden, 2007{Bliden, 2007 202 /id} 17291930 USA NR	100 Caucasian male 60 African-American male 12 66±11	NR NR NR CABG 31 NR 13 NR 40 NR	83 56 HTN 74; systolic 145±22; diastolic 76±16 44	NR 100 100 NR	100 DES 75 BMS 24 NR	Non-emergent coronary stenting	Clopidogrel therapy (75 mg qd) for ≥1 month before undergoing non-emergent coronary stenting were enrolled after giving informed consent. A clopidogrel loading dose was not administered. All patients had received at least 81 mg aspirin for 7 days before the procedure.	Eptifibatide was administered at the discretion of the treating physician with the ESPRIT study protocol as a double bolus (180 ug/kg) followed by an infusion (2 ug/kg/min) for 18 to 24 h after procedure. Unfractionated heparin was administered according to the ESPRIT dosing regimen (60 U/kg) as a bolus to all patients in the catheterization laboratory immediately before stenting.
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	746 NR 75 68±12	NR NR NR PCI 23; coronary artery surgery 6 33 40 NR 25 26	hyper 49 23 HTN 61 20	NR NR NR NR	100 DES 93 multi 57	not used	All patients received aspirin (325 mg) and a loading dose of 600 mg of clopidogrel followed by a maintenance dose of 75 mg daily.	Patients on a maintenance dose of ticlopidine or clopidogrel at the time of admission received a loading dose of clopidogrel (600 mg).
Gurbel, 2010{Gurbel,	225	NR	hyper 80	NR	NR	not used	Clopidogrel: 300 (n=73) to 600	Eptifibatide (n=123)

2010 68 /id} 20691842 USA PREPARE POST-STENTING	White male: 54 African American male: 13 66±12	NR CVA 12 PTCA 35;CABG 24 NR NR 8 33 NR	55 Systolic BP, mm Hg: 144 ± 25 Diastolic BP, mm Hg 75 ± 17;HTN: 74 41	NR NR 34	NR NR		mg (n=75) LD + 75 mg/d MD; no LD for pts on clopidogrel (n=77) Aspirin: 325 mg LD + 81-325 mg MD	Unfractionated heparin to achieve a clotting time of 200 to 250 seconds (for those given GPIIb/IIIa inhibitor) and >300 seconds (all other patients)
Matetzky, 2004{Matetzky, 2004 188 /id} 15184279 Israel No	60 NR 80 58±13	55 NR NR NR NR NR NR 13 100	28 47 18 27	NR NR NR NR	NR NR NR	NR	All received 300 mg of chewable aspirin on admission and 200 mg/d thereafter throughout the study period. Clopidogrel was administered as a loading dose of 300 mg on completion of the PCI, followed by doses of 75 mg/d for 3 months.	Heparin was administered during the procedure but was discouraged after the procedure. Eptifibatide was administered for a mean of 14±2 hours.
Angiolollo, 2007{Angiolillo, 2007 194 /id} 17936152 Spain NR	173 173 (100) 113 (65) 67±9	127 (73) NR 7(4) 7(4) NR	118 (68) 23(13) 112 (65) 100	NR 100 100 NR	108 (62) Drug-eluting stent 127 (73)	Patients with coronary artery disease (CAD)	Treatment with clopidogrel (75 mg/day) had been prescribed for 12 months. Aspirin (100 mg/day) was used indefinitely.	

		NR 21 (12) 92 (53) NR						
Aradi, 2008{Aradi, 2008 236 /id} 18388039 Hungary NR	134 NR 79 (58.96%) 61.07 ± mean ± SD	NR NR NR NR NR NR NR 25 (18.66%) previous MI NR	15 (11.19%) Hypecholesterinaemia Ever 57 (42.54%)/Current 28 (20.90%) HTN 104 (77.61%) (>140/90 or receiving antiHTN treatment) 32 (23.88%)	NR NR NR NR	100% Bare metal NR	Patients referred for PCI with stenting	Antiplatelet agents were given at the time of the procedure, 300 mg ASA with 300 mg clopidogrel or 500 mg ticlopidine, orally at the discretion of the operator. After PCI, 100 mg ASA supplemented by 75 mg clopidogrel or 2 x 250 mg ticlopidine were given daily to patients until 12 months.	PCI done after administration of 60 to 90 IU/body weight kilograms of unfractionated heparin. No platelet glycoprotein IIb/IIIa receptor blocker was used.
Bellemain-Appaix, 2010{Bellemain-Appaix, 2010 87 /id} 20170822 France ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis)	96 NR 76 (79%) mean: 61.7	NR NR NR NR NR NR NR 100% n-STEMI: 100%	hyperlipidemia: 51% Tobacco use: 30% High BP: 57%1 21.9%	NR NR 39.5% NR	NR NR NR	Patients with ACS	In the RCT, patients were allocated to receive a clopidogrel LD of 300, 600, or 900 mg orally on the morning of day 1 of the study. All patients received an LD of 250 to 500 mg of aspirin twice daily.	All patients received low molecular weight heparin twice daily.
Breet, 2011{Breet, 2011 15 /id}	951 NR	NR NR	Hyper 769 (80.9) 107 (11.3)	NR 489 (51.4)	Total length 28.3±17.1	Patients scheduled for PCI with stent	All patients on aspirin 80-100 mg daily for >0	

21478385 The Netherlands POPular	717 (75.4) 64±10.6	NR NR NR NR NR 519 (54.6) NR	737 (77.5) 175 (18.4)	NR 270 (28.4)	DES 604 (63.8) NR	implantation	days unless they were on long-term anticoagulation with coumarin derivatives; clopidogrel - chronic maintenance therapy of 75 mg for >5 days or a clopidogrel loading dose of 300 mg at least 24 h before PCI or 600 mg at least 4 h before PCI. Aspirin 80-100 mg daily for ≥10 days unless they were on long-term anticoagulation with coumarin derivatives.	
Breet, 2010{Breet, 2010 50 /id} 20695984 Netherlands Substudy of a larger cohort (Breet 2010 PMID: 20179285)	692 NR NR NR	NR NR NR NR NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR	Patients with PCI and stent implantation	Clopidogrel and aspirin maintenance doses were 75 mg and 80 to 100 mg daily, respectively. [These details are obtained from original study]	
Buonamici, 2007{Buonamici, 2007 200 /id} 17572245 Italy NR	804 NR 602 (75) NR	NR NR NR 186 (23)	405 (50) 179 (22) 501 (62) 169 (21)	NR 100 100 NR	100 Drug-eluting 457 (57)	Patients received successful drug eluting stent implantation	All patients received aspirin (325 mg) and a loading dose of 600 mg of clopidogrel followed by a maintenance	

		275 (34) 312 (39) NR 206 (26) NR					dose of 75 mg daily. Patients on a maintenance dose of ticlopidine or clopidogrel at the time of admission received a loading dose of clopidogrel (600 mg).	
Campo, 2007{Campo, 2007 197 /id} 17868803 Italy NR	143 NR 99 (69) 67±10	NR NR NR PCI 25 (17)/ CABG 7 (5) NR NR NR 26 (18) NR	NR 31 (22) 104 (73) 32 (27)	NR 100 NR NR	NR NR NR	Patients undergoing PCI	clopidogrel 300-mg loading dose, followed by 75 mg/day+ aspirin (250 mg intravenously) . for patients with STEMI. Patients with stable angina (SA) received aspirin (100 mg once a day) at least 7 days and clopidogrel at least 6 h before procedure. Aspirin (100 mg once a day) was given to all patients indefinitely, whereas thienopyridines were given for 1 or 6 months according to implanted stent.	All pts received , heparin (50 to 70 U/kg), and glycoprotein IIb/IIIa inhibitors
Cuisset, 2009 19736156 France NR	597 NR 456 (76.4%) Mean: 64.2	NR NR NR NR NR	54.1% Current: 44.2% HTN: 59.8% 28.5%	NR NR NR NR	NR NR NR	Patients admitted with a NSTE ACS for coronary angiography/PCI	Clopidogrel 600 mg LD + Aspirin 250 mg LD at least 12 hours before coronary angiography and PCI as indicated	

		NR NR NR NR						
Cuisset, 2006{Cuisset, 2006 212 /id} 16371119 France NR	106 NR 82 (77%) 64 ± 10 mean ± SD	NR NR NR NR NR NR NR NR NR	59 (56%) 40 (38%) HTN 62 (58%) 26 (25%)	NR NR NR NR	NR NR NR	Patients with clinical symptoms compatible with acute myocardial ischemia admitted for PCI and stenting	Patients on chronic therapy with a daily dose of 75 mg clopidogrel for >5 days did not receive a loading dose of clopidogrel. Other patients received 300 mg of clopidogrel at least 12 h before stenting. All patients received aspirin 160 mg daily administered at least 12 h before stenting.	
Cuisset, 2006{Cuisset, 2006 237 /id} 17010792 France NR	292 NR 222 (76%) 64.7	Previous ACS: 44.5% NR NR NR NR NR NR NR NSTEMI: 100%	55.5% Current: 46% HTN:57% 31%	NR NR NR NR	NR NR NR	Patients undergoing percutaneous coronary intervention (PCI) for NSTEMI ACS	Patients were randomly assigned to receive a 300-mg or 600-mg loading dose of clopidogrel at least 12 h before stenting. All patients received aspirin 160 mg daily after a loading dose of 250 mg administered at least 12 h before stenting.	For all patients, anticoagulation was begun before PCI in the intensive care unit and performed with low-molecular-weight heparin (enoxaparin), or unfractionated heparin in patients over 75 years old or with renal insufficiency.
Cuisset, 2007{Cuisset, 2007 204 /id} 17264958 France	190 NR 146 (76.8)	NR NR NR	190 (100) 91 (47.9) 110 (57.9)	NR 42 (22.1) 89 (46.8)	NR NR NR	NSTE ACS patients	After collecting baseline blood samples for troponin I (TnI), patients received oral loading	Anticoagulation was performed with low-weight-molecular heparin

NR	NO PMI 66±11/PMI 64±13	NR NR NR NR NR NR	64 (33.7)	NR			doses of 250 mg aspirin and 600 mg of clopidogrel at least 12 h before stenting	(LWMH) (enoxaparin) when possible, or unfractionated heparin (UFH) in patients over 75 years or with renal failure. Use of a GPIIb/IIIa antagonist was allowed at the operator's discretion.
Geisler, 2008{Geisler, 2008 184 /id} 17949474 Germany NR	1092 NR 806 (73.8%) 67.5 ±10.8 yr	100% NR NR NR 529 (48%) NR NR 222 (27.4%) 193 (17.7%)/225 (20.6%)	Hyperlipidemia 641 (58.7%) 425 (38.9%) HTN 876 (80.2%) 363 (33.2%)	NR 155 (14.2%) around 90% NR	100% DES 206 (18.9%)/BMS 793 (72.6%)/Both 93 (8.5%) NR	Adults undergoing coronary stenting for symptomatic CAD	300 or 600 mg clopidogrel given as loading dose before PCI and stenting. After, daily dose was 75 mg for 3 mo. 500 mg ASA given as loading dose, followed by 100 mg/day.	Unfractionated heparin given periprocedurally (70 U per kg of body weight).
Geisler, 2006{Geisler, 2006 210 /id} 17005534 Germany NR	363 NR 277 (73.1) 67.5±10	NR NR NR NR NR NR NR NR NR	220 (60.6) 151 (41.6) 289 (79.6) 126 (34.7)	NR 100 100 NR	NR NR NR	CAD patients	A loading dose of 600 mg clopidogrel was given to all patients prior to PCI followed by a daily dose of 75 mg for at least 3 months. All patients received a standard dose of aspirin 100 mg daily before enrolment in the study.	
Geisler,	1019	NR	Hyperlipidemia:	NR	100%	Patients with	Clopidogrel: 600	Unfractionated

2010{Geisler, 2010 101 /id} 19812059 Germany NR	NR 756 (74.2%) mean: 67.8	NR NR NR NR NR NR NR NR	59.6% 37.9% HTN: 80.4% 33.1%	NR NR NR	BMS: 72.7%/DES: 27.3% Multivessel: 76.1%	CAD & ACS for PCI	mg LD (300 mg for those on clopidogrel therapy) + 75 mg/d MD x 6-12 months Aspirin: 500 mg LD + 100 mg/d MD	heparin was peri-procedurally administered to all patients at a dosage of 70 U/kg body weight
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	804 (of whom 772 consented to participation in the genetics substudy) NR 576 (74.6%) NR	NR LVEF = 47% ±12% NR PCI = 161 (20.9%)/CABG = 58 (7.5%) 262 (33.9%) 310 (40.2%) NR 197 (25.5%) NR	Dyslipidemia = 461 (59.7%)/ Statin = 690 (89.4%) 266 (34.4%) HTN = 505 (65.4%) 171 (22.2%)	NR NR (100% on current study) NR (100% on current study) 732 (94.8%)	772 (100%) 100% DES (sirolimus or paclitaxel) 439 (56.8%) had multi-vessel disease; NR if all received multiple stents	Patients with ACS or CAD undergoing PCI with stenting	All patients received aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance). Loading dose was administered before the procedure	UFH was used during the procedure as the anticoagulant
Gori, 2008 {Gori, 2008 164 /id} 18718420 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	764 NR 563 (75.4%) 68.1	100% NR NR PCI: 22.8%/CABG: 6% 33.4% 39.9% NR 24.5%	Hypercholesterolemia: 49.5% 22.8% HTN: 62.3% 20.4%	NR NR NR NR	NR Sirolimus-eluting stent: 54.8%/Paclitaxel-eluting stent: 38.6%/Both stent types: 6.6% NR	Patients with CAD & ACS treated with PCI and stenting	600 mg clopidogrel LD + 75-mg MD Aspirin 325 mg MD	

		NR						
Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	297 213/293 white (73%) [n=4 had missing data] 193/293 (66%) [n=4 had missing data] 65 +/-12 (mean/SD)	Family history of CAD 140 (47%) NR NR PCI 119 (40%)/CABG 66 (22%) NR NR NR 100 (34%) NR	Hyperlipidemia 244 (82%) 162 (55%) 74+/-16 diastolic/ 143+/-23 systolic/ HTN 221 (74%) 123 (41%)	NR 115 (39%) NR NR	NR DES 56%/BMS 42% NR	patients undergoing nonemergent PCI	On the day of PCI, 113 patients (38%) received 600 mg clopidogrel loading dose and 68 patients (23%) received a 300 mg loading dose. One-hundred fifteen patients (39%) were on maintenance therapy with a 75 mg daily dose at the time of PCI and were not reloaded. All patients received 81–325 mg aspirin daily for at least 1 week prior to PCI and 325 mg on the day of the procedure. Aspirin (325 mg/qd) and clopidogrel (75 mg/qd) were prescribed in all patients at the time of hospital discharge according to ACC/ AHA guidelines.	All patients received bivalirudin (n =94) or heparin therapy (n =203) either with eptifibatide (n =122) or without eptifibatide (n =175). Anticoagulant therapy was discontinued at the completion of the procedure in all patients.
Gurbel, 2004{Gurbel, 2004 220 /id} 15154601 USA None	94 Caucasian or African American? 71 (65%) [reporting unclear] 60 (64%)	NR NR NR PTCA 22 (23%)/CABG 18 (19%) NR	Hypercholesterolemia 65 (70%) <6 mo ago 22 (23%); >6 mo ago 32 (34%); Never 40 (43%) NR 48 (42%)	NR NR 100% NR	100% NR NR	Patients undergoing elective PCI	All patients received 300 mg clopidogrel in th catheterization laboratory after successful coronary artery stent implantation followed by 75	Intravenous unfractionated heparin to achieve an activated clotting time >300 s was administered to all patients immediately

	Mean +/- SE 65 +/17 yr	NR NR 30 (32%) NR					mg daily for 30 days. In addition, all patients had received at least 81 mg aspirin for 7 days prior to the procedure and were administered 325 mg on the day of the procedure and daily thereafter.	before stent implantation. GP IIb/IIIa inhibitors were not given as specified by the research protocol.
Hochholzer, 2006{Hochholzer, 2006 208 /id} 17084243 Germany EXCELSIOR	802 NR 627 (78.2) 66.4±9.1	NR NR NR 112 (14) NR NR NR 184 (22.9) NR	NR 87 (10.8) 660 (82.3) 199 (24.8)	NR 100 100 NR	NR Drug-eluting stents 178 (22.2) NR	Patients undergoing elective coronary stent placement	After PCI, all patients received aspirin (≥100 mg/day) and 75 mg/day clopidogrel for the duration of the study.	
Htun, 2011{Htun, 2011 20 /id} 21273381 Germany NR	1567 Caucasian 100% 1170 (74.7) 67.4± 0.27	NR NR NR NR NR NR NR NR NR	943 (60.2) 521 (33.2) 1259 (80.3) 499 (32.4)	70 (4.5) 698 (44.6) NR NR	NR bare metal 1143 (74.1) drug eluting 297 (19.2) NR	patients underwent coronary stenting	600-mg clopidogrel loading dose and 100 mg of aspirin. All of the patients were prescribed clopidogrel (75 mg/d) and aspirin (100 mg/d) treatment for at least 3 months after the index PCI.	
L'Allier 2008{L'Allier, 2008 178 /id}	148 NR	NR NR	Hypercholesterolemia 122 (82%)	NR NR	NR NR	Patients with suspected or documented	Group A, clopidogrel 300 mg the day	

18342223 Canada PREPAIR study	116 (78%) 61.7 (9.2) yr mean (SD)	NR Coronary angioplasty 31 (21%); Coronary bypass 14 (9%) NR NR NR 36 (24%) NR	Current smoker 35 (24%) HTN 106 (72%) 37 (25%)	144 (97%) NR	NR	coronary artery disease admitted to our hospital for elective coronary angiography and PCI when appropriate	before (≥15 h) plus 75 mg the morning of the procedure; Group B, clopidogrel 600 mg the morning of the procedure (≥ 2 h); and Group C, clopidogrel 600 mg the day before (≥ 15 h) and 600 mg the morning of the procedure (≥ 2 h); All stented patients received 75 mg of clopidogrel daily for at least 30 days as clinically indicated after implantation.	
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	111 [NB 2 withdrew before 12 hr] Chinese 100% 73 (66%) Mean/SD 66.2/8.9 yr	NR NR NR PCI 13% CABG 4% NR NR NR NR NR	Hypercholesterolemia 16% 47% HTN 78% 32%	NR 100% 100% 51%	100% NR NR	Patients undergoing elective stenting	A loading dose of 300 mg of clopidogrel was administered on the first day, approximately 12 h before PCI. A maintenance dose (75 mg) was administered daily after PCI. In addition, all patients received 100 mg of aspirin for 7 days before the procedure and 100 mg daily thereafter.	Heparin was administered as a bolus to all patients immediately before stenting.
Muller, 2003{Muller, 2003 223 /id} 12719773	105 NR	100% NR	NR 14%	NR NR	NR NR	patients with stable coronary artery disease undergoing	All patients received regular aspirin therapy with a daily dose	

Germany None	65 (71%) 65+/-10 mean +/-SD	NR NR NR NR NR NR NR	HTN 77% 21%	NR NR	NR	coronary angiography	of 100 mg. Before coronary angiography, initial dose of 600 mg clopidogrel	
Muller, 2010{Muller, 2010 51 /id} 20728084 Germany NR	903 NR 673 (75.5%) 68.5±10.7	ACS:56.9% NR NR NR NR NR NR NR NR	Hyperlipidemia (triglycerides ≥175 mg/dl and/or LDL-cholesterol ≥100 mg/dl and/or taking any of lipid lowering drugs): 62.4% Tobacco use: 41.5% HTN:80.7% 32.3	NR NR NR NR	NR NR NR	Patients undergoing percutaneous coronary intervention (PCI) for ACS and CAD	Clopidogrel: 600 mg LD + 75 mg MD Aspirin: 100 mg/d MD	
Obradovic, 2009{Obradovic, 2009 123 /id} 19318922 Serbia NR	total 52 NR 42 (80.8) 59.9±9.2	NR NR NR elective PCI 30 (57.7); urgent PCI 22 (42.3) 17 (32.7) 35 (67.3) NR NR	NR 15 (28.8) 34 (65.4) 10 (23.1)	NR NR NR NR	100 NR 29 (55.8)	PCI patients	After the angiogram, patients with one or two vessel disease suitable for PCI were scheduled for PCI 3-4 h later, and these patients received a loading dose of clopidogrel of 300 mg.	Patients scheduled for PCI received clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily together with 100 mg of aspirin once daily for at least 5 days before PCI. Patients received nonenteric-coated aspirin (300mg) and subcutaneous

		NR						enoxaparin (1mg/kg) at admission and had a priority for the angiogram.
Saw, 2008{Saw, 2008 243 /id} 19038679 Canada ELAPSE trial	33 (but 7 withdrew, so baseline & follow-up data reported for only 26) NR 22 (84.6%) 63.0 +/- 8.6 mean +/- SD	NR NR NR NR NR NR NR NR NR	Hyperlipidemia 25 (96.2%) 2 (7.7%) HTN 21 (80.8%) 4 (15.4%)	NR 0% 100% NR	1 DES 18 (69.2%) NR	patients undergoing coronary stenting	Patients were already receiving aspirin. Clopidogrel 600 mg was given before stenting. Clopidogrel 75 mg/day and aspirin 325 mg/day were continued for 1 year	Procedural anticoagulant choice was at the discretion of the interventionalists. Eptifibatide or tirofiban was permitted, but had to be discontinued 10 h before the next day's blood work. Abciximab was not permitted due to its long effective half-life.
Trenk, 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	802 NR 627 (78%) 66.4 ± 9.1 (SD)	NR NR; Left ventricular ejection fraction <55%: 35.8% NR Previous balloon angioplasty:34.2%; Previous CABG: 14% CANADIAN Cardiovascular Society angina class III or IV: 24.8% NR NR 22.9% NR	NR Active smokers: 10.8% arterial hypertension (definition NR): 82.3% 24.8	NR NR 100% NR	36.4 Drug-eluting stents multivessel PCI: 22.2%	Patients undergoing percutaneous coronary intervention (PCI), including those who have undergone PCI with stent implantation, and those who have undergone coronary artery bypass grafting surgery	Pretreatment: with pre-treatment with 600 mg of clopidogrel & aspirin (100 mg per day for at least 5 days); After PCI: All patients received aspirin (≥100 mg per day) lifelong & clopidogrel (75 mg per day) for 30 days after placement of bare-metal stents or for 6 months after placement of at least 1 drug-eluting stent.	During procedure: All patients received an intra-arterial dose of 100 to 140 U/kg heparin;

Wang, 2010{Wang, 2010 37 /id} 21171668 China None	154 NR 90 (58%) mean±SD 60±10 yr	NR NR NR NR NR NR NR NR NR	97 (63%) 47 (31%) HTN 107 (69%) 56 (36%)	NR NR NR NR	100% DES 100% Single 40 (26%); Dual 74 (48%); Multi 40 (26%)	patients who underwent selective PCI with DES	A 300 mg loading dose of clopidogrel was given to all patients at least 6 hours prior to PCI, followed by a daily dose of 150 mg for 2 weeks and then 75 mg for a minimum of 11.5 mo. In addition, from the first day of the procedure, all patients were administered aspirin 300 mg daily for 1 mo nth and then 100 mg for the lifetime of the patient.	Use of glycoprotein IIb-IIIa inhibitors at discretion of the operator. A weight-adjusted intra-procedural unfractionated heparin (with a goal activated clotting time of 250 – 300 seconds) was administered during the procedure and was routinely discontinued at the end of the procedure.
Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	386 NR male 257 (66.6) 68.8±9.2	NR NR NR PCI 49 (12.7); CABG 15 (3.9) NR NR NR 86 (22.3) NR	190 (49.2) 162 (41.9) 262 (67.9) 128 (33.2)	NR 100 100 NR	100 NR NR	Patients for elective coronary intervention in symptomatic stable coronary artery disease (CAD)	A loading dose of 300 mg clopidogrel was given to all patients at least 6 h prior to PCI, followed by a daily dose of 75 mg for a minimum of 12 months. In addition, all patients were administered 300 mg aspirin daily, begun the day of the procedure.	the use of Glycoprotein IIb/IIIa inhibitors at discretion of the operator. Weight adjusted intra-procedural unfractionated heparin (with a goalactivated clotting time 250 s to 300 s) was administered during the procedure andwas routinely discontinued at the end of the procedure.
Yong, 2009{Yong, 2009 146 /id} 19081397 Australia	256 (all subjects) NR	NR NR NR	Hypercholesterolemia : 50.4% Current: 30%	NR NR 39.8	NR NR Multivessel	Patients undergoing percutaneous coronary intervention	An open-label 300-mg LD of clopidogrel and then pts randomized to	All other treatments were administered at the discretion of

Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary intervention in Acute coronary Lesions (PRACTICAL) Trial	180 (70.3%) Mean: 62.7	 PCI: 11.3%; CABG: 7.4% NR NR NR 18.4 NR	HTN: 52% 21.5	 NR	disease: 53.9%	(PCI) for ACS	300 mg of clopidogrel (clopidogrel 600-mg group) or matching placebo (clopidogrel 300-mg group).	the treating physician.
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA No	63 NR 60 67±11	NR NR NR CABG 18 NR NR NR 24 NR	hyper 60 NR HTN 72 39	NR 100 100 NR	100 NR NR	elective stenting	all received ± 81 mg of aspirin for 7 days before the procedure. All patients received the same clopidogrel regimen (300 mg in the catheterization laboratory after stent implantation, then 75 mg/day for 30 days) with 325 mg/day aspirin.	Heparin (activated clotting time >300 seconds) was administered to all patients immediately before stent implantation, and per protocol, GP IIb/IIIa inhibitors were not given.
Gurbel, 2005{Gurbel, 2005 215 /id} 16286165 USA PREPARE POST-STENTING	182 White: 115 (59%) 108 (56) 65±12	NR NR NR PTCA:39.6/CABG:24.5% NR NR NR 36.9%	Hyperlipidemia: 66.7% 43.8% HTN: 66.2% 42.2%	NR 100 NR NR	96% DES: 69.8%/BMS: 28.1% NR	PCI for ACS	Clopidogrel (loading dose of 300 or 600 mg or continuation of pre-enrollment maintenance dose; maintenance dose 75 mg daily) + aspirin (81- to 325-mg daily dose for seven days before the procedure, and 325 mg on day	

		NR					of procedure and daily thereafter)	
Gurbel, 2003{Gurbel, 2003 222 /id} 12796140 USA NR	96 NR NR NR	NR NR NR NR NR NR NR NR NR	NR NR NR NR	NR NR 100% NR	NR NR NR	Patients undergoing PCI with stenting	All patients received aspirin (325 mg). Clopidogrel (300 mg) was administered in the catheterization laboratory and followed by 75 mg daily.	

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;ACC/AHA=American College of Cardiology/American Heart Association;

Appendix Table E6: Baseline characteristics of patients with peripheral artery disease in studies assessing the predictive ability of LTA

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	Total N Enrolled Race (% by group) Male (%) Age[13]	Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)	Stent implantation(%) Type of stent(%) Multi-or single vessel(%)			
Linnemann, 2010{Linnemann, 2010 82 /id} 20153859 Germany NR	54 NR 29 (53.7%) Median: 68 (range 53-94)	IHD: 38.9% NR CVD:18.5% prior cerebral infarction: 5.6% PCI: 24.1% CABG: 11.1% NR NR 100% 14.8% NR	hyperlipidemia: 81.5% Current: 24.1% HTN: 77.8% 33.3%	NR 100% NR NR	NR NR NR	Patients with Peripheral artery occlusive disease on clopidogrel	Clopidogrel 75 mg daily	

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;ACC/AHA=American College of Cardiology/American Heart Association;

[13] Mean (standard deviation), unless otherwise stated.

Appendix Table E7: Study design characteristics of studies assessing the predictive ability of LTA in patients with ischemic heart disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Geisler, 2010{Geisler, 2010 54 /id} 20526607 Germany NR	Prospective	NO	Consecutive	Patients with diabetes and symptomatic CAD undergoing PCI	March 2005-May 2008	Total 30 days after PCI	Inpatient and then 30 day followup of outpatients	YES [NR]	NR
Cuisset, 2009{Cuisset, 2009 111 /id} 19801028 France NR	prospective Cohort	No	Consecutive	NSTE ACS patients	NR	NR	CHU Timone inpatient	NR	non-industry (grants from the Assistance publique hôpitaux de Marseille, Marseille, France)
Frere, 2007{Frere, 2007 193 /id} 17938809 France NR	Prospective observational	No	Selected patients with coronary stenting	Patients had undergone successful coronary stenting	March 2005-may 2006	One-month follow up	Department of Cardiology inpatient	NR	NR
Hoshino, 2009{Hoshino, 2009 143 /id} 19106460 Japan NR	Prospective observational	NO	NR	Patients undergoing percutaneous coronary intervention (PCI) for ischemic heart disease	NR	Max 30 days	followup after intervention	NR	Non-industry (Health and Labor Sciences Research Grant for Cardiovascular Research and a Grant from the Japan Cardiovascular Research Foundation.)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands NR	prospective Cohort	No	Patients scheduled for PCI with stent implantation	Patients with PCI and stent implantation	Dec 2005-Dec 2007	1-year	Hospital inpatient	Yes. 80%	NR
Gurbel, 2010{Gurbel, 2010 84 /id} 20194878	Prospective cohort derived from an crossover	YES	Consecutive	Patients with CAD on aspirin therapy	May 19, 2008 - March 25, 2009	NR (At least 28 days for completion of period 1 and period	community (non–health care setting)	YES; Accrual >80%	Industry (AstraZeneca)

10 study sites in North America and Europe RESPOND	RCT					2)			
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	prospective cohort	no	consecutively enrolled	unselected patients treated with coronary stenting for symptomatic coronary artery disease, including acute myocardial infarction (AMI) and chronic clopidogrel therapy	December 2007 to June 2009	6 months	Department of Cardiology of the Gyeongsang National University hospital inpatient	NR	NR
Angiolillo, 2008{Angiolillo, 2008 180 /id} 18312754 USA OPTIMUS	prospective Cohort	No	Patients underwent PCI and were treated with standard clopidogrel	Patients underwent PCI and were treated with standard clopidogrel	NR	1 months	Hospital inpatient	Yes; Accrual>80%	NR
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	prospective Cohort	No	Selected sample?	Patients with an elevated risk to develop ST acute MI within 48 hours undergoing emergency or elective PCI	NR	6 months	Department of cardiology in University Hospital Aachen inpatient	NR	NR
Bliden, 2007{Bliden, 2007 202 /id} 17291930 USA NR	prospective Cohort	no	Consecutive	Patients receiving clopidogrel	NR	12 months	Hospital inpatient	With the sample size calculation from SigmaStat software, it is estimated that the sample size required for 95% power with the alpha of 0.05 is approximately 100 patients.	Partly industry (NIH and Bayer)
Gori, 2008{Gori, 2008 151	Prospective	NR but probably NO	Consecutive	RECLOSE patients	July 2005 to Februar	Total 6 months	Outpatient followup of cohort	YES [YES]	Nonindustry

/id} 19132241 Italy RECLOSE				who underwent DES implantation for whom complete AA- and collagen-induced platelet aggregation values were available.	y 2006		at 1, 3, and 6 mo		
Gurbel, 2010{Gurbel, 2010 68 /id} 20691842 USA PREPARE POST-STENTING	Prospective observational study	NO	Consecutive	Patients undergoing percutaneous coronary intervention (PCI)	2004 and 2005	Max of 36 months	Follwoup after intervention	YES; Accrual>80%	Non-industry (Sinai Hospital, Baltimore & NIH grant R44-HL059753)
Matetzky, 2004{Matetzky, 2004 188 /id} 15184279 Israel No	prospective	NR	Consecutive	STEMI patients	NR	total 6 months	Outpatient follow up	NO	NR
Angiolollo, 2007{Angiolillo, 2007 194 /id} 17936152 Spain NR	prospective Cohort	No	Type 2 diabetes mellitus patients with coronary artery disease (CAD) on chronic treatment with dual antiplatelet therapy were eligible for this study.	Type 2 diabetes mellitus patients with coronary artery disease (CAD) on chronic treatment with dual antiplatelet	Jan 2003 to Feb 2005	One year	Hospital inpatient	NR	Partly industry
Aradi, 2008{Aradi, 2008 236 /id} 18388039 Hungary NR	Prospective	NR	NR	Patients referred for PCI with stenting	NR	10 mo	Inpatient and then outpatient after PCI, followed till 10 mo	NR	NR
Bellemain-Appaix, 2010{Bellemain-Appaix, 2010 87 /id} 20170822 France ALBION (Assessme	Substudy of ALBION RCT	YES	Selected sample (Patients with platelet aggregation data from RCT)	Patients with ACS	NR	max: 1 day	Inpatient	NO	NR [Industry funding for authors is reported]

nt of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis)									
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	prospective Observational study	NR	Consecutive	Patients scheduled for PCI with stent implantation	NR	1 year	Hospital inpatient	NR	NR
Breet, 2010{Breet, 2010 50 /id} 20695984 Netherlands Substudy of a larger cohort (Breet 2010 PMID: 20179285)	prospective Cohort	No	Patients scheduled for PCI with stent implantation	Patients with PCI and stent implantation	Dec 2005-Dec 2007	1-year	Hospital inpatient	Yes. The study was designed on the basis of the superiority principle to have 80% power to observe an incidence of the primary end point in patients exhibiting high on-treatment platelet reactivity of 10% and 4% in patients without high on-treatment platelet reactivity.	NR [Authors report no COI]
Buonamici, 2007{Buonamici, 2007 200 /id} 17572245 Italy NR	prospective Cohort	No	Consecutive patients	Patients received successful drug eluting stent implantation	July 2005 to August 2006	6 months	Academic hospital inpatient	Yes. To have a power of 0.80 to detect the hypotesized effect size with a 1-sided p value <0.05, a sample size of at least 800 was needed.	NR
Campo, 2007{Campo, 2007 197 /id} 17868803 Italy NR	prospective Cohort	No	Patients undergoing PCI	Patients undergoing PCI	Nov 2005-may 2006	Every 4 months	Hospital inpatient	No	NR
Cuisset, 2009 19736156 France NR	Prospective observational study	NO	Consecutive	Patients admitted with a NSTE ACS for coronary angiography/PCI	NR	Total 30 days	followup after intevention	NO	non-inducstry (Assistance Publique Hôpitaux of Marseille)

Cuisset, 2006{Cuisset, 2006 212 /id} 16371119 France NR	Prospective	NO	Consecutive	Patients with clinical symptoms compatible with acute myocardial ischemia admitted for PCI and stenting	June-Dec 2004	Total 1 mo	Outpatient after PCI	NR	NR
Cuisset, 2006{Cuisset, 2006 237 /id} 17010792 France NR	Prospective; 2 arms of an RCT are separate cohorts	NO	RCT	Patients undergoing percutaneous coronary intervention (PCI) for NSTEMI ACS	June 2004 – Oct 2005	Max 1 month	followup after intervention	NR	Non-industry [Assistance Publique Hôpitaux de Marseille]
Cuisset, 2007{Cuisset, 2007 204 /id} 17264958 France NR	prospective Cohort	No	Consecutive patients	NSTE ACS patients	May 2005-Feb 2006	24 hours after PCI	Hospital inpatient	No	NR
Geisler, 2008{Geisler, 2008 184 /id} 17949474 Germany NR	Prospective	NO	Consecutive	Unselected adults undergoing coronary stenting for symptomatic CAD	March 2005-Dec. 2006	Total 30 days	Inpatient for stenting, then follow up by phone 30 days after discharge	NO	Nonindustry only
Geisler, 2006{Geisler, 2006 210 /id} 17005534 Germany NR	prospective Cohort	No	Consecutive Patients admitted for CAD	CAD patients	March to August 2006	3 months	Hospital inpatient	Yes. With a probability of 80% that the study will detect a minimal hazard ratio (HR) of 2.25% for the primary endpoint at a one-sided 5.0% significance level and a presumed low responder rate of up to 10%, we estimated a sample size of 335 patients.	NR
Geisler, 2010{Geisler, 2010 101 /id} 19812059 Germany NR	Prospective observational	NO	Consecutive	Patients with CAD & ACS for PCI	March 2005-March 2007	max 3 months	followup after intervention	YES; Accrual>80%	non-industry (‘Deutsche Forschungsgemeinschaft’,

									'Sonderforschungsbereich Transregio TR-19', and the Karl&Lore-Klein-Stiftung.)
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Prospective observational study of patients enrolled in the RECLOSE study in a single center	NO (single center recruitment for this study)	Consecutive patients consenting to genetic study identified from the RECLOSE study population	Patients with ACS or CAD undergoing PCI with stenting	July 2005 to August 2006 [recruitment period of the RECLOSE study; information from pmid = 17572245]	6 months (unclear what metric; from the KM curves implied maximum FU)	In hospital (PCI)	NO	Non-industry only
Gori, 2008 {Gori, 2008 164 /id} 18718420 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Prospective cohort	NO	Consecutive	Patients with CAD & ACS treated with PCI and stenting	NR	6 months	Followup after intervention	NR	NR
Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	Prospective	NO	Consecutive	patients undergoing nonemergent PCI	Jan. 29, 2004, to May 1, 2007	546 days (median)	Inpatient during PCI, then outpatient follow-up	YES (YES)	Non-industry only
Gurbel, 2004{Gurbel, 2004 220 /id} 15154601 USA None	Prospective	NR	NR	Patients undergoing elective PCI	NR	Total 30 days	Inpatient with subsequent followup for 30 days as outpatient	NR	Non-industry only
Hochholzer, 2006{Hochholzer, 2006 208 /id}	prospective Cohort	No	Patients undergoing elective coronary stent	Patients undergoing elective coronary stent	NR	30 days	Hospital inpatient	Yes. We intended to have a power of 0.80 to detect an effect size of	NR

17084243 Germany EXCELSIOR			placement	placement				0.015 (e.g., 3-fold risk in the fourth quartile) with a 2-sided p value <0.05.	
Htun, 2011{Htun, 2011 20 /id} 21273381 Germany NR	prospective cohort	no	consecutive, unselected patients	patients underwent coronary stenting	NR	365 days	university hospital inpatient	yes. With an estimated prevalence of 35%, a sample size of 1090 was calculated to detect this difference of event rate with a statistical power of90%at a two-sided alpha level of5%.	NR
L'Allier 2008{L'Allier, 2008 178 /id} 18342223 Canada PREPAIR study	Randomized	NR	Consecutive	Patients with suspected or documented coronary artery disease admitted to our hospital for elective coronary angiography and PCI when appropriate	NR	Total 1 month	Inpatient and followup at 1 mo after discharge	YES (YES—80%)	Nonindustry only
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Prospective	NO	Consecutive	Patients undergoing elective stenting	NR	Total 3 month	Inpatient and then 12 hr, 36 hr, 1 mo, and 3 mo after stenting (most as outpatient visit)	NO	All Industry
Muller, 2003{Muller, 2003 223 /id} 12719773 Germany None	Prospective	NO	NR	patients with stable coronary artery disease undergoing coronary angiography	NR	NR	Inpatient and then followup as outpatient	NO	Non-industry only
Muller, 2010{Muller, 2010 51 /id} 20728084 Germany NR	Prospective observational study	NO	Consecutive	Patients undergoing percutaneous coronary intervention (PCI)	March 2005 to May 2008	mean : 344 days	Followup after intervention	YES; Accrual>80%	Non-industry ["Deutsche Forschungsgemeinschaft", the "Sonderfor

				for ACS and CAD					schungsbereich Transregio TR-19", the Karl&Lore-Klein-Stiftung and a personal grant "Atherothrombosis Grant" of the European Society of Cardiology (TG).]
Obradovic, 2009{Obradovic, 2009 123 /id} 19318922 Serbia NR	prospective Cohort	No	Selective patients with PCI	PCI patients	NR	24 h	Catheterization lab of the Military medical Academy inpatient	NR	NR
Saw, 2008{Saw, 2008 243 /id} 19038679 Canada ELAPSE trial	Prospective	NO	NR	patients undergoing coronary stenting who were on aspirin for 5 days but not previously on clopidogrel	Sept. 2005-Aug. 2006	Total 1 yr	Inpatient for PCI, then outpatient visits for 1 yr of follow-up	YES [YES]	Non-industry only
Trenk, 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel- Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	Observational study	NO	Substudy of the EXCELSIOR prospective study	Patients undergoing percutaneous coronary intervention (PCI), including those who have undergone PCI with stent implantation, and those who have undergone coronary artery bypass grafting surgery	NR	30 day follow up for all patients, and 12 month follow up for 795 patients (99.1%)	followup after intervention	YES; Accrual 100%; reported in Hochholzer 2006 17084243	non-industry university Funding (Herz-Zentrum, Bad Krozingen, Germany)
Wang,	Prospectiv	NO	Selected	patients	January	Total 1 year	Inpatient	NR	No

2010{Wang, 2010 37 /id} 21171668 China None	e		for the same type of DES	who underwent selective PCI with DES	2006 to January 2008	after discharge	and then outpatient followup		funding
Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	prospective Cohort	No	Patients for elective coronary intervention in symptomatic stable coronary artery disease (CAD)	Patients for elective coronary intervention in symptomatic stable coronary artery disease (CAD)	Oct 2006-March 2007	One year	Hospital inpatient	Yes. We estimated a sample size of 373 patients would provide 80% power to detect an 70% relative difference in the rate of events using a one-sided 0.05 significance level, with a presumed event rate of 5.0% in normal responders and a resistance rate of up to 15%.	NR
Yong, 2009{Yong, 2009 146 /id} 19081397 Australia Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary intervention in Acute coronary Lesions (PRACTICAL) Trial	Pooled data from 2 arms of an RCT	YES	Consecutive	Patients undergoing percutaneous coronary intervention (PCI) for ACS	January 2004 and November 2005	Max 6 months	Followup after intervention	YES (for RCTs main outcome) [Accrual < 80%]	Industry
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA No	Prospective	NO	NR	Patients undergoing PCI with stenting	NR	NR	Inpatient and then outpatient visit at 30 days	NR	All Industry
Gurbel, 2005{Gurbel, 2005 215 /id} 16286165 USA PREPARE POST-STENTING	Prospective, observational	NO	Consecutive patients	Patients undergoing percutaneous coronary intervention (PCI) for ACS	NR	NR	Hospital, then outpatient	NO	NR
Gurbel,	Prospectiv	No	Consecut	Patients	NR	30 days	Hospital,	NO	Industry

2003{Gurbel, 2003 222 /id} 12796140 USA NR	e		ive	undergoing percutaneous coronary intervention (PCI) with stenting			then outpatient		(Sinai Center for Thrombosis Research and Platelet and Thrombosis Research, LLC)

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-elevation; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; DES=drug eluting stent; CABG=coronary artery bypass grafting; AA= arachidonic acid; SD=standard deviation; RCT=randomized controlled trial; NR=not reported;

Appendix Table E8: Study design characteristics of studies assessing the predictive ability of LTA in patients with peripheral artery disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Linnemann 2010{Linnemann, 2010 82 /id} 20153859 Germany NR	Prospective observational study	NO	Consecutive	Patients with Peripheral artery occlusive disease on clopidogrel	July 2003-Jan 2006	Median: 17.5 months (range 10.5-40.4 months)	Outpatient	NO	NR

Appendix Table E9: Phenotypic test details in studies assessing the predictive ability of LTA in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer*	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Angiolollo, 2007{Angiolillo, 2007 194 /id} 17936152 Spain NR	Light transmittance aggregometry ChronoLog 490 Model ChronoLog Corp., Havertown, Pennsylvania	ADP	Blood samples for platelet function assays were collected 2 to 4 h after antiplatelet therapy intake NR 2 to 4 h after antiplatelet therapy intake. NR	HRP (set a cutoff of 62% Aggmax) non HRP	Based on ROC curve	HRP (set a cutoff of 62% Aggmax.): n=45(26) non HRP: n=128 (73)
Aradi, 2008{Aradi, 2008 236 /id} 18388039 Hungary NR	Optical aggregometry Carat TX4 optical aggregometer Carat Diagnostics, Budapest, Hungary	adenosine diphosphate 5 and 10 umol, collagen 2 ug/ml, and adrenaline 10 umol	10 mL blood was drawn by direct venipunc ture for optical aggregometry into a sodium citrate vacuum tube Sodium citrate Clopidogrel given at time of PCI and stenting and platelets tested at 30 ± 5 days after coronary stent implantation 2 hours	Lower 50% of ADP 5 umol Induced Aggregation Upper 50% of ADP 5 umol Induced Aggregation	Not explicitly reported	Lower 50% of ADP 5 umol Induced Aggregation: NR but maybe can ascertain from Fig 1A (distribution of aggregation %s) Upper 50% of ADP 5 umol Induced Aggregation: NR but maybe can ascertain from Fig 1A (distribution of aggregation %s)
Bellemain-Appaix, 2010{Bellemain-Appaix, 2010 87 /id} 20170822 France ALBION (Assessment of the Best Loading	LTA NR NR	20 µmol/l ADP	Samples obtained at baseline and 0.5, 1, 2, 3, 4, 5, 6, and 24 h NR Less than 1 day; Clopidogrel came first NR	Slow responders (maximal platelet aggregation <10% within the first hour after loading) Fast responders (maximal platelet aggregation ≥10% within the first hour after loading)	Not explicitly reported	Slow responders (maximal platelet aggregation <10% within the first hour after loading): 53 (55%) Fast responders (maximal platelet aggregation ≥10% within the first hour after loading): 46 (45%)

Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis)				Low response (maximal platelet aggregation <10% over 24 hrs) Responders (maximal platelet aggregation ≥10% over 24 hrs)		Low response (maximal platelet aggregation <10% over 24 hrs): 9 (9.3%) Responders (maximal platelet aggregation ≥10% over 24 hrs) : 7 (90.7%)
Bliden, 2007{Bliden, 2007 202 /id} 17291930 USA NR	Platelet aggregation/Chronolog Lumi-Aggregometer Model 490-4D Chronolog, Havertown, Pennsylvania	5 umol/LADP and 1 mmol/Larachidonic acid (AA)	from patients in a fasting state in the catheterization laboratory through the indwelling femoral vessel sheath. 3.8% trisodium citrate or lithium heparin Baseline samples were obtained before coronary intervention and at 3 h and 18 to 24 h after stenting Within 2h	HPR=high on-treatment platelet reactivity based on LTA-5 umol/L ADP (%)	Based on literature	HPR=high on-treatment platelet reactivity based on LTA-5 umol/L ADP (%) : 22%Gori
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	Platelet aggregation /Densitometrically-determined measurement of platelet aggregation APACT 4 S Plus platelet aggregometer Rolf Greiner Biochemica, Flacht, Germany	10 µM ADP	The blood samples were obtained 72–96 h after stent placement. Interval at least 8 days 3.2% citrate All patients were given 75 mg clopidogrel and 100 mg aspirin once a day at least five days prior to PCI. The blood samples were obtained 72–96 h after stent placement. Interval at least 8 days Within 1 h	NR	NR	NR
Breet, 2010{Breet, 2010 50 /id} 20695984 Netherlands Substudy of a larger cohort (Breet 2010 PMID: 20179285)	LTA four-channel APACT 4004 aggregometer LABiTec, Arensburg, Germany	NR	NR 3.2% citrate NR 2h	High on-treatment platelet reactivity with native platelet rich plasma Non-high on-treatment platelet reactivity with native platelet rich plasma (Cutoffs NR) High on-treatment	Not explicitly reported	High on-treatment platelet reactivity with native platelet rich plasma (Cutoffs NR) : 200 (28.9%) Non-high on-treatment platelet reactivity with native platelet rich plasma (Cutoffs NR):

				platelet reactivity with adjusted platelet rich plasma (Cutoffs NR) Non-high on-treatment platelet reactivity with adjusted platelet rich plasma (Cutoffs NR)		492 (71.1%) High on-treatment platelet reactivity with adjusted platelet rich plasma (Cutoffs NR): 243 (35.1%) Non-high on-treatment platelet reactivity with adjusted platelet rich plasma (Cutoffs NR): 449 (64.9%)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	Light transmittance aggregometry NR NR	5 µmol/L ADP 20 µmol/L ADP	Before Heparinization 3.2% citrate NR Within 2 hours after blood collection.	High on-treatment platelet reactivity ≥42.9% aggregation LTA-ADP 5 µmol/L N=445 Not High on-treatment platelet reactivity <42.9% aggregation LTA-ADP 5 µmol/L N=604 High on-treatment platelet reactivity <64.5% aggregation LTA-ADP 20 µmol/L n=659 Not high on-treatment platelet reactivity ≥64.5% aggregation LTA-ADP 20 µmol/L n=392	Based on ROC curves	High on-treatment platelet reactivity ≥42.9% aggregation LTA-ADP 5 µmol/L: N=445 Not High on-treatment platelet reactivity <42.9% aggregation LTA-ADP 5 µmol/L: N=604 High on-treatment platelet reactivity ≥64.5% aggregation LTA-ADP 20 µmol/L: n=392 Not high on-treatment platelet reactivity <64.5% aggregation LTA-ADP 20 µmol/L: n=659
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Light transmission aggregometry Four-channel APACT 4004 aggregometer LABiTec, Arensburg, Germany	ADP	NR 3.2% Sarstedt citrate NR 2h	No HCPR (LTA5) With HCPR (LTA5) No HCPR (LTA20) With HCPR (LTA20) Cutoff 43% aggregation for LTA5, 65% for LTA20	Based on literature	No HCPR (LTA5): 536 With HCPR (LTA5): 385 No HCPR (LTA20): 588 With HCPR (LTA20): 335
Buonamici, 2007{Buonamici, 2007 200 /id} 17572245	LTA APACT 4 light transmittance aggregometer	ADP	Blood samples anticoagulated with 0.129 mol/l sodium citrate (ratio 9:1) for platelet reactivity assessment was obtained 12 to 18 h from clopidogrel loading	Responders Non-responders Patients with platelet aggregation by 10-mol	Not explicitly reported	Responders : 699/804(86.9) Non-responders: 105/804 (13.1)

Italy NR	Helena Laboratories, Milan, Italy		0.129 mol/l sodium citrate 12-18 h from clopidogrel loading NR	ADP ≥90th percentile of controls (70%) were defined as nonresponders.		
Campo, 2007{Campo, 2007 197 /id} 17868803 Italy NR	Platelet aggregation NR NR	ADP	NR NR T0 baseline before thienopyridine; T1, 5-7 days after baseline; T2, 7-10 days after T1 NR	Responder to both thienopyridines Clopidogrel nonresponders Ticlopidine nonresponders Nonresponder to both thienopyridines [Based on thienopyridine responsiveness]	Not explicitly reported	Responder to both thienopyridines: 90 Clopidogrel nonresponders: 30 Ticlopidine nonresponders: 28 Nonresponder to both thienopyridines: 5
Cuisset, 2006{Cuisset, 2006 212 /id} 16371119 France NR	light transmittance PAP4 Aggregometer Biodata Corp, Wellcome, Paris, France	ADP 10 umol/L	first blood millimeters discarded to avoid platelet activation induced by needle puncture and blood was immediately collected in vacutainer tube, filled to capacity, and then inverted three to five times for gentle mixing 3.8% Trisodium citrate before the PCI at least 12 h after the loading dose of clopidogrel and the aspirin administration and before administration of tirofiban if needed Immediately	Quartiles of (mean ± SD) ADP-induced maximal intensity of platelet aggregation (with threshold for low response ≥70%) Q1, Q2, and Q3: responsive to clopidogrel Q4 (82 ± 1 2%): nonresponsive to clopidogrel	The quartile data—Q4 range determined the cutoff	Q1, Q2, and Q3: responsive to clopidogrel: 83 Q4 (82 ± 1 2%): nonresponsive to clopidogrel: 23
Cuisset, 2006{Cuisset, 2006 237 /id} 17010792 France NR	Light transmission PAP4 Aggregometer Biodata Corporation, Wellcome, Paris, France	10 µmol/L ADP	Before PCI after clopidogrel LD 3.8% trisodium citrate 0.5 days (12 hours)Clopidogrel came first NR	high post treatment platelet reactivity (ADP induced platelet aggregation >70%) in 300 mg group normal post treatment platelet reactivity (ADP induced platelet aggregation <70%) in 300 mg group high post treatment platelet reactivity (ADP induced platelet aggregation >70%) in 600 mg group	Not explicitly reported	high post treatment platelet reactivity (ADP induced platelet aggregation >70%) in 300 mg group: 36 (24.7%) normal post treatment platelet reactivity (ADP induced platelet aggregation <70%) in 300 mg group: 110 (75.3%) high post treatment platelet reactivity (ADP induced platelet

				normal post treatment platelet reactivity (ADP induced platelet aggregation <70%) in 600 mg group		aggregation >70%) in 600 mg group: 22 (15.1%) normal post treatment platelet reactivity (ADP induced platelet aggregation <70%) in 600 mg group: 124 (84.9%)
Cuisset, 2007{Cuisset, 2007 204 /id} 17264958 France NR	Light transmission PAP4 Aggregometer Biodata Corporation, Wellcome, Paris, France	ADP	Blood samples for testing platelet reactivity were drawn in the catheterization laboratory from a 6-French arterial sheath before the PCI 3.8% trisodium citrate Blood samples were drawn before the PCI, at least 12 h after the loading dose of clopidogrel and aspirin, and before administration of tirofiban if needed NR	HPPR ADP10 >70 No HPPR ADP10 <70 [Based on high post-treatment platelet reactivity (HPPR) defined as >70% by ADP LTA]	Based on literature	HPPR ADP10 >70: 42 (22) No HPPR ADP10 <70: 148 (78)
Cuisset, 2009{Cuisset, 2009 111 /id} 19801028 France NR	light transmission aggregometry PAP4 aggregometer Bio data welcome, Paris France	10 umol/L ADP	blood samples were obtained 72–96 h after stent placement Citrate Interval at least 8 days. NR	Non-responder: ADP-Ag of >67% Responder: ADP-Ag of ≤67%	As per the ROC curve created using data from study subjects	Non-responder: ADP-Ag of >67%: 31% Responder: ADP-Ag of ≤67%: 69%
Cuisset, 2009{Cuisset, 2009 246 /id} 19736156 France NR	Light transmission aggregometry PAP4 Aggregometer Biodata Corporation, Wellcome, Paris, Francea	ADP	Blood drawn after cardiac catheterization NR 0.5 days (12 hours after the loading dose of clopidogrel and aspirin) NR	Hyper-responder (quartile 1: ADP-induced aggregation <40%) Non hyperresponder (quartile 2-4: ADP-induced aggregation ≥40%)	Not explicitly reported	Hyper-responder (quartile 1: ADP-induced aggregation <40%): 150 (25.1%) Non hyperresponder (quartile 2-4: ADP-induced aggregation ≥40%): 447 (74.9)
Frere, 2007{Frere, 2007 193 /id}	light transmission aggregometry	ADP	before the PCI at least 12 h after the loading dose of clopidogrel and aspirin, and before administration of	ADP-Ag ≥ 70% ADP-Ag <70%	As per the ROC curve created using data from study subjects	ADP-Ag ≥ 70%: 11/14 (79%)

17938809 France NR	PAP4 aggregometer Bio data welcome, Paris France		tirofiban if needed. 3.8% trisodium citrate After 12hours after the loading dose of clopidogrel With 1 hour			ADP-Ag <70%: 3/14 (21%)
Geisler 2008{Geisler, 2008 184 /id} 17949474 Germany NR	Turbidoaggregometry Chronolog Lumi aggregometer with Aggro-link software NR	20 umol ADP	Venous blood. RPA measured 5 min after ADP addition 3.8% citrate At least 6 hr after loading dose (median, 24.8 hr) if 600 mg; if 300 mg (for those previously on clopidogrel), at least 24 hr after loading dose NR	RPA tertile 1 (lowest) RPA tertile 2 RPA tertile 3 (highest)	Not explicitly reported	RPA tertile 1 (lowest) NR RPA tertile 2 NR RPA tertile 3 (highest) NR
Geisler 2010{Geisler, 2010 54 /id} 20526607 Germany NR	Turbidometry; Chronolog Lumi Aggregometer Chronolog	ADP (20 umol/l)	NR Samples were collected the day following PCI blood was collected at least 6 h (median 23.6 h interquartile range 20.8 h) after first administration of 600 mg clopidogrel NR	Diabetics with ADP-induced aggregation in the top tertile vs. lowest tertile (among n=413 patients followed)	Prestudy data by the authors in a smaller, different patient group (data reported in current paper but not extracted)	NR
Geisler, 2006{Geisler, 2006 210 /id} 17005534 Germany NR	NR Chronolog Lumi aggregometer with Aggro-Link Software NR	ADP	Blood samples were collected in 3.8% citrate plasma 3.8% citrate plasma Patient blood was collected at least 6 h (mean 34.8+25.9 h) after first administration of 600 mg clopidogrel NR	Adequate response (<70%) Low response (>70%) Based on post-treatment aggregation	Based on literature	Adequate response (<70%): 341/363(93.9) Low response (>70%): 22/363 (6.1)
Geisler, 2010{Geisler, 2010 101 /id} 19812059 Germany NR	light transmission aggregometry Chronolog Lumi aggregometer NR	ADP	6 hrs after clopidogrel dose 3.8% citrate 0.25 days (6 hours); Clopidogrel came first NR	Clopidogrel low responders (tertile 3) Clopidogrel responders (tertile 1 & 2)	Not explicitly reported	Clopidogrel low responders (tertile 3): 329 (32.3%) Clopidogrel responders (tertile 1 & 2): 690 (67.7%)

Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Turbidimetric aggregometry APACT4 (4 channel aggregometer) Helena Laboratories (Milan, Italy)	ADP (10 µM)	Venous blood was obtained Citrated blood Venous blood was obtained 12-18 h from clopidogrel loading; for patients administered IIb/IIIa inhibitors blood was obtained 6 d after catheterization NR	Residual platelet reactivity (RPR) (ADP-induced platelet aggregation ≥70%) No residual platelet reactivity (RPR)	Based on literature	Residual platelet reactivity (RPR) (ADP-induced platelet aggregation ≥70%): 110 (14.2%) No residual platelet reactivity (RPR): 662 (85.8%)
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	LTA/NR APACT 4 light transmittance aggregometer Helena Laboratories, Milan, Italy	10 umol ADP or 2 µg/ml collagen	NR 0.109 M sodium citrate Platelet reactivity measured 12 to 18 hr after clopidogrel loading For patients receiving in the catheterization laboratory both the loading dose of clopidogrel and a IIb/IIIa inhibitor, blood samples were obtained after six days while the patient was on the 75-mg maintenance dose of clopidogrel NR	All patients RPR ≥70% by LTA with ADP No RPR RPR by LTA with collagen >90th percentile of patients' distribution No RPR RPR by LTA with ADP+LTA with collagen [NB Fig. 1 says n=32 but Table 3 says n=31) No RPR	LTA-ADP cutoff: Based on literature LTA-collagen cutoff: NR	All patients RPR ≥70% by LTA with ADP: 90/746 (12%) No RPR: 656/746 (88%) RPR by LTA with collagen >90th percentile of patients' distribution (56%): 78/746 (10%) No RPR: 668/746 (90%) RPR by LTA with ADP+LTA with collagen: 32/746 (4%) [NB Fig. 1 says n=32 but Table 3 says n=31) No RPR: 714/746 (96%)
Gori, 2008 {Gori, 2008 164 /id} 18718420 Italy RECLOSE study (Low Responsiveness to Clopidogrel and	light transmission aggregometry APACT4 Helena Laboratories, Milan, Italy	10-µM ADP (clopidogrel) , 1-mM arachidonic acid (aspirin), and 2-µg/ml collagen (clopidogrel)	In catheterization laboratory 0.129 mol/l sodium citrate 0.5-0.75 day (12 to 18 h); 6 days for those pm glycoprotein (GP) IIb/IIIa inhibitor clopidogrel came first NR	Clopidogrel responder (platelet aggregation by ADP <70%; by collagen was defined as platelet aggregation l below 90th percentile of aggregation value distribution that resulted in 56%) and Aspirin responder (platelet aggregation by arachidonic acid ≥20%)	Based on literature	Clopidogrel responder and Aspirin responder : 570 (76.4%) Clopidogrel nonresponder and aspirin nonresponder: 45 (6%) Clopidogrel nonresponder and aspirin responder : 45 (6%) Clopidogrel responder

Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)				Clopidogrel nonresponder (platelet aggregation by ADP ≥70%; by collagen was defined as platelet aggregation above the 90th percentile of aggregation value distribution that resulted in 56%) and aspirin nonresponsiveness (platelet aggregation by arachidonic acid ≥20%) Clopidogrel nonresponder (platelet aggregation by ADP ≥70%; by collagen was defined as platelet aggregation above the 90th percentile of aggregation value distribution that resulted in 56%) and aspirin responder (platelet aggregation by arachidonic acid ≥20%) Clopidogrel responder (platelet aggregation by ADP ≥70%; by collagen was defined as platelet aggregation above the 90th percentile of aggregation value distribution that resulted in 56%) and aspirin nonresponder (platelet aggregation by arachidonic acid ≥20%)		and aspirin nonresponder : 86 (11.6%)
Gurbel, 2010{Gurbel, 2010 68 /id} 20691842 USA PREPARE POST-STENTING	light transmission aggregometry LumiAggregometer Model 490-4D Chronolog,	5 µmol/L ADP (2 mmol/L arachidonic acid (AA) was also used)	Blood; 18 to 24 hours post-PCI or 5 days post-PCI (if eptifibatide used) 3.2% trisodium citrate NR; Clopidogrel came first NR	Quartile of LTA with ADP Quartile 1 <25 % Quartile 2 25-35 % Quartile 3 >35-45 % Quartile 4 >45 %	Quartiles: Not explicitly reported Also by ROC analysis within the same cohort	Quartile of LTA with ADP Quartile 1 <25 %: 56 (25%) Quartile 2 25-35 %: 56 (25%) Quartile 3 >35-45 %: 56 (25%) Quartile 4 >45 %: 57

	Havertown, PA					(25%)
Gurbel, 2003{Gurbel, 2003 222 /id} 12796140 USA NR	LTA Chronology Lumi-Aggregometer (Model 490-4D) Chronology, Havertown, Pennsylvania	5 µm ADP	Response assessed at day 5 3.8% trisodium citrate 2 hours NR	Drug resistance= <10% difference between baseline aggregation and posttreatment aggregation with 5 µmol/L ADP used as the agonist	Based on literature	Resistance Nonresistance
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA NR	Platelet aggregation NR NR & P-selectin expression by flow cytometry NR Parmingen, San Diego, California	ADP 5 and 20 umol/liter for LTA & ADP 200 umol/liter for Flow cytometry	Blood was collected in vacutainer tubes 3.8% trisodium citrate Blood was collected immediately before clopidogrel administration (baseline), and at 1, 5, and 30 days after stenting. NR	Nonresponder (change from baseline of <10%) Responder (change from baseline of <10%)	Not explicitly reported	Nonresponder (change from baseline of <10%) Aggregation by ADP 5 umol/liter: 23/63 (37%) Aggregation by ADP 20 umol/liter: 13/38 (34%) Responder (change from baseline of <10%) Aggregation by ADP 5 umol/liter: 40/63 (63%) Aggregation by ADP 20 umol/liter: 25/38 (66%)
Gurbel, 2004{Gurbel, 2004 220 /id} 15154601 USA None	aggregometry Chronolog Lumi-Aggregometer (model 4902D) with AggroLink software Chronolog, Hawerton [sic], PA	5 and 20 uM ADP	Blood was collected in vacutainer tubes filled to capacity, and then gently inverted 3–5 times for mixing 3.8% trisodium citrate obtained before clopidogrel administration and stenting (baseline); and at 2 h, 24 h, 5 days and 30 days post-stenting NR	heightened reactivity after stenting (post-stent aggregation > baseline aggregation) Non-heightened reactivity	Not explicitly reported	heightened reactivity after stenting (post-stent aggregation > baseline aggregation) : NR Non-heightened reactivity: NR
Gurbel, 2005{Gurbel, 2005 215 /id} 16286165 USA PREPARE POST-STENTING	LTA Chronology Lumi-Aggregometer (Model 490-4D) Chronology, Havertown, Pennsylvania	20um ADP	At discharge 3.8% trisodium citrate 2 hours NR	High LTA (maximum percent change in light transmittance from baseline) >67% Not high LTA (maximum percent change in light transmittance from baseline ≤67%)	Defined by ROC curve in the same study	High LTA : NR Not high LTA : NR

Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	Conventional aggregometry Chronolog LumiAggregometer (Model 490-4D) with the Aggrolink software package Chronolog, Havertown, PA	5 and 20 uM ADP	Post-procedural blood samples were drawn by venipuncture into vacutainer tubes. The tubes were filled to capacity and gently inverted 3–5 times to ensure complete mixing of the anticoagulant 3.2% trisodium citrate Platelet function was measured on the day of hospital discharge in patients not treated with eptifibatide or >=5 days post-discharge in patients treated with eptifibatide (all after clopidogrel dosing) Within 30 minutes	>46% platelet aggregation after 5 umol ADP stimulation (HPR) ≤46% (no HPR) >59% platelet aggregation after 20 umol ADP stimulation (HPR) ≤59% (no HPR)	ROC analysis in present study	>46% platelet aggregation after 5 umol ADP stimulation (HPR): 88 (30%) ≤46% (no HPR): 209 (70%) >59% platelet aggregation after 20 umol ADP stimulation (HPR):101 (34%) ≤59% (no HPR): 196 (66%)
Gurbel, 2010{Gurbel, 2010 84 /id} 20194878 10 study sites in North America and Europe RESPOND	light transmission aggregometry Chronolog Optical Aggregometer (model 490–4D) NR	20 µmol/L ADP	NR 3.2% trisodium citrate 0.25 -0.33 days (6-8 hrs); clopidogrel came first NR	Nonresponder (absolute change in maximum platelet aggregation (MPA) ≤10% between pre-dose and 6-8 hr post-dose measurements) Responder (absolute change in maximum platelet aggregation (MPA) >10% between pre-dose and 6-8 hr post-dose measurements)	Based on literature	Nonresponder (absolute change in maximum platelet aggregation (MPA) ≤10% between pre-dose and 6-8 hr post-dose measurements): 41/98 (41.8%) Responder (absolute change in maximum platelet aggregation (MPA) >10% between pre-dose and 6-8 hr post-dose measurements): 57/98 (58.2%)
Hochholzer, 2006{Hochholzer, 2006 208 /id} 17084243 Germany EXCELSIOR	turbidimetric aggregometry 4-channel Bio/Data PAP4 aggregometer Mölab, Langenfield, Germany	ADP	blood was drawn for platelet function assays We obtained the second blood sample at the time of catheterization before administration of heparin or contrast medium. 3.8% sodium citrate NR NR	Quartiles	NR	Quartiles
Hoshino, 2009{Hoshin	light transmission	5 and 20 µmol/L ADP	1) Baseline; 2) 4 h after loading; 3) 24 h after loading; 4) 48 h after	IPA <10% (clopidogrel non-responders)	Based on a previous report	IPA <10% (clopidogrel non-responders): 4

o, 2009 143 /id} 19106460 Japan NR	aggregometry 12-channel light transmission aggregometer MCM HEMA TRACER 313 MC Medical, Japan		loading; 5) 14 days after loading; 6) 28 days after loading 0.313% sodium citrate. Interval: 0.16 days (4 hrs), 1 day; 2 days; 14 days and 28 days; clopidogrel came first 0.1 days (2 hours)	10%≤ IPA <30% (hypo-responders) IPA ≥30% (responders)		(14.3%) 10%≤ IPA <30% (hypo-responders): 14 (50%) IPA ≥30% (responders): 10 (35.7%)
Htun, 2011{Htun, 2011 20 /id} 21273381 Germany NR	turbidimetric aggregometry two-channel Chronolog aggregometer (Nobis, Germany)	ADP	Blood samples for platelet function analysis were obtained at an earliest time point of 6 hours after administration of 600 mg of clopidogrel, NR Blood samples for platelet function analysis were obtained at an earliest time point of 6 hours after administration of 600 mg of clopidogrel, when A minority of patients already on chronic clopidogrel treatment received a loading dose of 300 mg and were measured approximately 24 hours after drug administration.	low responder 326 (20.8) responder 1009 (64.4) cutoff is beyond 75 percentile of all value in platelet aggregation as low responder.	Based on literature	low responder 326 (20.8) responder 1009 (64.4)
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	LTA ADP AggRam aggregometer Helena Laboratories Corp., Beaumont, TX	5 and 20 μmol/L ADP	Blood samples were drawn into vacutainer tubes containing 0.5 ml of sodium citrate 3.2% and processed within 60 min sodium citrate 3.2% clopidogrel- naı¨ve patients received a 300-mg loading-dose (LD) of clopidogrel at least 12 h before procedure, and blood sampling was performed after insertion of the arterial sheath. In the case of patients who were already on chronic clopidogrel therapy, blood sampling was performed at the	Aggregation <50% Aggregation ≥50%	Based on literature	Aggregation <50%: NR Aggregation ≥50%: NR

			catheterization lab without clopidogrel LD 60 minutes			
L'Allier 2008{L'Allier, 2008 178 /id} 18342223 Canada PREPAIR study	aggregometry light transmission aggregometer (Model 570VS) Chrono-Log Corporation, Havertown, Pennsylvania	ADP at concentrations of 5 and 20 umol/l	Blood was collected from the forearm citrate 3.2% Blood samples were obtained at the time of randomization (baseline), immediately before coronary angiography, and the next morning (12 to 24 h) when a PCI was performed (post- PCI) NR	Nonresponders (resistance) to clopidogrel <10% inhibition of peak aggregation <20% inhibition of peak aggregation <40% inhibition of peak aggregation	Based on literature	Nonresponders (resistance) to clopidogrel by 5 umol ADP per liter & 20 umol ADP per liter: <10% inhibition of peak aggregation 9 in Group A (18%), 8 in Group B (16%), 0 in Group C 11 in Group A (22%), 12 in Group B (24%), 3 in Group C (6%) <20% inhibition of peak aggregation 16 in Group A (33%), 18 in Group B (37%), 4 in Group C (8%) 21 in Group A (43%), 25 in Group B (51%), 9 in Group C (18%) <40% inhibition of peak aggregation 30 in Group A (618%), 29 in Group B (59%), 14 in Group C (28%) 38 in Group A (78%), 36 in Group B (73%), 20 in Group C (40%)
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Turbidometric method in a 4-channel light transmission aggregometer LBY-BJ4 Precil, China	ADP at concentrations of 5 and 20 umol/l	NR 3.8% trisodium citrate Blood samples were collected before clopidogrel administration (baseline and at 12 h (10-14) and 36 h (34-318) after the loading dose. The 12-hour sample was collected before the daily 75-mg clopidogrel dose, whereas the 36-hour sample was collected afterward NR	inhibition of platelet aggregation (IPA) with 5 umol ADP at 12 hr: <10% [clopidogrel nonresponders] 35 (32%) (IPA) < 30% but >/=10% [clopidogrel low responders] 28 (25%) (IPA) >/=30% [clopidogrel responders] 46 (41%)	Based on literature	inhibition of platelet aggregation (IPA) with 5 umol ADP at 12 hr: <10% [clopidogrel nonresponders] 35 (32%) (IPA) < 30% but >/=10% [clopidogrel low responders] 28 (25%) (IPA) >/=30% [clopidogrel responders] 46 (41%)

Matetzky, 2004{Matetzky, 2004 188 /id} 15184279 Israel No	turbidoaggregometry A routine aggregometer: PACKS-4 Helena Laboratory	ADP, 5 umol/L	NR Citrate Blood sampling done before clopidogrel dose (interval NR) and 6 days after NR	Quartile of % reduction of ADP-induced platelet aggregation at 6 days vs. baseline (before clopidogrel LD) [P<0.01 among the quartiles for both mean % reduction and inhibition of aggregation)	Not explicitly reported	1: mean±SD, 103±8% (low responders) : 15 (25%) 2: mean±SD 69±3%: 15 (25%) 3: mean±SD 58±7%: 15 (25%) 4: mean±SD 33±12%: 15 (25%)
Muller, 2003{Muller, 2003 223 /id} 12719773 Germany None	Lumi-aggregometry NR (article says done as previously described and cites ref 7—I skimmed reference and nothing special specified) NR	5 or 20 umol ADP	NR citrate Prior to, 4 and 24 h after clopidogrel administration, whole blood was collected; in some patients, blood was collected 7 and 14 days after PCI NR	Responder (>30% inhibition of aggregation) Nonresponder (inhibition <10%) Semiresponder (inhibition 10-29%)	Not explicitly reported	Response with 5 umol ADP & 20 umol ADP: Responder (>30% inhibition of aggregation) 90 (86%) 12 (11%) Nonresponder (inhibition <10%) 5 (5%) 27 (26%) Semiresponder (inhibition 10-29%) 10 (10%) 66 (63%)
Muller, 2010{Muller, 2010 51 /id} 20728084 Germany NR	light transmission aggregometry Chronolog Lumi aggregometer Chronolog, Havertown, Pennsylvania	ADP	NR 3.8% citrate plasma 0.25 -1 day (6-24 hrs); Clopidogrel came first NR	Stratum I: RPA & CRP <median Stratum II:RPA >median & CRP ≤median Stratum III:RPA ≤ median & CRP >median Stratum IV:RPA & CRP >median	Not explicitly reported	Stratum I: RPA & CRP <median:NR Stratum II:RPA >median & CRP ≤median:NR Stratum III:RPA ≤ median & CRP >median:NR Stratum IV:RPA & CRP >median:NR
Obradovic, 2009{Obradovic, 2009 123 /id} 19318922 Serbia NR	Platelet aggregation BCT-system Dade-Behring, Germany	20 umol/L ADP	Venous blood was sampled in tubes from an antecubital vein under minimal stasis. 3.8% sodium citrate After the angiogram, patients with one or two vessel disease suitable for PCI were scheduled for PCI 3-4 h later, and these patients received a loading dose of clopidogrel of 300 mg. Before PCI, 15 min after PCI, 24 h after PCI	High aggregation Low aggregation Platelet aggregation to ADP above the median was defined as high aggregation and below the median as low aggregation.	not explicitly reported	High aggregation:n=26 Low aggregation:n=26
Saw,	light-	5 umol/L ADP	Patients were fasting for 4h prior to	Absolute difference	Based on literature	<10% (resistance):4/26

2008{Saw, 2008 243 /id} 19038679 Canada ELAPSE trial	transmittance aggregometry lumi-aggregometer Chronolog Corp, Havertown, Pennsylvania		blood withdrawal. The first 3 ml of blood drawn were discarded. Baseline samples were collected from the arterial sheath. Post-PCI samples were drawn from peripheral venipunctures. EDTA, sodium citrate (3.2%), heparin Clopidogrel 600 mg was given before stenting. Platelet data measured at baseline (before clopidogrel); 1 day (16-24 hr) after PCI; and 1, 6, and 12 months after 2 h after blood withdrawal in duplicates (means reported as percent aggregation)	between baseline and post-clopidogrel platelet aggregation with LTA using 5.0 umol/l ADP: <10% (resistance) ≥10% or greater (nonresistance)		(16%) 1 day after PCI 10% or greater (nonresistance):22/26 (85%) 1 day after PCI
Trenk, 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	light transmission aggregometry 4-channel Bio/ Data PAP4 aggregometer Mölab, Langenfeld, Germany	5 and 20 umol ADP	Baseline, cardiac catheterization and at predischarge sample at day 1 3.8% sodium-citrate 0.08 – 0.16 days (2-4 hrs) after clopidogrel 0.04 (1 hour)	high on-treatment platelet reactivity (Residual platelet aggregation >14%) no high on-treatment platelet reactivity (Residual platelet aggregation ≤14%)	Based on literature	high on-treatment platelet reactivity (Residual platelet aggregation >14%) :217 (28.4%) no high on-treatment platelet reactivity (Residual platelet aggregation ≤14%):548 (71.6%)
Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	Chrono-Log Lume-Aggregometer Chrono-Log Lume-Aggregometer (model 700) and the Aggro/Link software package Chrono-Log	20 umol ADP	The first sample was defined as baseline. Blood samples were collected in evacuated container tubes containing 3.8% trisodium citrate. Tubes were filled to capacity and then inverted 3 to 5 times for gentle mixing. 3.8% trisodium citrate Patient blood samples were collected before clopidogrel administration, and at least 24	Clopidogrel resistance Normal clopidogrel response Drug resistance was defined as 10% or less absolute difference between aggregation at baseline and 24h after the 300mg loading dose of clopidogrel.	Based on literature	Clopidogrel resistance :65/386=16.8% Normal clopidogrel response :321/386=83.2%

	Corporation, Havertown, Pennsylvania, USA		hours after the first 300 mg clopidogrel dose to make sure maximum platelet inhibition has been achieved. NR			
Wang, 2010{Wang, 2010 37 /id} 21171668 China None	light transmittance aggregometry (LTA) Chrono-Log Lume-Aggregometer (model 700) with Aggro/Link software Chrono-Log Corpor ation, Havertown, PA	20umol/L ADP	Blood 3.8 % sodium citrate Before clopidogrel administration (baseline) and at least 24 (24 – 28) hours after loading with clopidogrel 300 mg NR	Clopidogrel resistance was defined as≤10 % absolute difference between baseline aggregation and post-administration aggregation Nonresistance (>10%)	Based on literature	Clopidogrel resistance:32 (21%) Nonresistance (>10%):122 (79%) : :
Yong, 2009{Yong, 2009 146 /id} 19081397 Australia Platelet Responsiven ess to Aspirin and Clopidogrel and Troponin Increment after Coronary intervention in Acute coronary Lesions (PRACTICAL) Trial	light transmission aggregometry 8 sites: Chronolog; 2 sites—Monitor IV Plus Chronolog instruments, Havertown, PA; Monitor IV Plus, Helena, Beaumont, TX	ADP 4, 10, and 20 µmol/L	before angiography (preangiography sample) and the morning after the procedure (morning-after sample) Citrate 2 hours 4 hours	Quartiles	not explicitly reported	Quartile cutoffs: NR

*If more than one test, they are presented in separate rows
ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E10: Phenotypic test details in studies assessing the predictive ability of LTA in patients with peripheral artery disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer *	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Linnemann, 2010{Linnemann, 2010 82 /id} 20153859 Germany NR	Light transmittance aggregometry Behring Coagulation Timer (BCT) Dade Behring, Düdingen, Switzerland	2 umol/l ADP	venous blood 3.2% citrate 0.04-1 day (1-24 hrs); clopidogrel came first 0.04 – 0.125 days (1-3 hrs)	Non-responsiveness (late aggregation (LateAggr) ≥42.9%) Responsiveness (late aggregation (LateAggr) <42.9%)	Based on guidelines (53rd Annual Scientific and Standardization Committee Meeting of the International Society of Thrombosis and Haemostasis, Geneva 2007)	Non-responsiveness (late aggregation (LateAggr) ≥42.9%): 19/34 (38.2%) Responsiveness (late aggregation (LateAggr) <42.9%): 21/34 (61.8)

*If more than one test, they are presented in separate rows
ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E11: Results from studies assessing the ability of LTA to predict death in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 5µmol/L	Death	death,	1-year	High OTPR N=445	Death	11 (2.5)	OR=2.53	0.93-6.88	<0.06 (high vs normal) [logistic regression]	No	NR	
						Normal OTPR N=604		6 (1)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 20 µmol/L	Death	death,	1-year	High OTPR N=392	Death	6(12)	OR=0.92	0.34-2.50	0.86 (high vs normal) [logistic regression]	No	NR	
						Normal OTPR N=659		11 (6.2)						
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	5umol/L ADP LTA	cardiac death	cardiac death	6 months	<50%	cardiac death	0.2%	OR=9.61	1.15-80.11	0.016 (<50 vs ≥ 50%) [logistic regression]	NR	NR	
						≥50%		1.5%						
Bliden, 2007{Bliden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	death	death	Day 0-30	HPR n=22	Death	0	OR (calculate) =3.5	NR	P=0.535 (HPR vs NPR) [Chi square]	NR	NR	

					Day 0-30	NPR N=78	death	0	NR	NR	NR	NR	NR	
					Day 31-365	HPR n=22	death	0						
					Day 31-365	NPR N=78	death	0						
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA5	Death	Death	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR N=385	Death,	9/385	OR (calculate) =2.1	NR	P=0.19 (HPR vs NPR) [Fishers exact]	NR	NR	
	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA20	Death	Death	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR N=335	Death,	5/335	OR (calculate) =0.86	NR	P=1.0 (HPR vs NPR) [Fishers exact]	NR	NR	
Buonamici, 2007{Buonamici, 2007 200 /id} 17572245 Italy NR	Clopidogrel LD 600 mg maintenance dose of 75 mg daily	LTA ADP	Cardic mortality	Cardic mortality	6 months	Responders N=699	Cardic mortality	10 (1.4)	NR	NR	<0.001 (responder vs nonrespondner) Chi-square	NR	NR	
						Nonrespondners N=105		9 (8.6)						
Campo, 2007{Campo, 2007 197 /id} 17868803 Italy NR	Clopidogrel 300-mg loading dose, followed by 75 mg/day	LTA ADP	Death	Death	6 months	Responder to both	Death	1/90 (1.1)	OR (calculate) =1.52	NR	P=1.0 (clopidogrel nonrespondner +dual nonrespondner vs other groups) [Fishers exact]	NR	NR	
						Clopidogrel – Ticlopidine+		0(0)						
						Clopidogrel + Ticlopidine -		1(4.3)						

						Nonresponder to both		1(20)						
Geisler, 2006{Geisler, 2006 210 /id} 17005534 Germany NR	Clopidogrel LD dose of 600 mg followed 75 mg daily	ADP LTA	Death from cardiovascular cause	Death from cardiovascular cause	3-month	Adequate response	Death from cardiovascular cause	10/341 (2.9)	NR	NR	0.006	NR	NR	
						Low response		4/22 (18.2)						
	Clopidogrel LD dose of 600 mg followed 75 mg daily	ADP LTA	Death from any cause	Death from any cause	3-month	Adequate response	Death from any cause	14/341 (4.1)	NR	NR	0.003	NR	NR	
						Low response		5/22 (22.7)						
Geisler 2010{Geisler, 2010 101 /id} 19812059 Germany NR	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	cardiovascular death	cardiovascular death	3 months	Low responder (Terrtile 3)	cardiovascular death	10 (1.4%)	OR=3.02	1.33-6.88	p=0.02 (low responder vs responder) [chi square]	NO	NR	Secondary outcome
						Responders (Tertile 1&2)		14 (4.3%)						
Gori 2008 {Gori, 2008 164 /id} 18718420 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	Cardiac death	Cardiac death	6 months	Clopidogrel responder and Aspirin responder	Cardiac death	9 (1.6)	NR	NR	p <0.05 (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders) p <0.0001 (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders)	NO	NR	Secondary endpoint

						Clopidogrel nonresponder and aspirin nonresponder		4 (8.9)	OR (calculate) =4.54	NR	P=0.008 (dual and single clopidogrel nonresponder vs responders) [Fishers exact]			
						Clopidogrel nonresponder and aspirin responder		2 (4.4)						
						Clopidogrel responder and aspirin nonresponder		1 (1.2)						
Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	Clopidogrel +aspirin	5 mcM ADP aggregation	Death		1 mo	>46% platelet aggregation (HPR)		0	OR (calculate) =2.4	NR	P=0.505 (HPR vs NPR over 1-24 months) [Fishers exact]	NR	NR	NR
					2-24 mo			1	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		1	NR	NR	NR	NR	NR	NR
					2-24 mo			0	NR	NR	NR	NR	NR	NR
	Clopidogrel +aspirin	20 mcM ADP aggregation	Death		1 mo	>46% platelet aggregation (HPR)		0	OR (calculate) =1.95	NR	P=1.0 (HPR vs NPR over 1-24 months) [Fishers exact]	NR	NR	NR
					2-24 mo			1	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		1	NR	NR	NR	NR	NR	NR

					2-24 mo			0	NR	NR	NR	NR	NR	NR
Hochholzer, 2006{Hochholzer, 2006 208 /id} 17084243 Germany EXCELSIOR	Clopidogrel 75 mg/day	ADP LTA	Death	death	30-day	1st quartile <4%	Death	0/209	OR (calculate) =7.3	NR	P=0.119 (3rd & 4th quartile vs 1st and 2nd quartile) [Fishers exact]	NR	NR	Cumulative incidence of major adverse cardiac events
						2nd quartile 4-14%		0/198						
						3rd quartile 15-32%		0/196						
						4th quartile >32%		3/199 (1.5%)						
Htun, 2011{Htun, 2011 20 /id} 21273381 Germany NR	clopidogrel LD 600 mg then 75 mg/d and aspirin 100 mg/d	LTA ADP	death	death e	1 year	low-responder group1 (K/DOQI index III –V)	death	17/165 (10.3)	NR	NR	0.04 low responder vs responder)	NR	NR	
						responder group 1 (K/DOQI index III –V)		22/396 (5.6)						
						low-responder group 2 (K/DOQI index I –II)		3/161 (1.9)			0.85 (low responder vs responder)			
						responder group 2 (K/DOQI index I –II)		10/613 (1.6)						
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Clopidogrel +aspirin		CV death			Nonrespoders		2	OR (calculate) =4.43	NR	P=0.25 (nonrespondder vs low + responder) [Fishers exact]			

						Low responders		1						
						Responders		0			0.288 across this and previous 2 rows (chi-square test)			
	Clopidogrel +aspirin	Aggregometry	CV death		1 mo after stenting	Nonresponders		2						
						Low responders		1						
						Responders		0			0.288 across this and previous 2 rows (chi-square test)			
Trenk, 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Death	Death	1 year	high on-treatment platelet reactivity (RPA>14%)	Death	7/217 (3.2%)	HR= 6	1.5-23.2	P=0.003 (between high and not high residual platelet reactivity)	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome

						no high on-treatment platelet reactivity (RPA≤ 14%)	Death	3/548 (0.5%)						
Wang, 2010{Wang, 2010 37 /id} 21171668 China None	Clopidogrel +aspirin	LTA	Cardiovascular death		1 year	Clopidogrel resistance		2 (6.25%)			0.191 vs. next row (Student's t)	NR		
						nonresistance		2 (1.64%)						
Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Cardiovascularf death	Cardiovascularf death,	One year	Clopidogrel resistance	Cardiovascularf death	5/65 (7.7)	NR	NR	0.068 comparing with the following group	NO	NO	
						Normal response		9/321 (2.8)						
						Total		14/386 (3.6)						
Gurbel 2003{Gurbel, 2003 222 /id} 12796140 USA NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Death	Death	30 days	Clopidogrel resistance	Death	0	OR (calculate) =1.25	NR	P=0.91 (resistance vs nonresistance) [Chi square]	NO	NO	
						Clopidogrel nonresistance		0						

Appendix Table E12: Results from studies assessing the ability of LTA to predict myocardial infarction in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 5µmol/L	MI	MI	1-year	High OTPR	MI	37/445 (8.3)	OR=2.19	1.29-3.72	<0.003	No	NR	
						Normal OTPR		24/604 (4)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 20 µmol/L	MI	MI	1-year	High OTPR	MI	37/392 (9.4)	OR=2.76	1.62-4.68	<0.0001	No	NR	
						Normal OTPR		24/659 (3.6)						
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	5umol/L ADP LTA	non-fatal myocardial infarction	non-fatal myocardial infarction	6 months	<50%	non-fatal myocardial infarction	1.9%	OR=3.15	1.55-6.4	0.001	NR	NR	
						≥50%		5.6%						

Bliden 2007{Bliden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Myocardial infarction	Myocardial infarction	Day 0-30	HPR n=22	Myocardial infarction	3/100	OR(calculated)=17.1	NR	P=0.003 (HPR vs NPR) [Fishers exact]	NR	NR	
					Day 0-30	NPR N=78	Myocardial infarction	1/100	NR	NR	NR	NR	NR	
					Day 31-365	HPR n=22	Myocardial infarction	1/100						
					Day 31-365	NPR N=78	Myocardial infarction	0/100						
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA5	MI	MI	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	MI	31/385	NR	NR	0.023comparing with NPR(normal on-treatment platelet reactivity)	NR	NR	
	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA20	MI	MI	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	MI	30/335	NR	NR	0.007comparing with NPR(normal on-treatment platelet reactivity)	NR	NR	
Buonamici, 2007{Buonamici, 2007 200 /id} 17572245 Italy NR	Clopidogre l LD 600 mg maintenance dose of 75 mg daily	LTA ADP	ST-segment elevation AMI	ST-segment elevation AMI	6 months	Responders	ST-segment elevation AMI	199/699	NR	NR	<0.001 comparing with the following group	NR	NR	
						Non-responders		18/105						
Campo, 2007{Campo, 2007 197 /id} 17868803 Italy NR	Clopidogrel 300-mg loading dose, followed by 75 mg/day	LTA ADP	Reinfarction	Reinfarction	6 months	Responder to both	Reinfarction	0/25	OR(calculated)=6.41	NR	P=0.15 (nonresponder vs responder) [Fishers exact]	NR	NR	

						Clopidogrel – Ticlopidine+		1/25						
						Clopidogrel + Ticlopidine -		1/25						
						Nonresponder to both		1/25						
Cuisset, 2007{Cuisset, 2007 204 /id} 17264958 France NR	Clopidogrel loading dose 600 mg	ADP LTA	Periprocedural MI	Periprocedural MI	NR	Non-responders	Periprocedural MI	43%	OR=2.43	1.18-4.97	0.0143 comparing with the following group	NR	NR	
						responders		24%						
Geisler, 2006{Geisler, 2006 210 /id} 17005534 Germany NR	Clopidogrel LD dose of 600 mg followed 75 mg daily	ADP LTA	Myocardial infarction	Myocardial infarction	3-month	Adequate response	Myocardial infarction	4/341 (1.2)	NR	NR	0.29	NR	NR	
						Low response		1/22 (4.5)						
Geisler 2010{Geisler, 2010 101 /id} 19812059 Germany NR	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	MI	NR	3 months	Low responder (Terrtile 3)	MI	14 (2%)	OR=2.15	1.01-4.57	p=0.04 (low responder vs responder) [chi square]	NO	NR	Secondary outcome
						Responders (Tertile 1&2)		14 (4.3%)						
Gurbel 2008{Gurbel, 2008 157 /id} 19012177 USA None	Clopidogrel+aspirin	5 mcM ADP aggregation	MI		1 mo	>46% platelet aggregation (HPR)		1	OR(calculated)=2.4	NR	P=0.37 (HPR vs NPR) [Fishers exact]	NR	NR	NR

					2-24 mo			2	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		0	NR	NR	NR	NR	NR	NR
					2-24 mo			3	NR	NR	NR	NR	NR	NR
	Clopidogrel+aspirin	20 mcM ADP aggregation	MI		1 mo	>46% platelet aggregation (HPR)		1	OR(calculated)=10.2	NR	P=0.012 (HPR vs NPR) [Fishers exact]	NR	NR	NR
					2-24 mo			4	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		0	NR	NR	NR	NR	NR	NR
					2-24 mo			1	NR	NR	NR	NR	NR	NR
Htun, 2011{Htun, 2011 20 /id} 21273381 Germany NR	clopidogrel LD 600 mg then 75 mg/d and aspirin 100 mg/d	LTA ADP	myocardial infarction	myocardial infarction	1 year	low-responder group1	myocardial infarction	17/165 (10.2)	NR	NR	0.024 comparing with the lower row	NR	NR	
						responder group 1		20/396 (5.1)			0.2			
						low-responder group 2		9/161 (5.7)			comparing with the lower row			
						responder group 2		21/613 (3.4)						
Saw, 2008{Saw, 2008 243 /id} 19038679 Canada ELAPSE trial	Clopidogrel+aspirin	LTA	NSTEMI	NR	12 mo	Clopidogrel resistant	YES event	0	OR(calculated)=0.62	NR	P=1.0 (resistant vs onresistant) [chi square]	NR	NR	NR

						Nonresistant		3						
Trenk, 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Nonfatal ST elevation MI	Nonfatal ST elevation MI	1 year	high on-treatment platelet reactivity (RPA>14%)	Nonfatal ST elevation MI	2/217 (0.9%)	HR=2. 6	0.4-18.1	P=0.33 (between high and not high residual platelet reactivity)	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%)		2/548 (0.4%)						

	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Nonfatal non-ST elevation MI	Nonfatal non-ST elevation MI	1 year	high on-treatment platelet reactivity (RPA>14%)	Nonfatal non-ST elevation MI	4/217 (1.8%)	HR=1.7	0.5-6.1	P=0.4 (between high and not high residual platelet reactivity)	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%)		6/548 (1.1%)						
Wang, 2010{Wang, 2010 37 /id} 21171668 China None	Clopidogrel+aspirin	LTA	MI			Clopidogrel resistance		3 (9.38%)			0.061 vs. next row (Student's t)	NR		
						nonresistance		2 (1.64)						
Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Non fatal-MI	nonfatal-MI	One year	Clopidogrel resistance	nonfatal-MI	4/65 (6.2)	NR	NR	0.126 comparing with the following group	NO		

						Normal response		8/321 (2.5)						
						Total		12/386 (3.1)						
Yong, 2009{Yong, 2009 146 /id} 19081397 Australia Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary intervention in Acute coronary Lesions (PRACTICAL) Trial	300-600 mg LD of clopidogrel	LTA using 4, 10, 20µmol/L	Post-PCI myonecrosis	Postprocedure troponin I level above the preprocedure troponin I level and greater than 5 times the upper limit of the reference range (0.1 ng/mL).	6 months	Quartile 1	Post-PCI myonecrosis	NR	NR	NR	NR	NR	NR	Data presented in Fig 2A; no pvalues are reporter for all concentrations of ADP
						Quartile 2	NR							
						Quartile 3	NR							
						Quartile 4	NR							
Gurbel, 2003{Gurbel, 2003 222 /id} 12796140 USA NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Q wave MI	Q wave MI	30 days	Clopidogrel resistance	Q wave MI	0	NR	OR(calculated) =1.2	NR	P=0.9 (HPR vs NPR) [Fishers exact]	NO	
						Clopidogrel nonresistance		0						

Appendix Table E13: Results from studies assessing the ability of LTA to predict stent thrombosis in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Cuisset, 2009{Cuisset, 2009 111 /id} 19801028 France NR	Clopidogrel LD 600 mg	ADP stimulated platelate aggregation	Subacute stent thrombosis	Subacute stent thrombosis	30 days	ADG-Ag >67% as non responders N=NR	Subacute stent thrombosis	31% as nonresponders	OR=5.8	1.9-24.6	0.003 [logistic regression]	NO	NR	
	Clopidogrel LD 600 mg	ADP stimulated platelate aggregation	Subacute stent thrombosis	Subacute stent thrombosis	30 days	ADG-Ag >67% as non responders N=NR	Subacute stent thrombosis	31% as nonresponders	OR=6.24	1.6-24.6	0.009 [logistic regression]	Yes. Age, gender, stent length, left ventricular ejection fraction, diabetes mellitus.	NR	
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 5μmol/L	Stent thrombosis	Stent thrombosis	1-year	High OTPR N=445	Stent thrombosis	7 (1.6)	OR=1.59	0.53-4.77	<0.40 (high vs normal) [logistic regression]	No	NR	
						Normal OTPR N=604		6 (1)						

	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 20 µmol/L	Stent thrombosis	Stent thrombosis	1-year	High OTPR N=445	Stent thrombosis	9 (2.3)	OR=3.85	1.18-12.58	<0.017 (high vs normal) [logistic regression]	No	NR	
						Normal OTPR N=604		4 (0.6)						
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	5umol/L ADP LTA	stent thrombosis	stent thrombosis	6 months	<50%	stent thrombosis	1.2%	OR=2.83	1.18-6.80	0.015 (<50 vs ≥ 50%) [logistic regression]	NR	NR	
						≥50%		3.4%						
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	75 mg clopidogrel	ADP-LTA	Stent thrombosis	Stent thrombosis	6 months	NR	NR	NR	OR=1.059	1.00-1.21	0.049 [logistic regression]	No	NR	
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	Clopidogrel+ aspirin	LTA-ADP	Stent thrombosis	definite or probable: ACS+either angiographic confirmation of thrombosis or pathological confirmation of thrombosis; or unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	6 mo	RPR (n=90)	YES event	6	NR	NR	<0.05 (RPR vs no RPR) [chi square]	NR	NR	NONE

						No RPR (n=656)		14	NR	NR		NR	NR	
		LTA-collagen				RPR (n=78)		8	NR	NR	<0.001 (RPR vs no RPR) [chi square]	NR	NR	
						No RPR (n=668)		11	NR	NR		NR	NR	
		LTA-ADP+LTA-collagen				RPR (n=32)		6	NR	NR	<0.001 (RPR vs no RPR) [chi square]	NR	NR	
						No RPR (n=714)		14	NR	NR		NR	NR	
		LTA-ADP	Stent thrombosis			RPR (n=90)			• AUC 0.65+/-0.06 (cutoff 46%) • 30% (11-54%)sensitivity • 88% (86-91%) specificity		NS			For this entire section of data: NR what ranges (e.g., "(11-54)" to the left) mean for clinical validity data Also ROC curves are in Fig 2 Also bootstrap data re cutoff in text

		LTA-collagen				RPR (n=78)		NA	• AUC 0.50+/-0.07 (cutoff 55%) • 45% (23-69%) sensitivity • 90% (88-92%) specificity		For specificity, "p<0.0001 vs RPR by collagen"	NR	NR	
		LTA-ADP+LTA-collagen				RPR (n=31)			• 30% (10-50%) sensitivity • 97% (95-98%) specificity		For specificity, <0.01 vs. LTA-ADP alone and vs. LTA-collagen			
		LTA-ADP among patients at high risk for AEs	Stent thrombosis			RPR (n=352)		NA	• 70% (50-90%) sensitivity • 53% (506-57%) specificity		For specificity, <0.0001 vs. LTA-collagen	NR	NR	
		LTA-collagen among patients at high risk for AEs				RPR (n=78)		NA	• 50% (28-72%) sensitivity • 91% (88-93%) specificity		For specificity, p<0.0001 vs. LTA-ADP	NR	NR	

		LTA-ADP+LTA-collagen among patients at high risk for AEs				RPR (n=61)		NA	• 45% (23-67%) sensitivity • 93% (91-95%) specificity		For specificity, <0.0001 vs. LTA-ADP alone and <0.0001 vs. LTA-collagen alone	NR	NR	
		LTA-ADP	Stent thrombosis			RPR			OR 3.28	1.23-8.75	0.018 Univariate analysis	NR	NR	
		LTA-collagen				RPR			OR 7.79	3.12-19.46	0.0001 Univariate analysis	NR	NR	
		LTA-ADP+LTA-collagen				RPR			OR 12.01	4.26-33.87	0.0001 Univariate analysis	NR	NR	

		LTA-ADP	Stent thrombosis			RPR		NR	OR 2.41	0.99-6.85	0.090 (RPR vs no RPR) [Logistic regression]	Clinical characteristics (age, sex, cardiovascular risk factors, ejection fraction, number of vessel disease, renal failure, total stent length, chronic total occlusion, bifurcation lesion and glycoprotein IIb/IIa inhibitors) were included in the logistic regression analysis as independent variables in a model in which each RPR was added separately.	NR	
		LTA-collagen				RPR		NR	OR 5.45	2.05-14.53	0.001 Multivariate analysis	YES	NR	
		LTA-ADP+LTA-collagen				RPR		NR	OR 7.50	2.40-23.43	0.001 Multivariate analysis	Yes	NR	

Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA5	ST	ST	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR N=385	ST	4	OR (calculated): 1.1	NR	P=1.0 (high + dual vs responders + high aspirin) [fishers exact]	NR	NR	
	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA20	ST	ST	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR N=335	ST	5	OR (calculated): 2.2	NR	P=0.3 (high + dual vs responders + high aspirin) [fishers exact]	NR	NR	
Buonamici, 2007{Buonamici, 2007 200 /id} 17572245 Italy NR	Clopidogrel LD 600 mg maintenance dose of 75 mg daily	LTA ADP	Stent thrombosis	Definite or probable stent thrombosis	6 months	Responders N=699	Stent thrombosis	16 (2.3)	NR	NR	<0.001 (responders vs nonresponders) [chi square]	NR	NR	
						Nonresponders N=105		9 (8.6)						

	Clopidogrel LD 600 mg maintenance dose of 75 mg daily	LTA ADP	Stent thrombosis	Stent thrombosis	6 months	Responders	Stent thrombosis	7/699 (3.5)	NR	NR	<0.001 (responders vs nonresponders) [chi square]	NR	NR	
						Non-responders		4/105 (22)						
	Clopidogrel LD 600 mg maintenance dose of 75 mg daily	LTA ADP	Stent thrombosis	Stent thrombosis	6 months	Nonresponsiveness	Stent thrombosis	105	HR=3.85	1.7-8.71	<0.001 [cox regression]	No	NR	
	Clopidogrel LD 600 mg maintenance dose of 75 mg daily	LTA ADP	Stent thrombosis	Stent thrombosis	6 months	Nonresponsiveness	Stent thrombosis	105	HR=3.08	1.32-7.16	0.009 [cox regression]	Yes. Acute myocardial infarction, total stent length, LVEF per 1% increase		
Geisler 2010{Geisler, 2010 101 /id} 19812059 Germany NR	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	Stent Thrombosis	Academic research consortium (ARC) definition	3 months	Low responder (Terrtile 3)	Stent Thrombosis	15 (2%)	NR	NR	p=0.03 (low responder vs responder) [KM survival analysis - log rank test]	NO	NR	primary outcome
						Responders (Tertile 1&2)		14 (4.6%)						

	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	Early Stent Thrombosis	Academic research consortium (ARC) definition	30 days	Low responder (Terrtile 3)	Early Stent Thrombosis	NR	NR	NR	p=0.02 (low responder vs responder) [KM survival analysis - log rank test]	NO	NR	primary outcome
						Responders (Tertile 1&2)		NR						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	Late Stent Thrombosis	Academic research consortium (ARC) definition	3 months	Low responder (Terrtile 3)	late Stent Thrombosis	NR	NR	NR	p=0.31 (low responder vs responder) [KM survival analysis - log rank test]	NO	NR	primary outcome
						Responders (Tertile 1&2)		NR						

	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	Stent Thrombosis	Academic research consortium (ARC) definition	3 months	Low responder (Terrtile 3)	Stent Thrombosis	15 (2%)	OR=2.31	1.1-4.84	p=0.02 (low responder vs responder) [Chi square]	NO	NR	primary outcome
						Responders (Tertile 1&2)		14 (4.6%)						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	Definite Stent Thrombosis	Academic research consortium (ARC) definition	3 months	Low responder (Terrtile 3)	definite Stent Thrombosis	7 (1%)	OR=1.2	0.35-4.13	p=0.02 (low responder vs responder) [Chi square]	NO	NR	primary outcome
						Responders (Tertile 1&2)		4 (1.2%)						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	Probable Stent Thrombosis	Academic research consortium (ARC) definition	3 months	Low responder (Terrtile 3)	Probable Stent Thrombosis	5 (0.7%)	OR=3.85	1.28-11.59	p=0.01 (low responder vs responder) [Chi square]	NO	NR	primary outcome
						Responders (Tertile 1&2)		9 (2.7%)						

	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	Possible Stent Thrombosis	Academic research consortium (ARC) definition	3 months	Low responder (Terrtile 3)	Possible Stent Thrombosis	2 (0.3%)	OR=2.1	0.3-15	p=0.45 (low responder vs responder) [Chi square]	NO	NR	primary outcome
						Responders (Tertile 1&2)		2 (0.6%)						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	LTA- ADP	Stent thrombosis	Definite or probable stent thrombosis. Definite = ACS + angiographic or pathologic confirmation of thrombosis; probable = unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	Maximum FU of 6 mo	Residual platelet reactivity (RPR) (ADP-induced platelet aggregation ≥70%)	Stent thrombosis present	8 (7.3%)	NR	NR	0.001 across groups (chi square test)	NO	NO	Primary outcome
						No residual platelet reactivity (RPR)		16 (2.4%)						

	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	Combination of genotypic and phenotypic tests: CYP2C19*2 + ADP residual platelet reactivity	Stent thrombosis	Definite or probable stent thrombosis. Definite = ACS + angiographic or pathologic confirmation of thrombosis; probable = unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	Maximum FU of 6 mo	*2/*2 + RPR N = 40	Stent thrombosis present	6 (15%)	NR OR=5.79	NR (1.04, 39.01)	<0.0001 across groups (chi square test) 0.033 (logistic regression)	NO Adjusted ("for traditional cardiovascular risk factors and clinical and procedural risk factors for stent thrombosis")	NO	Primary outcome
						*1/*1 or low RPR N = 732		18 (2.5%)						
	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	LTA-ADP	Stent thrombosis	Definite or probable stent thrombosis. Definite = ACS + angiographic or pathologic confirmation of thrombosis; probable = unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	Maximum FU of 6 mo	Residual platelet reactivity (RPR) (ADP-induced platelet aggregation ≥70%)	Stent thrombosis present	8 (7.3%)	OR=3.17 OR=3.08	(1.32, 7.59) (1.23, 7.72)	0.001 (chi square test) 0.016 (logistic regression)	NO (univariate) YES (ADP-RPR, traditional cardiovascular risk factors, clinical and procedural risk factors for ST)	NO	Primary outcome
						No residual platelet reactivity (RPR)		16 (2.4%)						

Gori, 2008 {Gori, 2008 164 /id} 18718420 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	definite or probable stent thrombosis	definite or probable stent thrombosis	6 months	Clopidogrel nonresponder	definite or probable stent thrombosis	NR	HR=1.44	0.54 to 3.82	P=0.463 [Cox regression]	YES; age (years), male gender, family history of CAD, smoker, HTN, hypercholesterolemia, diabetes mellitus, history of myocardial infarction, history of coronary surgery, acute coronary syndrome, acute STEMI, left ventricular ejection fraction (%), multivessel disease, bifurcation lesion, thrombus-containing lesion, chronic total occlusion, and stent length (mm).	NR	Primary endpoint

	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	definite or probable stent thrombosis	definite or probable stent thrombosis[1]	6 months	Clopidogrel & Aspirin nonresponder	definite or probable stent thrombosis	NR	HR=3.18	1.14 to 8.83	P=0.027 [Cox regression]	YES; age (years), male gender, family history of CAD, smoker, HTN, hypercholesterolemia, diabetes mellitus, history of myocardial infarction, history of coronary surgery, acute coronary syndrome, acute STEMI, left ventricular ejection fraction (%), multivessel disease, bifurcation lesion, thrombus-containing lesion, chronic total occlusion, and stent length (mm).	NR	Primary endpoint
	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	definite or probable stent thrombosis	definite or probable stent thrombosis**Error! Bookmark not defined.**	6 months	Clopidogrel non with r without Aspirin responder	definite or probable stent thrombosis	6 /90 (6.7)	HR=3.15	1.21 to 8.20	P=0.019 [Cox regression]	NO	NR	Primary endpoint

	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	definite or probable stent thrombosis	definite or probable stent thrombosis[1]	6 months	Clopidogrel responder and Aspirin responder	definite or probable stent thrombosis	12 (2.1)	NR	NR	p<0.0001; (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders) p<0.05 (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders)	NO	NR	Primary endpoint
						Clopidogrel nonresponder and aspirin nonresponder		5 (11.1)						
						Clopidogrel nonresponder and aspirin responder		1 (2.2)						

						Clopidogrel responder and aspirin nonresponder		2 (2.3)						
	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	definite or probable stent thrombosis	definite or probable stent thrombosis[1]	6 months	Clopidogrel responder and Aspirin responder	definite or probable stent thrombosis	NR	NR	NR	p<0.001; (dual nonresponders vs. dual responders) P=0.036 (dual nonresponders vs. aspirin nonresponders) P=0.096 (dual nonresponders vs. clopidogrel nonresponders)	NO	NR	Primary endpoint
	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	definite stent thrombosis	definite stent thrombosis**Error! Bookmark not defined.**	6 months	Clopidogrel responder and Aspirin responder	definite stent thrombosis	6 (1.1)	NR	NR		NO	NR	Primary endpoint

						Clopidogrel nonresponder and aspirin nonresponder		2 (4.4)						
						Clopidogrel nonresponder and aspirin responder		0						
						Clopidogrel responder and aspirin nonresponder		1 (1.2)						
	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	probable stent thrombosis	probable stent thrombosis **Error! Bookmark not defined.**	6 months	Clopidogrel responder and Aspirin responder	probable stent thrombosis	6 (1.1)	NR	NR	p <0.05 (dual clopidogrel and aspirin nonresponders versus clopidogrel and aspirin responders)	NO	NR	Primary endpoint
						Clopidogrel nonresponder and aspirin nonresponder		3 (6.7)						

						Clopidogrel nonresponder and aspirin responder		1 (2.2)						
						Clopidogrel responder and aspirin nonresponder		1 (1.2)						
Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	Clopidogrel+ aspirin	5 mcM ADP aggregation	Stent thrombosis		1 mo	>46% platelet aggregation (HPR)		1	NR	OR (calculated): 3.7	NR	P=0.16 (HPR vs NPR) [fishers exact]	NR	NR
					2-24 mo			2	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		2	NR	NR	NR	NR	NR	NR
					2-24 mo			0	NR	NR	NR	NR	NR	NR
	Clopidogrel+ aspirin	20 mcM ADP aggregation	Stent thrombosis		1 mo	>64.5% platelet aggregation (HPR)		1	NR	OR (calculated): 3	NR	P=0.34 (HPR vs NPR) [fishers exact]	NR	NR
					2-24 mo			2	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		2	NR	NR	NR	NR	NR	NR
					2-24 mo			0	NR	NR	NR	NR	NR	NR
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Clopidogrel+ aspirin	Aggregometry	Stent thrombosis			Nonresponders	34	0		OR (calculated): 16	NR	P=0.03 (HPR vs NPR) [fishers exact]		

						Low responders	28	0						
						Responders	44	0			NR			
	Clopidogrel+ aspirin	Aggregometry	Stent thrombosis			Nonresponders	34	0						
						Low responders	28	0						
						Responders	44	0			NR			
Muller, 2003{Muller, 2003 223 /id} 12719773 Germany None	Clopidogrel+ aspirin	Aggregometry	Subacute stent thrombosis	Day 6 or 7 after angiography	Day 6 or 7	Nonresponder (NB authors don't say according to which level of ADP or both)	Yes event	2	OR (calculated): 143	NR	P=0.001 (nonresp vs others) [fisher s exact]	NR	NR	NONE
						Semiresponder		0						
						Responder		0						

Muller, 2010{Muller, 2010 51 /id} 20728084 Germany NR	Clopidogrel 600 mg LD + 75 mg MD & Aspirin 100 mg/d MD	LTA	Stent thrombosis	Defined according to the Academic Research Consortium criteria	Mean follow up of 344 days	Stratum I: RPA & CRP <median	Stent thrombosis	NR	NR	NR	P=0.02 (Stratum IV vs I) P<0.001 (Stratum IV vs II) P=0.04 (Stratum IV vs III) P>0.05 (Stratum III vs I+II) P>0.05 (Stratum II vs I) [Log Rank]test	YES; age, gender, left ventricular function, acute coronary syndromes, hyperlipidemia and relevant comedication	NR	Primary
						Stratum II:RPA >median & CRP ≤median		NR						
						Stratum III:RPA ≤ median & CRP >median		NR						
						Stratum IV:RPA & CRP >median		NR						

Trenk, 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel - Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Any stent thrombosis	Any stent thrombosis	1 year	high on-treatment platelet reactivity (RPA>14 %) N=217	Any stent thrombosis	10(4.6%)	HR=3.7	1.4-9.6	P=0.008 (between high and not high residual platelet reactivity) [Cox regression]	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%) N=548		7 (1.3%)						

	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Definite or probable stent thrombosis	Definite or probable stent thrombosis	1 year	high on-treatment platelet reactivity (RPA>14 %) N=217	Definite or probable stent thrombosis	8 (3.7%)	HR=4.1	1.3-12.5	P=0.01 (between high and not high residual platelet reactivity) [Cox regression]	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%) N=548		5 (0.9%)						

	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Definite stent thrombosis	Definite stent thrombosis	1 year	high on-treatment platelet reactivity (RPA>14 %) N=217	Definite stent thrombosis	1(0.5%)	HR=1.3	0.1-14.1	P=0.84 (between high and not high residual platelet reactivity) [cox regression]	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%) N=548		2 (0.4%)						

	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Probable stent thrombosis	Probable stent thrombosis	1 year	high on-treatment platelet reactivity (RPA>14 %) N=217	Probable stent thrombosis	7 (3.2%)	HR=5.9	1.5-23	P=0.01 (between high and not high residual platelet reactivity) [cox regression]	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%) N=548		3 (0.5%)						

	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Possible stent thrombosis	Possible stent thrombosis	1 year	high on-treatment platelet reactivity (RPA>14 %) N=217	Possible stent thrombosis	2(0.9%)	HR=2.6	0.4-18.4	P=0.34 (between high and not high residual platelet reactivity) [cox regression]	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%) N=548		2(0.4%)						

Wang, 2010{Wang, 2010 37 /id} 21171668 China None	Clopidogrel+ aspirin	LTA	Definite or probable stent thrombosis	Academic Research Consortium (ARC) definitions: Definite—presence of ACS with angiographic or autopsy evidence of thrombus or occlusion Probable -- unexplained deaths within 1 month after the procedure or acute MI involving target-vessel territory without angiographic confirmation		Clopidogrel resistance		4 (12.5%)			0.017 (resisters vs nonresistant) (Student's t); p=0.025 from multivariate regression (for independent prediction)	YES for multivariate regression P value only (diabetes, BMI, and smoking status)		
						nonresistance		2 (1.64%)						
	Clopidogrel+ aspirin	LTA	Definite			Clopidogrel resistance		2 (6.25%)			0.110 (resisters vs nonresistant) (Student's t)	NR		
						nonresistance		1 (0.82%)						
	Clopidogrel+ aspirin	LTA	Probable			Clopidogrel resistance		2 (6.25%)			0.110 (resisters vs nonresistant) (Student's t)	NR		

						nonresistance		1 (0.82%)						
	Clopidogrel+ aspirin	LTA	Acute	within 24 hours		Clopidogrel resistance		0			NR	NR		
						nonresistance		0						
	Clopidogrel+ aspirin	LTA	Subacute	1–30 days after		Clopidogrel resistance		1 (3.13%)			0.373 (resisters vs nonresistant) (Student's t)	NR		
						nonresistance		1 (0.82%)						
	Clopidogrel+ aspirin	LTA	Late	30 days to 1 year after		Clopidogrel resistance		3 (9.38%)			0.028 (resisters vs nonresistant) (Student's t)	NR		
						nonresistance		1 (0.82%)						
Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Definite or probable stent thrombosis	Definite or probable stent thrombosis	12-months	Clopidogrel resistance	Definite or probable stent thrombosis	NR	HR=4.46	1.03-20.27	0.031 [cox regression]	Yes, LV dysfunction (EF<30%), Total stent length	NR	
	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Definite or probable stent thrombosis	Definite or probable stent thrombosis	One year	Clopidogrel resistance N=65	Definite or probable stent thrombosis	6 (9.2)	NR	NR	0.018 (resisters vs normal response)	NO	NO	

						Normal response N=321		8(2.5)						
	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Definite stent thrombosis	Definite stent thrombosis	One year	Clopidogrel resistance N=65	Definite stent thrombosis	3 (4.6)	NR	NR	0.096 (resisters vs normal response)	NO	NO	
						Normal response N=321		4(1.2)						
	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Probable stent thrombosis	Probable stent thrombosis	One year	Clopidogrel resistance N=65	Probable stent thrombosis	3 (4.6)	NR	NR	0.096 (resisters vs normal response)	NO	NO	
						Normal response N=321		4 (1.2)						
Gurbel, 2003{Gurbel, 2003 222 /id} 12796140 USA NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Stent thrombosis	Stent thrombosis	30 days	Clopidogrel resistance	Stent thrombosis	0/50	OR (calculated): 1.2	NR	P=0.9 (nonresp vs others) [fisher s exact]	NO	NO	
						Clopidogrel nonresistance		0/63						

Appendix Table E14: Results from studies assessing the ability of LTA to predict major adverse cardiovascular events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Geisler 2010{Geisler, 2010 54 /id} 20526607 Germany NR	Clopidogrel+aspirin	Lumi-aggrego meter	MACE	MI, cardiovascular events, and cardiovascular death	30 days after PCI	Top tertile of platelet aggregation (among the total 413 DM patients followed for 30 days) N=NR	MACE	NR	NR	NR	0.02 (log-rank test) vs. DM patients in lowest tertile	NR	NR	K-M curve in Fig 6
Frere, 2007{Frere, 2007 193 /id} 17938809 France NR	600 mg loading dose of clopidogrel and maintaining 75mg daily	ADP-induced platelet aggregation (ADP-Ag)	CV event	CV death, acute or subacute stent thrombosis, recurrent ACS and stroke	30 days after PCI	≥70% N=54	CV event	11/54 (20%)	AUC: 0.74±0.08	NR	NR	NR	NR	NR
						<70% N=127	CV event	3/127 (2.5%)	OR (calculate) =10.6		P value=0.000125 (≥70% vs <70%) [Fisher's exact test]			

Breet 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 5µmol/L	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR N=445	Death combined	52/445 (11.7)	OR=2.09	1.34-3.25	<0.001	No	NR	Figure 1 KM curves
						Normal OTPR N=604		36/604 (6)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 20 µmol/L	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR N=392	Death combined	47/392 (12)	OR=2.05	1.32-3.19	<0.001	No	NR	
						Normal OTPR N=659		41/659 (6.2)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 5µmol/L	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR ≥42.9% N=445	Death combined	52/445 (11.7)	AUC: 0.63 Sens: 0.602 Spec: 0.591	0.58-0.68 0.498-0.698 0.56-0.622	NR	No	NR	
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 20µmol/L	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR ≥64.5% N=392	Death combined	47/392 (12)	AUC: 0.62 Sens: 0.546 Spec: 0.639	0.56-0.67 0.442-0.645 0.608-0.668	NR	No	NR	

Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	5umol/L ADP LTA	composite	composite	6 months	<50%	composite	2.2%	OR=2.69	1.37-5.29	0.003	NR	NR	
						≥50%		5.6%						
Bliden, 2007{Bliden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Total patients with ischemic events	Total patients with ischemic events	Day 0-30	HPR n=22	Total patients with ischemic events	5/22	OR (calculated)=27.04	NR	P value<0.0001 (HPR vs NPR) [Fisher's exact test]	NR	NR	
					Day 0-30	NPR N=78	Total patients with ischemic events	1/78	NR	NR	NR	NR	NR	
					Day 31-365	HPR n=22	Total patients with ischemic events	11/22						
					Day 31-365	NPR N=78	Total patients with ischemic events	6/78						

	clopidogrel 75 mg qd	LTA	Ischemic events	Ischemic events	NR	HPR	Ischemic event	NR	OR=34.6	8.3-144.2	<0.001	Yes, age, presentation, diabetes, hypertension, current smoking, BMS(bare-metal stents)	NR	
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	Clopidogrel+aspirin	LTA-ADP	Stent thrombosis or cardiac death (composite)			RPR (n=90)		8	OR (calculated)=3.67	NR	P value=0.006 (RPR vs no RPR) [Fisher's exact test]	NR	NR	
						No RPR (n=656)		17	NR	NR		NR	NR	
		LTA-collagen				RPR (n=78)		11	OR (calculated)=7.67	NR	P value=0.00001 (RPR vs no RPR) [Fisher's exact test]	NR	NR	
						No RPR (n=668)		14	NR	NR		NR	NR	

		LTA-ADP	Stent thrombosis or cardiac death (composite)			RPR (n=90)			• 32% (15-54%) sensitivity • 89% (86-91%) specificity		NS			
		LTA-collagen				RPR (n=78)			• 44% (25-63%) sensitivity • 91% (88-93%) specificity		For specificity, “p<0.0001 vs RPR by collagen			
		LTA-ADP+LTA-collagen				RPR (n=31)		NA	• 28% (10-46%) sensitivity • 97% (95-98%) specificity		For specificity, <0.01vs. LTA-ADP alone and vs. LTA-collagen	NR	NR	
		LTA-ADP among patients at high risk for AEs	Stent thrombosis or cardiac death (composite)			RPR (n=352)		NA	• 64% (45-83%) sensitivity • 53% (50-57%) specificity		NS	NR	NR	

		LTA-collagen among patients at high risk for AEs				RPR (n=78)		NA	• 48% (28-68%) sensitivity • 91% (89-93%) specificity			NR	NR	
		LTA-ADP+LTA-collagen among patients at high risk for AEs				RPR (n=61)			• 40% (21-59%) sensitivity • 93% (91-95%) specificity		For sensitivity, p<0.01 vs. LTA-ADP For specificity, p<0.0001 vs. LTA-ADP	NR	NR	
		LTA-ADP	Stent thrombosis or cardiac death (composite)			RPR			OR 3.67	1.53-8.76	0.003 Univariate analysis	NR	NR	
		LTA-collagen				RPR			OR 7.67	3.35-17.57	0.0001 Univariate analysis	NR	NR	
		LTA-ADP+LTA-collagen				RPR			OR 11.29	4.31-25.59	0.0001 Univariate analysis	NR	NR	

Gurbel, 2010{Gurbel, 2010 68 /id} 2069184 2 USA PREPARE POST-STENTING	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	LTA-ADP	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	LTA-ADP >34%	MACE	NR	Sensitivity: 0.8 Specificity: 0.59 AUC: 0.75	0.68-0.8	P<0.001	NO	NR	Primary endpoint; 14/59 (24%) of first events occurred after clopidogrel stopped (mean duration of Tx=of 6.4 ± 3 months)
						LTA-ADP ≤34%		NR						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	LTA-ADP	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	LTA-ADP >34%	MACE	NR	HR=4.8	2.4-9.6	P<0.001	NO	NR	Primary endpoint
						LTA-ADP ≤34%		NR						

	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	LTA-ADP	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization[1]	First event over f/u of 36 months	LTA-ADP >34%	MACE	NR	HR=5.6	2.7-11.6	P<0.001	YES; History of prior PTCA and calcium-channel blockers	NR	Primary endpoint
						LTA-ADP ≤34%		NR						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	LTA-ADP	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization[1]	First event over f/u of 36 months	Quartile 1 <65 mm	MACE	6 (11%)	NR	NR	NR	NR	NR	Primary endpoint
						Quartile 2 65-69 mm		8 (15%)						
						Quartile 3 >69-72 mm		16 (30%)						
						Quartile 4 >72 mm		29 (52%)						
Matetzky, 2004{Matetzky, 2004 188 /id} 15184279 Israel No	Clopidogrel	Aggrego meter (not cone and platelet device)	Recurrent major adverse cardiovascular event	NR	6 months after PCI	Q1	Yes event	6 (40%)	NR	NR	0.007 for trend of Q1 through Q2, Q3 and Q4	NR	NR	NO

						Q2		1 (6.7%)						
						Q3		0						
						Q4		0						
Angiolollo, 2007{Angiolillo, 2007 194 /id} 17936152 Spain NR	clopidogrel (75 mg/day)	LTA-ADP	MACE	Major adverse cardiovascular events	2 years	HPR cutoff 62%	MACE	37.7%	OR=3.96	1.8-8.7	<0.001 comparing no-HPR	NR	NR	
						No HPR	MACE	13.3%						
						HPR cutoff 62%	MACE	37.7%	OR=3.35	1.68-6.66	0.0013 comparing no-HPR	Yes, renal failure, New York Heart Association functional class III to IV	NR	
						No HPR	MACE	13.3%						

Aradi 2008{Aradi, 2008 236 /id} 18388039 Hungary NR	Clopidogrel + aspirin	Platelet aggregometry	Cumulative event-free survival (events were cardiovascular death, myocardial infarction, revascularization, in-stent restenosis, stent thrombosis, or de novo lesion)	All deaths regarded as cardiovascular unless clear evidence of any other non-cardiovascular cause. MI defined as presence of at least 2 of the 3 criteria: typical chest pain, new ECG changes compatible with MI (Q-wave duration >0.04 sec or >1/4 of the corresponding R-wave's amplitude, ST segment elevation in >2 relevant leads over 0.1 mV), elevation of CK and CK-MB >2xULN in at least 2 different samples. Revascularizations included repeated PCI and CABG.	10 mo after stenting	Below 50th percentile of maximal ADP 5 mcmol aggregation	~60% eyeballed estimate	NR	NR	NR	<0.01 vs. next row (Kaplan-Meier test)	NR	NR	Fig 2A has survival curves

						Above 50th percentile of ADP 5 mcmol aggregation	~93% eyeball estimate							
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA5	Death, MI, ST, stroke	Death, MI, ST, stroke	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	Death, MI, ST, stroke	43/385	NR	NR	0.009 (HCPR vs NPR)	NR	NR	Kalpak-Meier curves (figure 1)
	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA20	Death, MI, ST, stroke	Death, MI, ST, stroke	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	Death, MI, ST, stroke	37/355	NR	NR	0.006 (HCPR vs NPR)	NR	NR	
	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA5	Death, MI, ST, stroke	Death, MI, ST, stroke	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	Death, MI, ST, stroke	NR	OR=2.63	1.17-5.92	0.02 (HCPR vs NPR) [Logistic regression]	Yes, age, impaired ejection fraction, LTA5: HAPR, LTA20 HAPR, hypertension, LTA20 HCPR, LTA5 DAPR, LTA20 DAPR, graft-stenting, bifurcation lesion, verifynow DAPR	NR	

	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA20	Death, MI, ST, stroke	Death, MI, ST, stroke	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	Death, MI, ST, stroke	NR	OR=3.31	1.47-7.5	0.004 (HCPR vs NPR) [Logistic regression]	Yes, age, impaired ejection fraction, LTA5: HAPR, LTA20 HAPR, hypertension, LTA5 HCPR, LTA5 DAPR, LTA20 DAPR, graft-stenting, bifurcation lesion, verifynow DAPR	NR	
Breet 2010{Breet, 2010 50 /id} 20695984 Netherlands Substudy of a larger cohort (Breet 2010 PMID: 20179285)	Clopidogrel 300-900 LD + 75 mg MD	LTA with 20 µmol/L	MACE	All-cause death, nonfatal MI, definite stent thrombosis and ischemic stroke	1-year	High on-treatment platelet reactivity with native platelet rich plasma	MACE	30	OR=2.45	1.45-4.15	P=0.001	No	NR	
						Normal on-treatment platelet reactivity with native platelet rich plasma		33						

	Clopidogrel 300-900 LD + 75 mg MD	LTA with 20 µmol/L	MACE	All-cause death, nonfatal MI, definite stent thrombosis and ischemic stroke	1-year	High on-treatment platelet reactivity with adjusted platelet rich plasma	MACE	30	OR=1.78	1.05-2.99	P=0.04	No	NR	
						Normal on-treatment platelet reactivity with adjusted platelet rich plasma		33						
	Clopidogrel 300-900 LD + 75 mg MD	LTA with 20 µmol/L	MACE	All-cause death, nonfatal MI, definite stent thrombosis and ischemic stroke	1-year	High on-treatment platelet reactivity with native platelet rich plasma	MACE	30	AUC=0.59	0.52-0.66	NR	No	NR	
	Clopidogrel 300-900 LD + 75 mg MD	LTA with 20 µmol/L	MACE	All-cause death, nonfatal MI, definite stent thrombosis and ischemic stroke	1-year	High on-treatment platelet reactivity with adjusted platelet rich plasma	MACE	30	AUC=0.59	0.52-0.66	NR	No	NR	
Buonamici, 2007{Buonamici, 2007 200 /id} 17572245 Italy NR	Clopidogrel LD 600 mg maintenance dose of 75 mg daily	LTA ADP	Composite of cardiac death and stent thrombosis	Composite of cardiac death and stent thrombosis	6 months	Responders	Composite of cardiac death and stent thrombosis	19/699 (2.7)	NR	NR	<0.001 comparing with the following group	NR	NR	
						Non-responders		11/105 (11)						

Campo, 2007{Campo, 2007 197 /id} 17868803 Italy NR	Clopidogrel 300-mg loading dose, followed by 75 mg/day	LTA ADP	MACE	MACE	6 months	Responder to both	MACE	2(2.2)	OR (calculated)=2.43	NR	P value=0.169 (clopidogrel and dual nonresponders vsother groups) [Fisher's exact test]	NO	NR	
						Clopidogrel – Ticlopidine+		3(12)						
						Clopidogrel + Ticlopidine -		5(22)						
						Nonresponder to both		2(40)						
Cuisset 2006{Cuisset, 2006 212 /id} 16371119 France NR	Clopidogrel+aspirin	PAP4 aggregometer	Cardiovascular event	CV death, acute or subacute stent thrombosis, ischemic stroke and recurrent ACS	1 month	Q1-Q3 (responder)	Yes event	3 (4%)	NR	NR	NR	NO	NR	NO
							No event	80 (96%)	NR	NR	NR	NO		
						Q4 (nonresponder)	Yes event	9 (39%)	OR vs Q1-3: 22.4	4.6-109	<0.05 (logistic regression) vs. Q1-3 yes event	NO		

									OR vs Q1-3: 19.6	4.24-90.3	<0.001 (l ogistic regress ion) vs. Q1-3 yes event	YES age, sex		
									OR vs Q1-3: 35	4.81-248	<0.001 (l ogistic regress ion) vs. Q1-3 yes event	YES age, sex, (hypert ension, diabete s, dyslipid emia, smokin g, ejection fraction) , heart rate, systolic blood pressur e and treatme nts.		

									OR vs Q1-3: 41.6	4.74-364	0.003 (logistic regression) vs. Q1-3 yes event	YES age, sex, (hypertension, diabetes, dyslipidemia, smoking, ejection fraction), heart rate, systolic blood pressure and treatments + P-selectin and CRP		
							No event	14 (61%)						
Cuisset 2006{Cuisset, 2006 237 /id} 17010792 France NR	Clopidogrel 300 mg LD	LTA	CV events	CV death, acute or subacute stent thrombosis, recurrent ACS, and stroke.	1 month	high post treatment platelet reactivity	CV events	12	OR=9.93	3.19-30.9	NR [logistic regression]	YES; Age, gender	NR	
						normal post treatment platelet reactivity		6						
	Clopidogrel 600 mg LD	LTA	CV events	CV death, acute or subacute stent thrombosis, recurrent ACS, and stroke.	1 month	high post treatment platelet reactivity	CV events	6	OR=43.16	4.89-381.1	NR [logistic regression]	YES; Age, gender	NR	

						normal post treatment platelet reactivity		1						
Geisler 2008{Geisler, 2008 184 /id} 17949474 Germany NR	Clopidogrel	Turbido aggregometry	Major adverse events (MI, ischemic stroke, death, or cardiovascular death		30 days	RPA tertile 1 (lowest)	Yes event	5 (1.5%)	OR (calculated)=2.37	NR	P value=0.026 (highest tertile vs tertile 1&2) [Fisher's exact test]	NO (not for these data)	NR	These data are for 950 patients (87% of the 1092) with 30-day followup data
						RPA tertile 2		8 (2.5%)						
						RPA tertile 3 (highest)		15 (4.8%)						
Geisler, 2006{Geisler, 2006 210 /id} 17005534 Germany NR	Clopidogrel LD dose of 600 mg followed 75 mg daily	ADP LTA	Composite CV endpoints	Composite CV endpoints	3-month	Adequate response	Composite CV endpoints	19/341 (5.6)	NR	NR	0.01	NR	NR	
						Low response		5/22 (22.7)						
	Clopidogrel LD dose of 600 mg followed 75 mg daily	ADP LTA	Cumulative events	Cumulative events	3-month	Adequate response	Cumulative events	23/341 (6.7)	NR	NR	0.005	NR	NR	
						Low response		6/22 (27.3)						

	Clopidogrel LD dose of 600 mg followed 75 mg daily	ADP LTA	Composite cardiovascular endpoints	Composite cardiovascular endpoints	3 months	Low response	Composite cardiovascular endpoints	N=22	HR=3.71	1.08-12.69	0.04	Yes, factors influencing cardiovascular outcome	NR	
Geisler 2010{Geisler, 2010 101 /id} 19812059 Germany NR	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	MACE	MI, ischemic stroke, cardiovascular death	3 months	Low responder (Terrtile 3)	MACE	30 (4.2%)	OR=2.21	1.31-3.73	p=0.002 (low responder vs responder) [chi square]	NO	NR	Secondary outcome
						Responders (Tertile 1&2)		30 (9.1%)						
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	LTA-ADP	MACE	Composite of cardiac mortality and stent thrombosis (definite or probable)	Maximum FU of 6 mo	Residual platelet reactivity (RPR) (ADP-induced platelet aggregation ≥70%)	Cardiac death or stent thrombosis	10 (9.1%)	NR	NR	0.001 across groups (chi square test)	NO	NO	Secondary outcome
						No residual platelet reactivity (RPR)		19 (2.1%)						

	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	Combination of genotypic and phenotypic tests: CYP2C19*2 + ADP residual platelet reactivity (see also KQ1b extraction form)	MACE	Composite of cardiac mortality and stent thrombosis (definite or probable)	Maximum FU of 6 mo	*2/*2 + RPR N = 40	Cardiac death or stent thrombosis	7 (17.5%)	NR OR=11.45	NR (1.84, 71.27)	<0.0001 (chi square test) 0.009 (logistic regression)	NO Adjusted ("for traditional cardiovascular risk factors and clinical and procedural risk factors for stent thrombosis")	NO	Secondary outcome
						*1/*1 or low RPR N = 732		22 (3%)						
	Aspirin (loading dose = 325 mg; maintenance dose = 325 mg per day) and clopidogrel (loading dose = 600 mg; 75 mg maintenance).	LTA-ADP	MACE	Composite of cardiac mortality and stent thrombosis (definite or probable)	Maximum FU of 6 mo	Residual platelet reactivity (RPR) (ADP-induced platelet aggregation ≥70%)	Cardiac death or stent thrombosis	10 (9.1%)	OR=3.38 OR=2.9	(1.53, 7.49) (1.08, 12.98)	0.003 (chi square test) 0.019 (logistic regression)	NO (univariate) YES (ADP-RPR, traditional cardiovascular risk factors, clinical and procedural risk factors for ST)	NO	Secondary outcome
						No residual platelet reactivity (RPR)		19 (2.1%)						

Gori 2008 {Gori, 2008 164 /id} 18718420 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	MACE	Cardiac death & stent thrombosis	6 months	Clopidogrel nonresponder	Cardiac death & stent thrombosis	NR	HR=2.23	0.85 to 5.82	P=0.101	YES; age (years), male gender, family history of CAD, smoker, HTN, hypercholesterolemia, diabetes mellitus, history of myocardial infarction, history of coronary surgery, acute coronary syndrome, acute STEMI, left ventricular ejection fraction (%), multivessel disease, bifurcation lesion, thrombus-containing lesion, chronic total occlusion, and stent length (mm)	NR	Secondary endpoint

	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	MACE	Cardiac death & stent thrombosis	6 months	Clopidogrel & Aspirin nonresponder	Cardiac death & stent thrombosis	NR	HR=2.94	1.17 to 7.41	P=0.022	YES; age (years), male gender, family history of CAD, smoker, HTN, hypercholesterolemia, diabetes mellitus, history of myocardial infarction, history of coronary surgery, acute coronary syndrome, acute STEMI, left ventricular ejection fraction (%), multivessel disease, bifurcation lesion, thrombus-containing lesion, chronic total occlusion, and stent length (mm)	NR	Secondary endpoint

	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	MACE	Cardiac death & stent thrombosis	6 months	Clopidogrel responder and Aspirin responder	Cardiac death & stent thrombosis	15 (2.6)	NR	NR	P<0.0001; (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders) P<0.05; (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders)	NO	NR	Secondary endpoint

						Clopidogrel nonresponder and aspirin nonresponder		6 (13.3)			p <0.05 (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders) p <0.0001 (dual clopidogrel and aspirin nonresponders versus aspirin nonresponders)			
						Clopidogrel nonresponder and aspirin responder		2 (4.4)						
						Clopidogrel responder and aspirin nonresponder		2 (2.3)						

	600 mg clopidogrel LD + 75-mg MD & Aspirin 325 mg MD	LTA	MACE	Cardiac death & stent thrombosis**Error! Bookmark not defined.**	6 months	Clopidogrel responder and Aspirin responder	Cardiac death & stent thrombosis	NR	NR	NR	P<0.0001; (dual nonresponders vs. dual responder) P=0.011 (dual nonresponders vs. aspirin nonresponders) P=0.127 (dual nonresponders vs. clopidogrelnonresponders)	NO	NR	Secondary endpoint
Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	Clopidogrel+aspirin	5 mcM ADP aggregation	Any first ischemic event	Death, MI, stent thrombosis, revascularization (target or nontarget vessel), stroke, rehospitalization for ischemia without revascularization	1 mo	>46% platelet aggregation (HPR)	YES event	4 (5%)	NR	NR	NR	NR	NR	NR

					2-24 mo			47 (53%)	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		5 (2%)	NR	NR	NR	NR	NR	NR
					2-24 mo			25 (12%)	NR	NR	NR	NR	NR	NR
									AUC 0.77; Also sensitivity 63%, specificity 82%	NR	0.0001			95% CIs are in Fig 3
	Clopidogrel+aspirin	5 mcM ADP aggregation	Any first ischemic event		0-24 mo	>46% platelet aggregation (HPR)		51 (58%)	HR vs. next row, 3.9	1.9-8.4	0.001 vs. next row (Fisher's exact and also multivariate Cox regression for HR)	NR	NR	NR
						<=46%		30 (14%)	NR	NR	NR	NR	NR	NR
	Clopidogrel+aspirin	20 mcM ADP aggregation	Any first ischemic event	Death, MI, stent thrombosis, revascularization (target or nontarget vessel), stroke, rehospitalization for ischemia without revascularization	1 mo	>59% platelet aggregation (HPR)	YES event	4 (4%)	NR	NR	NR	NR	NR	NR
					2-24 mo			50 (50%)	NR	NR	NR	NR	NR	NR

					1 mo	<=59%		5 (3%)	NR	NR	NR	NR	NR	NR
					2-24 mo			22 (11%)	NR	NR	NR	NR	NR	NR
									AUC 0.78; Also sensitivity 68%, specificity 78%	NR	0.0001			95% CIs are in Fig 4
	Clopidogrel+aspirin	20 mcM ADP aggregation	Any first ischemic event			>59% platelet aggregation (HPR)		54 (54%)	HR vs. next row, 3.8	1.8-7.9	0.001 vs. next row (Fisher's exact and also multivariate Cox regression for HR)	NR	NR	NR
Gurbel, 2004{Gurbel, 2004 220 /id} 15154601 USA None	Clopidogrel+aspirin	Aggrecometry	Stent thrombosis, target vessel revascularization, cerebrovascular ischedmic event, or death	NR	Within 30 days after PCI	Heightened reactivity	Yes event	0	NR	NR	NR	NR	NR	NO
						No heightened reactivity		0						
Hochholzer, 2006{Hochholzer, 2006 208 /id} 17084243 Germany EXCELSIOR	Clopidogrel 75 mg/day	ADP LTA	Any MACE	Any MACE	30-day	1st quartile <4%	Any MACE	209	Mean 1(0.5)	NR	0.03	NR	NR	

						2nd quartile 4-14%		198	1(0.5)					
						3rd quartile 15-32%		196	6 (3.1)					
						4th quartile >32%		199	7(3.5)					
	Clopidogrel 75 mg/day	ADP LTA	Any MACE or major bleeding	Any MACE or major bleeding	30-day	1st quartile <4%	Any MACE or major bleeding	209	Mean 4(1.9)	NR	0.44	NR	NR	
						2nd quartile 4-14%		198	3(1.5)					
						3rd quartile 15-32%		196	7(3.6)					
						4th quartile >32%		199	7(3.5)					
	Clopidogrel 75 mg/day	Platelet aggregation(PA)	MACE	Major adverse cardiac event	30 days	10% increase in ADP-induced PA	MACE	NR	OR=1.32	1.04-1.61	0.026	Yes. Demographic, clinical and angiographic variables, time from clopidogrel loading and baseline platelet aggregation	NR	
									OR=1.31	1.03-1.67	0.026	No		

Htun, 2011{Htun, 2011 20 /id} 21273381 Germany NR	clopidogrel LD 600 mg then 75 mg/d and aspirin 100 mg/d	LTA ADP	combined major event within follow-up	myocardial infarction, ischemic stroke, and death	1 year	low-responder group	combined major event within follow-up	326/1567	HR=2.08	1.42-3.03	<0.001 comparing with responder	no	NR	
	clopidogrel LD 600 mg then 75 mg/d and aspirin 100 mg/d	LTA ADP	combined major event within follow-up	myocardial infarction, ischemic stroke, and death	1 year	low-responder group	combined major event within follow-up	326/1567	HR=1.64	1.06-2.54	0.026 comparing with responder	yes, diabetes mellitus, acute coronary syndromes, impaired left ventricular, gender arterial hypertension, tobacco use, age, cardiovascular comedication, antiplatelet pretreatment, clopidogrel low response, and age.	NR	

L'Allier 2008{L'Allier, 2008 178 /id} 18342223 Canada PREPAIR study	clopidogrel LD 600 mg then 75 mg/d and aspirin 100 mg/d	LTA ADP	combined major event within follow-up	myocardial infarction, ischemic stroke, and death	1 year	low-responder group1	combined major event within follow-up	30/165 (18.2)	NR	NR	0.038 comparing with the lower row	NR	NR	
						responder group 1		46/396 (11.6)						
						low-responder group 2		11/161 (6.8)			0.59 comparing with the lower row			
						responder group 2		35/613 (5.7)						
	Clopigogrel—Group A, B, and C (differing clopidogrel regimens)	Aggregometry	Major bleeding, death, rehospitalization for MI, or repeat target-vessel revascularization	Major bleeding defined as intracranial or clinically relevant bleeding with decrease in hemoglobin of >5 g/dl	within 1 mo after discharge	All nonresponder groups as listed above	Yes event	0 in each group	NR	NR	NR	NO	NO	Each outcome here reporter independently in paper

Liu 2011{Liu, 2011 12 /id} 21613806 China None	Clopidogrel+aspirin	Aggregometry	Any CV event	NR	1 mo after stenting	Nonrespoders	34	6	NR	NR	NR	NR	NR	For all clinical data, n=106 patients because 3 more were lost to followup
						Low responders	28	2						
						Responders	44	0			0.014 across this and previous 2 rows (chi-square test)			
	Clopidogrel+aspirin	Aggregometry	Any CV event		3 mo after stenting	Nonrespoders	34	11						
						Low responders	28	2						
						Responders	44	0			<0.0001 across this and previous 2 rows (chi-square test)			

Muller, 2010{Muller, 2010 51 /id} 20728084 Germany NR	Clopidogrel 600 mg LD + 75 mg MD & Aspirin 100 mg/d MD	LTA	MACE	composite of myocardial infarction and death	Mean follow up of 344 days	Stratum I: RPA & CRP <median	MACE	NR	NR	NR	P<0.001 (Stratum IV vs I) P<0.001 (Stratum IV vs II) P=0.06 (Stratum IV vs III) P=0.01 (Stratum III vs I) P>0.05 (Stratum III vsI I) P>0.05 (Stratum II vs I) [Log Rank]test	YES; age, gender, left ventricular function, acute coronary syndromes, hyperlipidemia and relevant comedication	NR	Primary
						Stratum II:RPA >median & CRP ≤median		NR						
						Stratum III:RPA ≤ median & CRP >median		NR						
						Stratum IV:RPA & CRP >median		NR						

	Clopidogrel 600 mg LD + 75 mg MD & Aspirin 100 mg/d MD	LTA	MACE	composite of myocardial infarction and death	Mean follow up of 344 days	By Quartiles (not defined)	MACE	NR	NR	NR	NR	NO	NR	"Most events occurred in patients with a platelet aggregation in the upper quartile of the collective"

Trenk, 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	Composite of death and MI	MI: new rise in troponin T ≥0.03 mg/l associated with typical symptoms and/or typical electrocardiogram changes and/or typical angiographic finding Death: as reported in phone interview	1 year	high on-treatment platelet reactivity (RPA>14%)	MI or death	13/217 (6%)	HR= 3	1.4-6.8	P=0.004 (between high and not high residual platelet reactivity)	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%)		11/548 (2%)						

Wang, 2010{Wang, 2010 37 /id} 21171668 China None	Clopidogrel+aspirin	LTA	composite of cardiovascular death, MI and revascularization	death of acute MI, coronary artery disease, or heart failure; any typical increase or decrease of cardiac biomarker along with clinical symptoms consis ent with cardia c ischemia, following the American College of Cardiology definition; or bypass surgery and PCI	Within 1 yr after discharge	Clopidogrel resistance	YES event	7 (21.88%)	NR	NR	0.006 vs. next row (Student's t); P=0.008 from multivariate regression (for indpendent prediction)	YES for multivariate regression P value only (diabetes, BMI, and smoking status)	NR	NONE
						nonresistance		6 (4.92%)						
Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Composite thrombotic events	Cardiovascularf death, confatal-MI stent thrombosis or CVA	12-months	Clopidogrel resistancce	Cardiovascularf death, confatal-MI stent thrombosis or CVA	NR	HR=2.44	1.09-5.45	0.031	Yes, diabetes , LV dysfunction (EF<30 %)	NR	

	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	Composite end points	Cardiovascularf death, confatal-MI stent thrombosis or CVA	One year	Clopidogrel resistance	Composite end points	11/65 (16.9)	NR	NR	0.01comparing with the following group	NO	NO	2 Kaplan-Meier curves for 12-month event-freee survival from composite thrombotic events
						Normal response		20/321 (6.2)						
						Total		31/386 (8.0)						

Yong, 2009{Yong, 2009 146 /id} 19081397 Australia Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary intervention in Acute coronary Lesions (PRACTICAL) Trial	300-600 mg LD of clopidogrel	LTA using 4, 10, 20µmol/L	MACE	death, nonfatal MI, nonfatal stroke, hospitalization for recurrent ischemia	6 months	Quartile 1	Post-PCI myonecrosis	NR	NR	NR	NR	NR	NR	Data presented in Fig 2B; no pvalues are reporter for all concentrations of ADP
						Quartile 2	NR							
						Quartile 3	NR							
						Quartile 4	NR							

Gurbel, 2005{Gurbel, 2005 215 /id} 16286165 USA PREPARE POST-STENTING	Clopidogrel (300-600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/dx 7 days LD + 325 md/f MD)	LTA	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	High LTA - Quartile 4 (>67%)	Ischemic events	NR	OR=2.7	0.565-12.964	P=0.2129 (Mulitple logistic regression)	NO	YES; Low TEG-R (reaction time< 3.9 mins), High TEG-MA (Max amplitude >72 mm) and combination of High TEG-MA and low R	Tab 4; it's not clear if all predictor were in the same model
	Clopidogrel (300-600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/dx 7 days LD + 325 md/f MD)	LTA	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	High LTA - Quartile 4 (>67%)	Ischemic events	NR	Sens=0.37 Spec=0.79	NR	NR	NO	No	

	Clopidogrel (300-600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/dx 7 days LD + 325 md/f MD)	LTA	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	Quartile 1 (<50%)	Ischemic events	10%	NR	NR	P=0.02 (Q1 vs Q4) P=0.35 (Q2 vs Q4) P=0.37 (Q3 vs Q4) Logistic regression with appropriate contrasts	NO	NR	Fig 4
						Quartile 2 (50-61%)		24%						
						Quartile 3 (62-67%)		22%						
						Quartile 4 (>67%)		32%						

Appendix Table E15: Results from studies assessing the ability of LTA to predict stroke in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 5µmol/L	stroke	Stroke	1-year	High OTPR N=445	Stroke	6 (1.3)	OR=1.17	0.39-3.49	<0.78 (high vs normal) [logistic regression]	No	NR	
						Normal OTPR N=604		7 (1.2)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	ADP LTA 20 µmol/L	stroke	Stroke	1-year	High OTPR N=392	Stroke	5 (1.3)	OR=1.05	0.34-3.24	<0.93 (high vs normal) [logistic regression]	No	NR	
						Normal OTPR N=659		8 (1.2)						
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	5umol/L ADP LTA	ischemic stroke	ischemic stroke	6 months	<50%	ischemic stroke	0.2%	OR=1.58	0.10-25.36	1.000 (<50 vs ≥ 50%) [logistic regression]	NR	NR	
						≥50%		1.2%						

Bliden, 2007{Bliden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Stroke	Stroke	Day 0-30	HPR n=22	Stroke	0	OR (calculated)=16.1	NR	P=0.535 (HPR vs NPR at 1 year) [chi square]	NR	NR	
					Day 0-30	NPR N=78	Stroke	0	NR	NR	NR	NR	NR	
					Day 31-365	HPR n=22	Stroke	0						
					Day 31-365	NPR N=78	Stroke	0						
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA5	Stroke	Stroke	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR N=385	Stroke	5	NR	NR	NR	NR	NR	
	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	LTA20	Stroke	Stroke	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR N=335	Stroke	3	NR	NR	0.045 comparing with NPR(normal on-treatment platelet reactivity)	NR	NR	
Geisler, 2006{Geisler, 2006 210 /id} 17005534 Germany NR	Clopidogrel LD dose of 600 mg followed 75 mg daily	ADP LTA	Stroke	Stroke	3-month	Adequate response N=341	Stroke	5 (1.5)	NR	NR	0.43 (adequate vs low response) [Chi square]	NR	NR	
						Low response N=22		0						

Geisler, 2010{Geisler, 2010 101 /id} 19812059 Germany NR	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 500 mg LD + 100 mg MD	LTA	ischemic stroke	NR	3 months	Low responder (Terrtile 3)	ischemic stroke	6 (0.9%)	OR=0.7	0.14-3.48	p=0.66 (low responder vs responder) [chi square]	NO	NR	Secondary outcome
						Responders (Tertile 1&2)		2 (0.6%)						
Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	Clopidogrel+aspirin	5 mcM ADP aggregation	Stroke		1 mo	>46% platelet aggregation (HPR)		0	OR (calculated)=12.1	NR	P=0.09 (HPR vs NPR at 2 year) [Fishers exact]	NR	NR	NR
					2-24 mo			2	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		0	NR	NR	NR	NR	NR	NR
					2-24 mo			0	NR	NR	NR	NR	NR	NR
	Clopidogrel+aspirin	20 mcM ADP aggregation	Stroke		1 mo	>46% platelet aggregation (HPR)		0	OR (calculated)=9.9	NR	P=0.12 (HPR vs NPR at 2 year) [Fishers exact]	NR	NR	NR
					2-24 mo			2	NR	NR	NR	NR	NR	NR
					1 mo	<=46%		0	NR	NR	NR	NR	NR	NR
					2-24 mo			0	NR	NR	NR	NR	NR	NR

Htun, 2011{Htun, 2011 20 /id} 21273381 Germany NR	clopidogrel LD 600 mg then 75 mg/d and aspirin 100 mg/d	LTA ADP	ischemic stroke	ischemic stroke	1 year	low-responder group1 (K/DOQI index III-V) N=165	ischemic stroke	2(1.2)	NR	NR	0.08 (low responder vs responder)	NR	NR	
						responder group 1 (K/DOQI index III-V) N=396		16 (4.1)						
						low-responder group 2 (K/DOQI index I-II) N=161		1 (0.6)			0.67 (low responder vs responder)			
						responder group 2 (K/DOQI index I-II) N=613		6 (1.0)						
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Clopidogrel+aspirin	Aggregometry	Ischemic stroke	New focal neurologic deficit without bleeding on tomodensitoemtry confirmed by a neurologist to have occurred within the time frame (1 or 3 mo after PCI)	1 month	Nonrespoders	34	3	OR (calculated)=16.1	NR	P=0.03 (nonresponder vs resp + low resp at 1month) [Fishers exact]	NR		
						Low responders	28	0						
						Responders	44	0			0.38 across this and previous 2 rows (chi-square test)			

Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	CVA	Cerebrovascular ischemia accident (CVA)	One year	Clopidogrel resistance	CVA	2/65 (3.1)	NR	NR	0.199 comparing with the following group	NO	NO	
						Normal response		3/321 (0.9)						
Gurbel, 2003{Gurbel, 2003 222 /id} 12796140 USA NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	cerebrovascular ischemic events	cerebrovascular ischemic events	30 days	Clopidogrel resistance	cerebrovascular ischemic events	0/50	OR (calculated)=1.25	NR	P=0.91 (nonresponder vs resp + low resp at 1month) [Fishers exact]	NR	NO	
						Clopidogrel nonresistance		0/63						

Appendix Table E16: Results from studies assessing the ability of LTA to predict bleeding events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	5umol ADP-induced PRmax ≥50%	TIMI bleeding	TIMI bleeding(major, minor)	6 months	HPPR - 5umol ADP-induced PRmax≥50% N=NR	TIMI bleeding	6.8% (major 4.6%, minor 2.2%)	NR	NR	0.381 (HPPR vs no HPPR)	NR	NR	
						no HPPR N=NR		4.5% (major 1.9%, minor 2.6%)						
Bliden 2007{Bliden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Major bleeding	Major bleeding	Day 0-30	HPR n=22	Major bleeding	1	OR (calculated)= 10.95	NR	P= 0.15 (HPR vs NPR) [Fisher's exact]	NR	NR	
						NPR N=78		0	NR	NR	NR	NR	NR	
				Major bleeding	Day 31-365	HPR n=22		0	OR (calculated)=3.5	NR	P=0.54 (HPR vs NPR) [Fisher's exact]			
						NPR N=78		0						

	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Minor bleeding	Minor bleeding	Day 0-30	HPR n=22	Minor bleeding	1	OR (calculated)= 3.67	NR	P= 0.37 (HPR vs NPR) [Fisher's exact]	NR	NR	
						NPR N=78		1	NR	NR	NR	NR	NR	
					Day 31-365	HPR n=22		0	OR (calculated)=3.5	NR	P=0.54 (HPR vs NPR) [Fisher's exact]			
						NPR N=78		0						
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	bleeding events	bleeding events	Day 0-30	HPR n=22	bleeding events	2	OR (calculated): 7.7	NR	P=0.120 (HPR vs NPR at 1 year) [Fishers exact]]	NR	NR	
						NPR N=78		1						
					Day 31-365	HPR n=22	Bleeding events	0	OR (calculated): 3.5	NR	P=0.54 (HPR vs NPR at 1 year) [Fishers exact]]			
						NPR N=78		0						
Cuisset 2009{Cuisset, 2009 246 /id} 19736156 France NR	Clopidogrel 600 mg LD + Aspirin 250 mg LD	LTA	Bleeding composite	non·CABG related TIM I major and minor bleeding	30 days	Hyper-responder (quartile 1: ADP-induced aggregation <40%) N=151	Major and minor bleeding +	10 (6.6%)	NR	NR	P=0.001 (hyper-responder versus non hyper-responder) Chi square	NO	NR	Primary

						Non hyperresponder (quartile 2-4: ADP-induced aggregation ≥40%) N=429		6 (1.4%)						
Cuisset 2006{Cuisset, 2006 237 /id} 17010792 France NR	Clopidogrel 300 mg LD	LTA	Bleeding	major bleeding defined as intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin of 5 g/dL	1 month	high post treatment platelet reactivity	bleeding	0	NR	NR	NR	NR	NR	
						normal post treatment platelet reactivity		0						
	Clopidogrel 600 mg LD	LTA	Bleeding		1 month	high post treatment platelet reactivity	bleeding	0	NR	NR	NR	NR	NR	
						normal post treatment platelet reactivity		0						

Hochholzer, 2006{Hochholzer, 2006 208 /id} 17084243 Germany EXCELSIOR	Clopidogrel 75 mg/day	ADP LTA	TIMI major bleeding	TIMI major bleeding	30-day	1st quartile <4% N=209	TIMI major bleeding	3/209 (1.4%)	OR (calculated): 0.615	NR	P= 0.73 (3rd & 4th quartile vs 1st and second quartiles) [Fishers exact]	NR	NR	
						2nd quartile 4-14% N=198		2/198 (1%)	2(1)					
						3rd quartile 15-32% N=196		2/196(1%)	2(1)					
						4th quartile >32% N=199		1/199(0.5 %)	1(0.5)					
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Clopidogrel+aspirin	Aggregometry	Any bleeding event	BleedScore classifications	1 month	Nonresponders N=34	Any bleeding event	0						
						Low responders N=28		0						
						Responders N=44		6			0.011 (responder, nonresponders and low responders) (chi-square test)			
	Clopidogrel+aspirin	Aggregometry	Alarming bleeding event	Requiring transfusion, intracranial bleeding or any life-threatening event	1 month	Nonresponders N=34	Alarming bleeding event	0						

						Low responders N=28		0						
						Responders N=44		0						
	Clopidogrel+aspirin	Aggregometry	Internal bleeding event	Hematoma, epistaxis, blood loss from mouth or vagina, melena, eye bleed, hematuria, or hematemesis	1 month	Nonrespoders N=34	Internal bleeding event	0						
						Low responders N=28		0						
						Responders N=44		1			0.491 (responder, nonresponders and low responders) (chi-square test)			
	Clopidogrel+aspirin	Aggregometry	Superficial bleeding event	Easy bruising, bleeding from small cuts, petechia, or ecchymosis	1 month	Nonrespoders N=34	Superficial bleeding event	0						
						Low responders N=28		0						
						Responders N=44		5			0.025 (responder, nonresponders and low responders) (chi-square test)			

	Clopidogrel+aspirin	Aggregometry	Any bleeding event	BleedScore classifications	3 month	Nonrespoders N=34	Any bleeding event	1						
						Low responders N=28		1						
						Responders N=44		14			0.1 (responder, nonresponders and low responders) (chi-square test)			
	Clopidogrel+aspirin	Aggregometry	Alarming bleeding event	Requiring transfusion, intracranial bleeding or any life-threatening event	3 month	Nonrespoders N=34	Alarming bleeding event	0						
						Low responders N=28		0						
						Responders N=44		0						
	Clopidogrel+aspirin	Aggregometry	Internal bleeding event	Hematoma, epistaxis, blood loss from mouth or vagina, melena, eye bleed, hematuria, or hematemesis	3 month	Nonrespoders N=34	Internal bleeding event	0						
						Low responders N=28		1						

						Responders N=44		3			0.292 (responder, nonrespond ers and low responders) (chi-square test)			
	Clopidogrel+aspirin	Aggregometry	Superficial bleeding event	Easy bruising, bleeding from small cuts, petechia, or ecchymosis	3 month	Nonrespoders N=34	Superficial bleeding event	01						
						Low responders N=28		0						
						Responders N=44		11			0.001 (responder, nonrespond ers and low responders) (chi-square test)			

Appendix Table E17: Results from studies assessing the ability of LTA to predict other clinical events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Bliden, 2007{Bliden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Target vessel revascularization	Target vessel revascularization	Day 0-30	HPR n=22	Target vessel revascularization	0/22	OR(calculated)=14.25	NR	P=0.001 (HPR vs NPR) [Fisher's exact test]	NR	NR	
					Day 0-30	NPR N=78	Target vessel revascularization	0/78	NR	NR	NR	NR	NR	
					Day 31-365	HPR n=22	Target vessel revascularization	6/22						
					Day 31-365	NPR N=78	Target vessel revascularization	2/78						
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Nontarget vessel revascularization	Nontarget vessel revascularization	Day 0-30	HPR n=22	Nontarget vessel revascularization	0/22	OR(calculated)=7.7	NR	P=0.12 (HPR vs NPR) [Fisher's exact test]	NR	NR	
					Day 0-30	NPR N=78	Nontarget vessel revascularization	0/78	NR	NR	NR	NR	NR	
					Day 31-365	HPR n=22	Nontarget vessel revascularization	2/22						
					Day 31-365	NPR N=78	Nontarget vessel revascularization	1/78						

	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Rehospitalization for ischemia	Rehospitalization for ischemia	Day 0-30	HPR n=22	Rehospitalization for ischemia	2/100	OR(calculated)=5.5	NR	P=0.04 (HPR vs NPR) [Fisher's exact test]	NR	NR	
					Day 0-30	NPR N=78	Rehospitalization for ischemia	0/100	NR	NR	NR	NR	NR	
					Day 31-365	HPR n=22	Rehospitalization for ischemia	2/100						
					Day 31-365	NPR N=78	Rehospitalization for ischemia	3/100						
Campo, 2007{Campo, 2007 197 /id} 17868803 Italy NR	Clopidogrel 300-mg loading dose, followed by 75 mg/day	LTA ADP	TVR	TVR	6 months	Responder to both	TVR	23	1/90(1.1)	OR(calculated)=1.95	NR	P=0.605 (clopidogrel + dual nonrespondER vs responder) [Fisher's exact test]	NR	
						Clopidogrel nonresponders Ticlopidine responders			2/25(8)					
						Clopidogrel responders Ticlopidine nonresponders			3/23(13)					
						Nonresponder to both			0/5					
Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	Clopidogrel+aspirin	5 mcM ADP aggregation	revascularization (target vessel)		1 mo	>46% platelet aggregation (HPR)		1	NR	OR(calculated)=7.39	NR	P<0.0001 (HPR vs NPR) [Fisher's exact test]	NR	NR
						<=46%		0	NR	NR	NR	NR	NR	NR

					2-24 mo	>46% platelet aggregation (HPR)		19	NR	NR	NR	NR	NR	NR
						<=46%		8	NR	NR	NR	NR	NR	NR
	Clopidogrel+aspirin	5 mcM ADP aggregation	revascularization (nontarget vessel)		1 mo	>46% platelet aggregation (HPR)		0	NR	OR(calculated)=4.34	NR	P=0.008 (HPR vs NPR) [Fisher's exact test]	NR	NR
						<=46%		1	NR	NR	NR	NR	NR	NR
					2-24 mo	>46% platelet aggregation (HPR)		10	NR	NR	NR	NR	NR	NR
						<=46%		5	NR	NR	NR	NR	NR	NR
	Clopidogrel+aspirin	5 mcM ADP aggregation	Rehospitalization for ischemia, no revascularization		1 mo	>46% platelet aggregation (HPR)		1	NR	OR(calculated)=3.14	NR	P=0.01 (HPR vs NPR) [Fisher's exact test]	NR	NR
						<=46%		1	NR	NR	NR	NR	NR	NR
					2-24 mo	>46% platelet aggregation (HPR)		11	NR	NR	NR	NR	NR	NR
						<=46%		9	NR	NR	NR	NR	NR	NR
	Clopidogrel+aspirin	20 mcM ADP aggregation	revascularization (target vessel)		1 mo	>46% platelet aggregation (HPR)		1	NR	OR(calculated)=3.17	NR	P=0.005 (HPR vs NPR) [Fisher's exact test]	NR	NR
						<=46%		0	NR	NR	NR	NR	NR	NR

					2-24 mo	>46% platelet aggregation (HPR)		16	NR	NR	NR	NR	NR	NR
						<=46%		11	NR	NR	NR	NR	NR	NR
	Clopidogrel+aspirin	20 mcM ADP aggregation	revascularization (nontarget vessel)		1 mo	>46% platelet aggregation (HPR)		0	NR	OR(calculated)=4.66	NR	P=0.004 (HPR vs NPR) [Fisher's exact test]	NR	NR
						<=46%		1	NR	NR	NR	NR	NR	NR
					2-24 mo	>46% platelet aggregation (HPR)		11	NR	NR	NR	NR	NR	NR
						<=46%		4	NR	NR	NR	NR	NR	NR
	Clopidogrel+aspirin	20 mcM ADP aggregation	Rehospitalization for ischemia, no revascularization		1 mo	>46% platelet aggregation (HPR)		1	NR	OR(calculated)=4.71	NR	P=0.0007 (HPR vs NPR) [Fisher's exact test]	NR	NR
						<=46%		1	NR	NR	NR	NR	NR	NR
					2-24 mo	>46% platelet aggregation (HPR)		14	NR	NR	NR	NR	NR	NR
						<=46%		6	NR	NR	NR	NR	NR	NR

Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Clopidogrel+aspirin	Aggregometry	Acute coronary syndrome	presence of symptoms compatible with recurrent ischemia requiring hospitalization and angiocoronarography	1 month	Nonrespoders	34	1		OR(calculated) =15.2	NR	P=0.004 (HPR vs NPR) [Fisher's exact test]		
						Low responders	28	1						
						Responders	44	0			0.447 across this and previous 2 rows (chi-square test)			
	Clopidogrel+aspirin	Aggregometry	Acute coronary syndrome	presence of symptoms compatible with recurrent ischemia requiring hospitalization and angiocoronarography	3 month	Nonrespoders	34	6						
						Low responders	28	1						
						Responders	44	0			0.006 across this and previous 2 rows (chi-square test)			

Trenk, 2008{Trenk, 2008171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	600 mg clopidogrel LD + 75 mg/day MD (for 30 d w/ bare-metal stents or 6 mth w/ atleast 1 drug-eluting stent	LTA	target lesion intervention	target lesion intervention	1 year	high on-treatment platelet reactivity (RPA>14%)	target lesion intervention	26/217 (12%)	HR=1.1	0.7-1.8	P=0.67 (between high and not high residual platelet reactivity)	YES; Age, HTN, DM, BMI, platelet count, verapamil, insulin and antidiabetic medication use, previous angioplasty and CABG, LV function, angina class, PCI, stent implantation, LAD affected, stenosis length ad diameter of stenosis	NR	Primary outcome
						no high on-treatment platelet reactivity (RPA≤ 14%)		60/548 (10.9%)						
Wang, 2010{Wang, 2010 37 /id} 21171668 China None	Clopidogrel+aspirin	LTA	Revascularization		1 year	Clopidogrel resistance		2 (6.25%)			0.191 vs. next row (Student's t)	NR		
						nonresistance		2 (1.64%)						
Gurbel, 2003{Gurbel, 2003 222 /id} 12796140 USA NR	LD 300 mg clopidogrel and maintaining 75 mg daily	ADP-LTA	target-vessel revascularization	target-vessel revascularization	30 days	Clopidogrel resistance	target-vessel revascularization	0	NR	OR(calculated) =1.25	NR	P=0.91 (resistant vs nonresistant) [Chisquare test]	NO	

						Clopidogrel nonresistance		0						

Appendix Table E18: Results from studies assessing the ability of LTA to predict platelet reactivity during followup (when used as a continuous measurement) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Matetzky, 2004{Matetzky, 2004188 /id} 15184279 Israel No	Clopidogrel	Aggregometer (not cone and platelet device)	% Change from baseline in ADP-induced platelet aggregation	NR	6 days vs. baseline	Q1	15	-9%	NR	NR	NR	NR	<0.05 (P for trend") [2-tailed Fisher's exact test]	NR	NR	NO
						Q2	15	-22%								
						Q3	15	-28%								
						Q4	15	-45%								
Angiolollo, 2007{Angiolillo, 2007194 /id} 17936152 Spain NR	clopidogrel (75 mg/day)	LTA-ADP	Platelet aggregation (late)	Platelet aggregation (late)	1 year	HPR +	First quartile	Mean 24.7	11.3	ANOVA	NR	NR	<0.0001	NR	NR	
						HPR +	Second quartile	Mean 36.8	11.4							
						HPR +	Third quartile	Mean 48.2	7							
						HPR +	Fourth quartile	Mean 65.1	8.4							

	clopidogrel (75 mg/day)	LTA-ADP	Platelet disaggregation	Platelet disaggregation	1 year	HPR +	First quartile	Mean 30.5	26.2	ANOVA	NR	NR	<0.0001	NR	NR	
						HPR +	Second quartile	Mean 22.9	23.3							
						HPR +	Third quartile	Mean 15.4	10.3							
						HPR +	Fourth quartile	Mean 5.4	7							
Bellemain-Appaix 2010{Bellemain-Appaix, 2010 87 /id} 20170822 France ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis)	Clopidogrel LD= 300 mg or 600 mg or 900 mg)	LTA	VASP Index	VASP index was calculated from the median fluorescence intensity (MFI)	6 hrs	Slow responders	50	76.4	15.8 (SD)	Linear regression	NR	NR	0.0192 (slow vs fast)	YES; NR	NR	
							38	66.4	20.3 (SD)							

	Clopidogrel LD= 300 mg or 600 mg or 900 mg)	LTA	VASP index	VASP index was calculated from the median fluorescence intensity (MFI)	24 hrs	Slow responders	50	70.2	22.2 (SD)	Linear regression	NR	NR	0.0192 (slow vs fast)	YES; NR	NR	
							38	61.5	19.1 (SD)							
Cuisset, 2006{Cuisset, 2006 212 /id} 16371119 France NR	Clopidogrel +aspirin	PAP4 aggregometer	P-selectin expression after ADP stimulation	Measured in mean channel fluorescence intensity (MFI)	NR	Q1 (highest responder)	NR	0.44 mean MFI	0.38	NR	NR	NR	0.04 for Q1 vs. Q4 (general linear model with ADP-induced aggregation as dependent variable)	NR	NR	NO
						Q4 (nonresponder)	23	0.57 mean MFI	0.29							
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Clopidogrel +aspirin	Aggregometry	Mean maximal aggregation rate, 5 mcmol ADP	NR	36 hr after stenting	Nonresponders	35 (32%)	48.65 %	15.46%	NR	NR	NR	NR	NR	NR	NONE
						Low responders	28 (25%)	45.20 %	14.70%							
						Responders	46 (41%)	30.31 %	16.04%				<0.0001 vs. two rows above and <0.05 vs. previous row (ANOVA)			

	Clopidogrel +aspirin	Aggregometry	Mean maximal aggregation rate, 20 mcmol ADP		36 hr after stenting	Nonresponders	35 (32%)	63.54 %	14.81%							
						Low responders	28 (25%)	62.53 %	17.64%							
						Responders	46 (41%)	45.74 %	19.94%				<0.0001 vs. two rows above and <0.05 vs. previous row (ANOVA)			
Obradovic, 2009{Obradovic, 2009 123 /id} 19318922 Serbia NR	Clopidogrel LD 300 mg	ADP-PA	ADP-PA	ADP-PA	Before PCI	PA>20 %	26	47.35(34.95-68.8)	NR	NR	NR	NR	<0.001 comparing with the lower row	NR	NR	NR
					Before PCI	PA<20 %	26	8.5 (2.3-14.15)	NR	NR	NR	NR		NR	NR	NR
	Clopidogrel LD 300 mg	ADP-PA	ADP-PA	ADP-PA	24 h afterPCI	PA>20 %	26	23.4 (12.97 - 48.35)	NR	NR	NR	NR	<0.001 comparing with the lower row	NR	NR	NR
					24 h afterPCI	PA<20 %	26	7.5 (0.8-16.75)	NR	NR	NR	NR		NR	NR	NR

Appendix Table E19: Results from studies assessing the ability of LTA to predict platelet reactivity during followup (when used as a discrete outcome) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Hoshino, 2009{Hoshino, 2009 143 /id} 19106460 Japan NR	300 mg clopidogrel LD + 74 mg MD	12-channel light transmission aggregometer	Responder	based on the the inhibition of platelet aggregation (IPA)	28 days	IPA <10% (clopidogrel non-responders)	In Fig 2	In Fig 2	In Fig 2	In Fig 2	In Fig 2	NR	NR	NR	Data is presented in Fig 2 which can be digitized to obtain the change in status within the three phenotype groups
						10%≤ IPA <30% (hypo-responders)	In Fig 2	In Fig 2	In Fig 2	In Fig 2	In Fig 2	NR	NR	NR	
						IPA ≥30% (responders)	In Fig 2	In Fig 2	In Fig 2	In Fig 2	In Fig 2	NR	NR	NR	
Gurbel, 2010{Gurbel, 2010 84 /id} 20194878 10 study sites in North America and Europe RESPOND	600-mg clopidogrel LD + 75-mg daily MD	LTA	On treatment high platelet reactivity (HPR) by LTA associated with long-term ischemic event occurrence	Platelet aggregation (20 mol/L ADP, maximum extent) ≤59%	30 days	Nonresponder (absolute change in maximum platelet aggregation (MPA) ≤10% between pre-dose and 6-8 hr post-dose measurements)	On treatment high platelet reactivity (HPR) +	20/33 (61%, 95% CI: 44–77)	≤10	NR	NR	0.15 (fisher's exact calculated from data)	NO	NR	NR

						Responder (absolute change in maximum platelet aggregation (MPA) >10% between pre-dose and 6-8 hr post-dose measurements)	On treatment high platelet reactivity (HPR) +	41/54 (76%, 95% CI: 65–87)	≤10						
	600-mg clopidogrel LD + 75-mg daily MD	LTA	On treatment high platelet reactivity (HPR) by VerifyNow P2Y12 associated with long-term ischemic event occurrence	VerifyNow P2Y12-PRU ≤235	30 days	Nonresponder (absolute change in maximum platelet aggregation (MPA) ≤10% between pre-dose and 6-8 hr post-dose measurements)	On treatment high platelet reactivity (HPR) +	17/32 (53%, 95% CI: 36–70)	≤10	NR	NR	0.258 (fisher's exact calculated from data)	NO	NR	NR
						Responder (absolute change in maximum platelet aggregation (MPA) >10% between pre-dose and 6-8 hr post-dose measurements)	On treatment high platelet reactivity (HPR) +	35/53 (66%, 95% CI: 53–79)	≤10						

	600-mg clopidogrel LD + 75-mg daily MD	LTA	On treatment high platelet reactivity (HPR) by VASP associated with long-term ischemic event occurrence	VASP-PRI ≤50%	30 days	Nonresponder (absolute change in maximum platelet aggregation (MPA) ≤10% between pre-dose and 6-8 hr post-dose measurements)	On treatment high platelet reactivity (HPR) +	10/34 (29%, 95% CI: 14-45)	≤10	NR	NR	0.00458 (fisher's exact calculated from data)	NO	NR	NR
						Responder (absolute change in maximum platelet aggregation (MPA) >10% between pre-dose and 6-8 hr post-dose measurements)	On treatment high platelet reactivity (HPR) +	28/53 (53%, 95% CI: 39–66)	≤10						
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA No	Clopidogrel+aspirin	Platelet aggregation ADP 5 mcmol/liter	Continued nonresponse since baseline	NR	5 days	Nonresponders at baseline (n=23)	Nonresponders at 5 days	15/23 (66%)	<10% change from baseline	NR	NR	<0.0001 (fisher's exact calculated from data)	NR	NR	NONE
						Responders at baseline (n=40)	Responders at 5 days	38/40 (95%)							
					30 days	Nonresponders at baseline (n=23)	Nonresponders at 30 days	7/13 (54%) with data (10 were not measured at 30 days)				0.013 (fisher's exact calculated from data)			
						Responders at baseline (n=40)	Responders at 30 days	18/20 (90%) with data (20 were not measured at 30 days)							

		Platelet aggregation ADP 20 mcmol/liter	Continued nonresponse since baseline		5 days	Nonresponders at baseline (n=13)	Nonresponders at 5 days	9/13 (69%)				0.003 (fisher's exact calculated from data)			
						Responders at baseline (n=25)	Responders at 5 days	22/25 (88%)							
					30 days	Nonresponders at baseline (n=13)	Nonresponders at 30 days	3/8 (38%) with data (5 were not measured at 30 days)				0.25 (fisher's exact calculated from data)			
						Responders at baseline (n=25)	Responders at 30 days	12/13 (92%) with data (12 were not measured at 30 days)							

Appendix Table E20: Results from studies assessing the ability of LTA to predict platelet reactivity during followup (when used as a discrete outcome) in patients with peripheral artery disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Linneman n, 2010{Linnemann, 2010 82 /id} 20153859 GermanyNR	Clopidogrel 75 mg MD	LTA	Non-responsiveness	Late aggregation ≥42.9%	median 17.5 months	Non-responsiveness	Non-responsiveness	5	≥ 42.5%	NR	NR	0.02 (fisher's exact calculated from data)	NO	NR	
						Non-responsiveness	Responsiveness	8							
						Responsiveness	Non-responsiveness	1							
						Responsiveness	Responsiveness	20							

Appendix Table E21: Quality Assessment of studies assessing the predictive ability of LTA in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Geisler, 2010{Geisler, 2010 54 /id} 20526607 Germany NR	yes	yes	yes	low	low	NR	yes	unclear	low	yes	NR	unclear	low	no	yes	yes	no	high
Cuisset, 2009{Cuisset, 2009 111 /id} 19801028 France NR	yes	No	yes	low	low	NR	No	unclear	high	yes	NR	Low	low	no [30 days]	yes	yes	yes	low
Frere, 2007{Frere, 2007 193 /id} 17938809 France NR	yes	No	yes	low	low	NR	No	High	Low	yes	NR	Unclear	low	no [30 days]	yes	yes	yes	low
Hoshino, 2009{Hoshino, 2009 143 /id} 19106460 Japan	No	Yes	yes	low	low	NR	Yes	unclear	high	No	NR	high	high	NO [28 days]	yes	yes	yes	low

NR																		
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	yes	yes	yes	low	low	NR	no	high	low	yes	yes	low	low	yes	yes	yes	yes	low
Gurbel, 2010{Gurbel, 2010 84 /id} 20194878 10 study sites in North America and Europe RESPOND	yes	yes	yes	low	low	Yes	Yes	Low	High	No	Yes	high	high	NO [30 days]	yes	yes	No	High
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	yes	yes	yes	low	low	NR	yes	unclear	high	Yes	NR	unclear	Low	no [6 months]	yes	yes	yes	low
Angiolillo, 2007{Angiolillo, 2008 180 /id} 18312754 USA OPTIMUS	NO	yes	yes	low	low	NR	NR	unclear	unclear	No	NR	unclear	high	no [1 month]	yes	yes	yes	low

Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	NO	NO	yes	HIGH	LOW	NR	No	unclear	high	yes	NR	Unclear	low	no [6 months]	yes	yes	yes	low
Bliden, 2007{Bliden, 2007 202 /id} 17291930 USA NR	**yes**	**yes**	**yes**	**low**	**low**	**NR**	**yes**	**unclear**	**high**	**yes**	**NR**	**unclean**	**low**	**yes**	**yes**	**yes**	**yes**	**low**
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	**yes**	**yes**	**yes**	**low**	**low**	**NR**	**yes**	**unclear**	**low**	**yes**	**NR**	**unclear**	**low**	**no**	**yes**	**yes**	**yes**	**low**
Gurbel, 2010{Gurbel, 2010 68 /id} 20691842 USA PREPARE POST-STENTING	**yes**	**yes**	**yes**	**low**	**low**	**NR**	**NO**	**high**	**high**	**yes**	**yes**	**low**	**low**	**yes**	**yes**	**yes**	**yes**	**low**
Matetzky, 2004{Matetzky, 2004 188 /id} 15184279	yes	yes	yes	low	low	NR	no	high	low	no	yes	low	low	no	yes	yes	yes	low

Israel No																		
Angiolollo, 2007{Angiolillo, 2007 194 /id} 17936152 Spain NR	NO	yes	yes	low	low	NR	NR	unclear	low	Yes	NR	Unclear	low	Yes [2 years]	yes	yes	yes	low
Aradi, 2008{Aradi, 2008 236 /id} 18388039 Hungary NR	NO	yes	yes	low	low	NR	No	High	High	Yes	NR	Unclear	low	No [~9 months]	yes	yes	yes	low
Bellemain-Appaix 2010{Bellemain-Appaix, 2010 87 /id} 20170822 France ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and	Yes [RCT substudy]	yes	yes	low	low	NR	No	High	High	No	NR	High	High	No [24 hrs	yes	yes	yes	low

Ongoing Necrosis)																		
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Yes	yes	yes	low	low	NR	Yes	Unclear	Unclear	Yes	Yes	Low	low	Yes [1 year]	yes	yes	yes	low
Breet, 2010{Breet, 2010 50 /id} 20695984 Netherlands Substudy of a larger cohort (Breet 2010 PMID: 20179285)	Yes	yes	yes	low	low	NR	No	Unclear	Low	Yes	Yes	Low	low	Yes [1 year]	yes	yes	yes	low
Buonamici, 2007{Buonamici, 2007 200 /id} 17572245 Italy NR	Yes	yes	yes	low	low	NR	No	Unclear	High	Yes	Yes	Low	low	No [6 months]	yes	yes	yes	low
Campo, 2007{Campo, 2007 197 /id} 178688	No	yes	yes	low	low	NR	No	Unclear	Unclear	Yes	NR	Unclear	low	No [6 months]	yes	yes	yes	low

03 Italy NR																		
Cuisset, 2009 19736156 France NR	Yes	yes	yes	low	low	Yes	No	High	High	Yes	NR	Unclear	low	No [30 days]	yes	yes	yes	low
Cuisset, 2006{Cuisset, 2006 212 /id} 16371119 France NR	Yes	yes	yes	low	low	NR	No	High	Low	Yes	Yes	Low	low	No [1 month]	yes	yes	yes	low
Cuisset, 2006{Cuisset, 2006 237 /id} 17010792 France NR	Yes	yes	yes	low	low	NR	No	High	Low	Yes	Yes	Low	low	No [1 month]	yes	yes	yes	low
Cuisset, 2007{Cuisset, 2007 204 /id} 17264958 France NR	Yes	yes	No	low	low	NR	Yes	Unclear	High	Yes	NR	Unclear	low	No [12 hrs]	yes	yes	No [20 patients who did not receive successful angioplasty were excluded from the study]	low
Geisler, 2008{Geisler, 2008 184 /id} 17949474 Germany	Yes	yes	yes	low	low	NR	No	High	High	Yes	Yes	Low	low	NO (30 days)	yes	yes	NO (~13% of patients were lost to followup)	High

NR																		
Geisler, 2006{Geisler, 2006 210 /id} 17005534 Germany NR	Yes	yes	yes	low	low	NR	Yes	Unclear	High	Yes	Yes	Low	low	No [3 months]	yes	yes	yes	low
Geisler, 2010{Geisler, 2010 101 /id} 19812059 Germany NR	Yes	yes	yes	low	low	Yes	No	High	High	Yes	Yes	Low	low	No [3 months]	yes	yes	yes	low
Giusti, 2009{Giusti, 2009 134 /id} 19268736 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Yes	yes	yes	low	low	NR	No	High	High	Yes	YES (states that event adjudication was blind to laboratory results)	Low	low	No [6 months]	yes	yes	yes	low

Gori, 2008 {Gori, 2008 164 /id} 18718420 Italy RECLOSE study (Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis)	Yes	yes	yes	low	low	Yes	Yes	Low	High	Yes	Yes	Low	low	No [6 months]	yes	yes	yes	low
Gurbel, 2008{Gurbel, 2008 157 /id} 19012177 USA None	Yes	yes	yes	low	low	NR	Yes	Unclear	Low	Yes	Yes	Low	low	Yes [2 years]	yes	yes	yes	low
Gurbel, 2004{Gurbel, 2004 220 /id} 15154601 USA None	NR	yes	yes	low	low	NR	No	High	Low	Yes	NR	Unclear	low	NO (30 days)	yes	yes	yes	High
Hochholzer, 2006{Hochholzer, 2006 208 /id} 170842	No	yes	yes	low	low	NR	NR	Unclear	High	Yes	NR	Unclear	low	NO (30 days)	yes	yes	yes	Low

43 Germany EXCELSIOR																		
Htun, 2011{Htun, 2011 20 /id} 21273381 Germany NR	Yes	yes	No [232 of 1567 patients excluded in final analysis]	low	low	NR	Yes	Unclear	High	Yes	NR	Unclear	low	Yes [1 year]	yes	yes	No [15% excluded in final analysis]	low
L'Allier, 2008{L'Allier, 2008 178 /id} 18342223 Canada PREPAIR study	Yes	yes	yes	low	low	Yes	Yes	Low	High	Yes	NR	Unclear	low	NO (1 month)	yes	yes	yes	Low
Liu, 2011{Liu, 2011 12 /id} 21613806 China None	Yes	yes	yes	low	low	NR	Yes	Unclear	Unclear	Yes	NR	Unclear	low	NO (3 months)	yes	yes	YES (~2% [2 patients] withdrew before 12 hr and three more [!3%] were lost to followup later)	Low
Muller, 2003{Muller, 2003 223 /id} 12719773 Germany	NR	yes	yes	low	low	NR	NR	Unclear	Low	Yes	NR	Unclear	low	NO [latest date mentioned is a 9-mo measurement, only in	yes	yes	yes	Low

None														1 pt]				
Muller, 2010{Muller, 2010 51 /id} 20728084 Germany NR	Yes	yes	yes	low	low	Yes	No	Unclear	High	Yes	Yes	Low	low	No [mean 344 days]	yes	yes	yes	Low
Obradovic, 2009{Obradovic, 2009 123 /id} 19318922 Serbia NR	No	yes	yes	low	low	NR	No	High	High	No	NR	High	High	No [24 hours]	yes	yes	yes	Low
Saw, 2008{Saw, 2008 243 /id} 19038679 Canada ELAPSE trial	NR	yes	yes	low	low	NR	Yes	Unclear	Low	Yes	NR	Unclear	low	Yes [12 months]	yes	yes	NO (22% withdrew [7 of 33 enrolled])	Low
Trenk, 2008{Trenk, 2008 171 /id} 18482659 Germany EXCELSIOR (Impact of Extent of Clopidogrel-	NO (included all patients in the prospective EXCELSIOR cohort that had genot	yes	No	high	low	Yes	Yes	Low	Low	No	No	High	Low	Yes [1 year]	yes	yes	yes	Low

Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate)	ypic information)																	
Wang, 2010{Wang, 2010 37 /id} 21171668 China None	No	yes	yes	low	low	NR	Yes	Unclear	Low	Yes	Yes	Low	low	Yes [1 year]	yes	yes	yes	Low
Wang, 2009{Wang, 2009 130 /id} 19041120 China NR	No	yes	yes	low	low	NR	Yes	Unclear	High	Yes	NR	Unclear	low	Yes [12 months]	yes	yes	yes	Low
Yong, 2009{Yong, 2009 146 /id} 19081397 Australia Platelet Responsiveness to Aspirin and Clopidogrel and Troponin	Yes	yes	yes	low	low	Yes	NR	Unclear	High	Yes	Yes	Low	low	No [6 months]	yes	yes	yes	low

Increment after Coronary intervention in Acute coronary Lesions (PRACTICAL) Trial																		
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA No	NR	yes	yes	low	low	NR	no	high	unclear	No	NR	high	yes	No (30 days)	yes	yes	No (many had no data at 30 days)	high
Gurbel 2005{Gurbel, 2005 215 /id} 16286165 USA PREPARE POST-STENTING	Yes	No	No	High	Low	NR	NR	Unclear	High	Yes	Yes	Low	Low	No [6 months]	yes	yes	yes	low
Gurbel 2003{Gurbel, 2003 222 /id} 12796140 USA NR	Yes	YES	Yes	Low	Low	Yes	Yes	Low	Low	Yes	NR	Unclear	Low	No [30 days]	Yes	Yes	Yes	Low

Appendix Table E22: Quality Assessment of studies assessing the predictive ability of LTA in patients with peripheral artery disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Linnemann 2010{Linnemann, 2010 82 /id} 20153859 Germany NR	Yes	yes	yes	low	low	NR	Yes	Unclear	High	No	NR	High	High	YES [median 17.5 months]	No	yes	No	High

Appendix Table E23: Baseline characteristics of patients with ischemic heart disease in studies assessing the predictive ability of VerifyNow

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[14]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	49 NR 67 63±11	NR NR 0 CABG 6 NR NR NR 29 NR	hyper 59 Ex-smoker 29 current 31 HTN 61 24	NR 100 94 39	NR NR one vessel 45 two vessel 10 three vessel 0	ACS	at least 300 mg clopidogrel loading dose if >12 prior to angiography followed by 75 mg daily as maintenance, or 600 mg loading if <12 h prior to angiography with 75 mg daily maintenance	NR
Angiolillo, 2007{Angiolillo, 2008 180 /id} 18312754 USA OPTIMUS	34 NR 22 (64.7) 64.5±9	NR NR NR CABG 6(17.6) NR NR NR	31 (91.2) 10 (29.4) 31 (91.2) 100	NR 100 100 NR	NR NR 27(79.4)	Patients underwent PCI and were treated with standard clopidogrel	Clopidogrel 75 mg/day, and 1 month after clopidogrel 150 mg/ day. Thereafter, all patients resumed the standard 75 mg/day maintenance dose.	None

[14] Mean (standard deviation), unless otherwise stated.

		14 (41.2) NR						
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	1069 NR 75 64±10.6	NR NR NR NR NR NR 54.5 NR	80.3 11.1 HTN 76.9 18.6	NR 100 89.4 27.8	100 DES 63.5 NR	coronary artery disease scheduled for elective PCI with stent	clopidogrel treatment (a maintenance of 75 mg/d therapy for>5 days or a loading dose of 300 mg ≥24 hours before PCI or 600 mg ≥4 hours before PCI) and aspirin (80-100 mg/d ≥10 days).	unless they were receiving long-term anticoagulation with warfarins
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	1058 NR 70.1 62.2±11.2	62.2±11.2 NR 3.6% PCI 30.4% NR NR NR 20.9% NR	19% 39.8% 52% 29%	NR 25.3% NR NR	NR NR 27.6%	Patients treated with coronary stenting for symptomatic coronary artery disease, including acute myocardial infarction (AMI) and on chronic clopidogrel therapy	scheduled coronary stenting procedures, 300-mg loading-dose (LD) of clopidogrel at least 12 h before procedure. In AMI patients, all received a 600-mg LD of clopidogrel immediately after emergency room arrival, followed by a maintenance dose of 75 mg daily.	If use of glycoprotein IIb/IIIa inhibitor (GPI) was deemed necessary, only tirofiban, which has a short half-life, was administered.
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	222 ?Asian 152 (69) 63.3 ± 10	100 NR CVA: 14.9PCI: 37 (16.7); CABG: 1 (0.5) NR	Hypercholesterolemia: 46.8 Current: 12.2 HTN: 72.1 32	NR 72.1 89.6 NR	100 Drug eluting Multi-vessel; Stents/pt: 1.8±1	Patients undergoing percutaneous coronary intervention (PCI) for CAD	All patients were pretreated with aspirin (100 mg/d) and clopidogrel (75 mg/d) at least 5 days before PCI or received oral loading doses	NR

		NR NR 5.9 NSTEMI: 10.1					of 250 mg aspirin and 300 mg clopidogrel 12 to 24 hours before PCI. Maintenance doses of 100 mg aspirin and 75 mg clopidogrel after PCI After PCI, dual antiplatelet therapy with 100 mg/d aspirin and 75 mg/d clopidogrel was continued for at least 6 months	
Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France, Spain 3T/2R trial	total 468 NR 349 (74.6) 67±10.5	NR NR NR PCI 195 (41.7); CABG 44 (9.4) 152 (32.5) NR NR 196 (41.9) NR	268 (57.3) 120 (25.6) 346 (73.9) 111 (23.7)	NR 396 (84.6) NR NR	NR 362 (77.4) multi 301 (64.3)	Patients scheduled for coronary angiography or PCI	clopidogrel 600 mg at least 2 h before or 300 mg at least 6 h before or 75 mg/day for at least 7 days. Aspirin (100 mg/day) was given to all patients indefinitely. Clopidogrel (75 mg/day) was given for at least 1 month to patients with stable disease as an indication for PCI and receiving bare metal stent implantation, whereas it was given for at least 1 year to patients with unstable angina and/or who were receiving	In poor responders, which were included in the 3T/2R main study, the use of tirofiban was randomized as previously reported . Conversely, in other patients, the use and type of glycoprotein (GP) IIb/IIIa inhibitors were according to the operator's choice.

							drug-eluting stent implantation.	
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	300 NR 231 (77%) 66 ± 13 mean±SD	NR NR NR PCI, 47 (16%); CABG, 34 (11%) NR NR NR 81 (27%) Non-STEMI ACS 184 (61%)	Hyperlipidemia 153 (51%) 71 (24%) HTN 215 (72%) 71 (24%)	NR 100%; at 6 mo, 290 (97%) 100%; at 6 mo, 298 (99%) 158 (53%)	NR DES 214 (71) Multivessel PCI 109 (36)	Patients undergoing PCI for ischemic heart disease	All patients were treated with aspirin (300 mg as loading dose [LD] at hospital admission, followed by 100 mg daily, independently to previous or not chronic use). Clopidogrel 600 mg was given as LD at least 12 h before PCI. After intervention, clopidogrel 75 mg/day was continued for 12 months.	Anticoagulant and glycoprotein IIb/IIIa inhibitors treatment was administered at the interventionalist 's discretion.
Cuisset, 2008{Cuisset, 2008 168 /id} 18549843 Belgium NR	122 NR 95 (77.9%) 67.2	NR NR NR Previous PCI/MI: 37% NR NR NR Previous PCI/MI: 37% NR	65.6% 29% HTN: 61.5% 30.3%	NR NR NR NR	NR NR NR	Patients undergoing PCI for ACS	loading doses of clopidogrel 600 mg and aspirin 500 mg the day before the procedure	All pts: received intravenous heparin to achieve a target activated clotting time of 250 to 350 seconds.
de_Miguel_Castro, 2009{de Miguel, 2009 136 /id}	161 NR 120 (75%) 67.6 ± 1.9	NR NR NR PCI: 12%; CABG: 7%	53 Current: 19% HTN: 59% 27%	NR 14% NR NR	NR NR LAD: 2% Multivessel: 54%	Patients with acute NSTE ACS undergoing coronary angiography	clopidogrel 300 mg LD + followed by 75 mg/d MD for 9 - 12 months Aspirin: 250 mg LD followed by	

19232185 Spain NR		NR NR NR 21% NR					100 mg/d MD.	
Gladding, 2008{Gladding, 2008 149 /id} 19463375 New Zealand Secondary (but not subgroup) analysis of PRINC (Plavix Response in Coronary Intervention) Trial	60 Caucasian: 57 (95%) 50 (83%) 68 (10) mean (SD)	NR CHF 2 (3%) NR Prior PCI: 12 (20%); Prior CABG: 6 (10%) NR NR NR NR 3 (5%)/4 (7%)	NR 6 (10%) HTN 34 (57%) 11 (18%)	NR 0% [exclusion criterion] 59 (98%) NR	NR Multiple stents 9 (15%); DES 21 (35%) NR	Patients undergoing elective PCI	All patients: 600-mg clopidogrel at the start of the PCI procedure. At 2 hours after, 37 patients received 600 mg clopidogrel and 23 received placebo. Starting the next day, all patients were separately randomized to receive clopidogrel 75 or 150 mg once daily for 1 week, followed by 75 mg once daily thereafter.	
Huczek, 2011{Huczek, 2011 239 /id} 21443410 Poland NR	374 NR 230 (61.5%) 66.6 ± 11.3	NR NR Ejection fraction: 47.5±10.1; Killip>I: 65 (17.4) NR NR NR NR NR	222 (59.4) 48.1% HTN: 67.1% 19.8%	NR NR NR 69.5%	NR; No. of stents 1.47±0.8 Drug-eluting stents: 16 (4.3%) Multi-vessel disease: 83 (22.2%)	Patients undergoing PCI for ACS	**Clopidogrel**: 600mg loading dose before PCI and 75mg daily for 30 days after PCI **Aspirin**: 300mg oral dose before PCI and 75mg daily after PCI	Unfractionated heparin was administered as weight adjusted bolus (70 IU/kg) and if needed additional boluses were given under the guidance of activated clotting time (ACT) in order to reach the range of 300–350

		NR STEMI: 44.9						
Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	110 NR 53 (48%) Mean +/-SD 66+/-9 yr	NR NR Previous stroke 3% PCI 5%/CABG 0% NR NR NR 2% NR	Hyperlipidemia 21.8 14% HTN 68% 42%	NR 100% 99% NR	100% DES 100% NR but no. of diseased vessels, 1—45% 2—31% 3—24%	patients with typical angina, not on statins and without elevated levels of cardiac enzymes scheduled for drug-eluting stent (DES) implantation in de novo coronary artery lesions	All patients received daily aspirin 100-200 mg and clopidogrel 75 mg starting from 7 days before the elective PCI. Patients were randomized to also receive cilostazol 200 mg/day for 7 days (Cilostazol group) or no pretreatment (control). All patients received clopidogrel 75 mg/day for at least 6 months in addition to continued aspirin (100 mg/day).	Before PCI, all patients received a 60 IU/kg intravenous bolus of unfractionated heparin. Glycoprotein IIb/IIIa inhibitors were administered at the operator's discretion.
Lee, 2009{Lee, 2009 230 /id} 20049136 South Korea NR	237 NR 160 (68%) 65.2±10.3 years mean±SD	NR NR NR PCI 10% NR 162 (68%) NR 8% NSTEMI 75 (32%)	NR Current smoker 21% HTN 51% 29%	NR 100% 100% NR	100% DES 100% NR	ACS patients undergoing DES stenting	Prior to stent insertion, all the patients received a pre-treatment using 600 mg clopidogrel and 300 mg aspirin. In patients who received a DES, 100 mg aspirin was administered for life and 75 mg clopidogrel was administered for at least 6 months in principle.	
Mangiac	250	NR	hyperlipidemia:	NR	NR	Patients	600-mg	Procedural

apra, 2010{Mangiacapra, 2010 83 /id} 20298992 Italy NR	NR 200 (80%) 65.6	NR NR PCI:40.4%;CABG: 5% 16% 84% NR 27.2% NR	73.6% Current: 21.2% HTN: 75.2% 33.2%	11.2% 100% 28%	NR NR	undergoing elective PCI	clopidogrel LD or were on therapy with clopidogrel 75 mg/day for at least 5 days. Chronic aspirin treatment (dose NR)	anticoagulation with unfractionated heparin (100 U/kg)
Mangiacapra, 2010{Mangiacapra, 2010 94 /id} 20129566 Belgium NR	338 NR 274 (81%) 67±10	NR NR NR multivessel PCI: 18% NR NR NR 25% NR	74% 19% HTN: 72% 37%	NR NR 100% 26%	Direct stenting: 37% Drug eluting: 43% NR	Patients undergoing angiography for stable angina or have stenotic coronary artery	clopidogrel 600 mg and aspirin 500 mg loading doses at least 12 h before PCI	
Mangiacapra, 2010{Mangiacapra, 2010 65 /id} 20723634 Italy NR	285 NR 224 (78.5%) 66.4	NR NR NR PCI: 38.6%/CABG: 5.6% NR NR NR 30.9% NSTEMI: 54%	hypercholesterolemia: 75.4% Current: 18.9% HTN (>140/90 mm Hg): 79.3% NR	NR 24.9% 100% 30.2%	NR NR NR	Patients undergoing elective PCI for stable angina or non–ST-elevation acute coronary syndromes	clopidogrel 600 mg LD + 75 mg MD Aspirin 100 md LD + 100 mg MD	Procedural anticoagulation: unfractionated heparin (100 U/kg)

Marcucci, 2009{Marcucci, 2009 144 /id} 19118249 Italy NR	683 NR 517 (75.6) 69 (range 29-94)	NR LVEF <40%: 25.5% NR NR NR NR NR NR STEMI: 28%	52.3% 30.8% HTN: 67.3% 26%	NR NR NR 92.9%	NR DES: 17.7% NR	Patients with ACS who underwent PCI	clopidogrel 600 mg LD + daily dose of 75 mg MD ASA 500 mg IV LD + daily dose of 100 to 325 mg PO MD	unfractionated heparin 70 IU/kg during the procedure
Patti, 2008{Patti, 2011 22 /id} 18804738 Italy ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome)	160 NR 129 (81) 66 ± 9	NR NR;Left ventricular ejection fraction (%): 56± 7 NR Previous coronary intervention: 39% NR NR NR 28% ACS/NSTEMI: 54%	Hypercholesterolemia: 74% NR NR NR	NR Chronic clopidogrel therapy: 40 (25%); everyone received clopidogrel before PCI 100 NR	149 (93%) Drug eluting: 41 (26%) Multivessel: 28 (18%)	Patients undergoing PCI for ACS, including those who have had a myocardial infarction	Clopidogrel before PCI: 600 mg loading dose approximately 6 h before intervention (n=120); 75 mg/day for ≥ 5 days (n=40) Post PCI: continued for 1 month after PCI (dose NR, presumable 75 mg/day) Aspirin: Dose NR	
Patti, 2011{Patti, 2011 22 /id} 21256470	310 NR 243 (78%)	NR NR 10 (3%)	Hypercholesterolemia (>200 mg/dl) : 220 (71%) NR	0% (exclusion criterion) 100% NR	NR DES 95 (31%) NR	clopidogrel-treated patients who underwent PCI	Patients receiving long-term clopidogrel therapy were not reloaded in the	All interventions were performed using the femoral approach, with weight-adjusted

Italy Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)–Bleeding Study (ARMYDA-BLEEDS)	67+/-10 (mean SD)	PCI 123 (40%) 210 (68%) UA or non-STEMI 100 (32%) NR 91 (29%) NR	NR 115 (37%)	NR			catheterization laboratory. Clopidogrel was continued (75 mg/day) for 1 month after PCI, except in patients receiving drug-eluting stents or treated for ACS, in whom the drug was discontinued 1 year after intervention. Aspirin was given to all patients and continued indefinitely.	intravenous unfractionated heparin (70 IU/kg body weight). During PCI, bivalirudin was used instead of unfractionated heparin in patients considered at high bleeding risk (age >75 years, history of previous bleeding, renal failure, low body weight); periprocedural use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion according to the presence of thrombus at the site of the index stenosis, occurrence of no reflow, or vessel closure.
Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on	1691 White race: 1652 (97.7%) 1193 (70.1%) Mean: 63.1	NR NR NR PCI: 45.5%;CABG: 20.7% 58.5% UA without ST-segment depression or elevated biomarker levels: 25.5% NR	Hyperlipidemia: 85.9% Current (smoker within previous 7 days): 16% HTN: 82.4% 40.7%	NR 600-mg loading dose: 52.5%; 75 mg/d >7 d: 37.3%; Loading dose ≥300 mg, followed by 75 mg/d >7 d: 10.2% 88.4% 26.2%	NR NR NR	PCI for ACS and MI	Before randomization: If not exposure before, clopidogrel 300-600 mg LD given Only Standard dose subjects included for KQ2b: loading dose of placebo followed by a dose of 75 mg and placebo tablet daily.	

Thrombosis And Safety (GRAVITAS)		29.8% NR					Aspirin: 75 to 162 mg daily	
Price, 2008{Price, 2008 174 /id} 18263931 USA NR	380 NR 292 (76.8) 68±11	NR NR NR NR 356 (93.7) NR NR 120 (31.6) NR	NR 34 (8.9) 335 (88.2) 110 (28.9)	NR 100 328 (86.3) NR	NR NR NR	Patients with one lesion ≥50% diameter stenosis requiring PCI.	All patients received aspirin 325 mg on the day of the procedure. Patients not previously on clopidogrel: 600 mg loading dose at the conclusion of the procedure. Patients were instructed to take aspirin 325 mg indefinitely and clopidogrel 75 mg daily for a minimum of 3 months post-procedure.	
Saw, 2008{Saw, 2008 242 /id} 19463380 Canada BRIEF-PCI	209 NR 169 (80.9) NR	NR NR NR PCI: 47 (22.5)/CABG: 10 (4.8) NR NR 11(5.2) 64 (30.6) NR	165 (78.9) 48 (23%) 120 (57.4) 31 (14.8)	NR 100 100 NR	NR DES 77(36.8) NR	Patients underwent PCI	aspirin (≥81 to 325 mg daily for at least 5 days) and clopidogrel (received 75 mg/day for ≥5 days or 300-mg loading dose ≥6 h prior or 600-mg loading dose ≥2 h prior)	
Valgimigli, 2009{Valgimigli, 2009 244 /id} 19528337 10 sites in Europe (Italy, Belgium,	263 (including aspirin nonresponders, who are not of interest) NR 193 (73%) 68+/-10 yr	NR NR 14 (5%) PCI 103 (39%)/CABG 17 (6%) 110 (42%) 86 (33%)	Hyperlipidemia 161 (61%) Current cigarette use 40 (15%) HTN 188 (71%) 69 (26%)	NR 81 (31%) 248 (94%) NR	NR NR NR	Adults with stable or troponin-negative non-STEMI ACS undergoing coronary angiography or PCI	Clopidogrel loading dose (300 or 600 mg) 2-6 hr before PCI except in those who'd been on clopidogrel for at least 7 days previously at a dose of 75 mg/day. IV aspirin was	Patients were randomized to tirofiban (50 ml) or placebo. Heparin or bivalirudin was permitted.

France, Spain) Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study		NR 113 (43%)					permitted at the time of angioplasty.	
Vavurankis, 2011{Vavurankis, 2011 245 /id} 21712606 Greece NR	74 NR 60 (81.1%) 60.9 ± 11.9	27% Impaired Killip class (≥ III): 20.3% NR Previous PCI: 13.5%/Previous CABG: 4.1% NR NR NR NR STEMI: 100%	47.3% 73% HTN: 45.9% 21.6%	NR 10.8% 24.3% NR	NR NR NR	Patients undergoing PCI for ACS (NSTEMI)	600 mg clopidogrel LD (300 mg LD in those already receiving it >1 week) + 75 mg MD 325 mg of acetylsalicylic acid from day 1-7 + 100 mg MD from day 7	glycoprotein IIb/IIIa inhibitor only in patients with total occlusion after successful crossing of the lesion with the guide wire Intravenous bolus unfractionated heparin (100 IU/kg) was given during PCI β-blockers and statins were given to all patients after PCI
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	951 NR 717 (75.4) 64±10.6	NR NR NR NR NR	Hyper 769 (80.9) 107 (11.3) 737 (77.5) 175 (18.4)	NR 489 (51.4) NR 270 (28.4)	Total length 28.3±17.1 DES 604 (63.8) NR	Patients scheduled for PCI with stent implantation	All patients on aspirin 80-100 mg daily for >0 days unless they were on long-term anticoagulation with coumarin derivatives; clopidogrel -	

		NR NR 519 (54.6) NR					chronic maintenance therapy of 75 mg for >5 days or a clopidogrel loading dose of 300 mg at least 24 h before PCI or 600 mg at least 4 h before PCI. Aspirin 80-100 mg daily for ≥10 days unless they were on long-term anticoagulation with coumarin derivatives.	
Suh, 2011{Suh, 2011 33 /id} 2123266 4 Korea CILON-T	915 NR 68.5 64.4±13	NR NR NR PCI 7.5; CABG 2.3 39.2 45.2 NR 10.2 NR	173/915 (18.9%) 25.3 SBP 128; DBP 78.8; HTN 65.7% 33.8	NR NR 98.4 2.3	NR TAXUS 50.4; ENDEAVOR 45 34.9	patients had angina pectoris or native coronary artery lesions	All patients were given aspirin and clopidogrel before coronary intervention. Loading doses of aspirin (300 mg) and clopidogrel (300 to 600 mg) were given to patients who had not taken aspirin or clopidogrel before. Aspirin (100 mg daily) and clopidogrel (75 mg daily) were given for at least 6 months.	The decision of pre-dilation or direct stenting was made by the operator, as was the use of glycoprotein IIb/IIIa inhibitor.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;

Appendix Table E24: Baseline characteristics of patients with cerebrovascular disease in studies assessing the predictive ability of VerifyNow

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel	Current antiplatelet regimen	Co-medication

						treatment		
Author, year [ref] UID Country Study Name	Total N Enrolled Race (% by group) Male (%) Age[15]	Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)	Stent implantation(%) Type of stent(%) Multi-or single vessel(%)			
Ryu, 2010{Ryu, 2010 229 /id} 21113358 South Korea NR	57 NR 24 (42%) Mean +/-SD 60.3 ± 12 years	NR NR NR NR NR NR NR NR NR	Hypercholesterolemia 10 (18%) NR NR 13 (23%)	NR 100% 100% NR	81% NR NR	Patients receiving a neurointervention	All patients were pre-medicated with 100mg of aspirin and 75 mg of clopidogrel for at least 72 hours before the procedure.	
Kang, 2010{Kang, 2010 1 /id} 20223886 South Korea NR	186 NR (?100% Asian) 57 (31%) 58.3±10.2	NR NR NR NR NR NR NR NR NR	NR; Total cholesterol level (mg/dL): 181.1 ± 36.8; Triglyceride level (mg/dL): 150.3 ± 85.6; HDL cholesterol level (mg/dL): 51.1 ± 17.5 ;LDL cholesterol level (mg/dL): 109.0 ± 32.5 Smoker (current and past smokers who have ever smoked 10 cigarettes per day for at least 1 year): 19% HTN: 51%	NR Clopidogrel loading (300 mg) only: 136 (73%); Previous other antiplatelet medication plus clopidogrel loading: 29 (16%); Continued clopidogrel medication without loading: 21 (11%)	NR NR NR	patients undergoing coil embolization for intracranial aneurysms	Clopidogrel: 300-mg LD day before procedure with 89% of patients getting additional 75 mg of CPG on the morning of the procedure ; after procedure, an antiplatelet agent was administered for ≥1 week Aspirin dose/regimen: NR	Heparin during procedure: 3000-IU IV bolus, followed by 1000 IU/h

[15] Mean (standard deviation), unless otherwise stated.

		NR	8%	NR NR				
Drazin 2011{Drazin, 2011 238 /id} 21990814 US NR	52 NR 20 (38%) 62.6+/-14.0 yr (mean/SD)	NR NR NR NR NR NR 54.5 NR	NR 3 (6%) NR 15 (29%)	NR 100% 100% 29%	100% NR NR	Patients undergoing neurovascular stenting	Loading dose of 600 mg of clopidogrel and 81 mg of aspirin at least 12 hr before stenting (except in 3 patients with ruptured aneurysm, who received clopidogrel on the day of stenting) and maintenance dose thereafter of 75 mg/day for clopidogrel and 81 mg/day for aspirin. Patients with initial clopidogrel-induced inhibition of 10-19% were given 300 mg more of clopidogrel; those with initial inhibition <10% were given 600 mg more.	Heparin also given but regimen NR, and abciximab given in at least 1 patient.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;

Appendix Table E25: Study design characteristics of studies assessing the predictive ability of VerifyNow in patients with ischemic heart disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	prospective Cohort	No	Patients with ACS history	Patients with ACS history	Jan-June , 2008	6 months	Hospital inpatient	NR	NR
Angiolillo, 2007{Angiolillo, 2008 180 /id} 18312754 USA OPTIMUS	prospective Cohort	No	Patients underwent PCI and were treated with standard clopidogrel	Patients underwent PCI and were treated with standard clopidogrel	NR	1 months	Hospital inpatient	Yes; Accrual>80%	NR
Breet ,2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	prospective Cohort	No	Patients scheduled for PCI with stent implantation	Patients with PCI and stent implantation	Dec 2005-Dec 2007	1-year	Hospital inpatient	Yes. 80%	NR
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	prospective cohort	no	consecutively enrolled	unselected patients treated with coronary stenting for symptomatic coronary artery disease, including acute myocardial infarction (AMI) and chronic clopidogrel therapy	December 2007 to June 2009	6 months	Department of Cardiology of the Gyeongsang National University hospital inpatient	NR	NR
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	observational study	YES	Consecutive patients	Patients undergoing percutaneous coronary intervention (PCI) for CAD	Aug-Oct 2009	30 days for all patients	followup after intervention	NO	Non-industry only - grant from Government & non-profit foundation
Campo, 2010{Campo, 2010	Sub-study of RCT	Yes	Patients scheduled for	Patients scheduled for	Feb, 2006-June,	1-year	Hospitals inpatient	NR	Partly industry

58 /id} 20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial			coronary angiography or PCI	coronary angiography or PCI	2008				
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	Prospective cohort	No	Consecutive	Patients undergoing PCI for ischemic heart disease who had a baseline and 1 month PRU evaluation and a baseline blood sample for genotyping	December 2008 to May 2009	Max, 1 year	Inpatient followed by outpatient followup	NO	NR but authors have COIs with drug companies
Cuisset, 2008{Cuisset, 2008 168 /id} 18549843 Belgium NR	Prospective observational study	NO	Consecutive patients	Patients undergoing percutaneous coronary intervention (PCI) for ACS	May – Oct 2007	NR	Followup after intervention	YES; Accrual >80%	NR
de_Miguel_Castro, 2009{de Miguel, 2009 136 /id} 19232185 Spain NR	Prospective observational study	NO	NR	Patients with acute NSTE ACS undergoing coronary angiography	Jan 2005 – Feb 2006	12 month followup	Followup	YES; Accrual=161/175 (92%)	non-industry (grant from the Fundación Investigación Sanitaria (Health Research Foundation) in León, Spain.)
Gladding, 2008{Gladding, 2008 149 /id} 19463375 New Zealand Secondary (but not subgroup) analysis of PRINC (Plavix Response in Coronary Intervention) Trial	2 by 2 factorial, randomized, placebo-controlled, double-blind study over the first 24 h, followed by a 1-week randomized, placebo-controlled, double-blind study	NR	Consecutive	Patients undergoing elective PCI	NR	7 Days total	Inpatient, with outpatient followup after the inpatient procedure	YES [YES ("~80%")]	Non-industry only except the VerifyNow platelet function analyzer was provided by Sanofi Aventis, New Zealand.
Huczek,	Prospectiv	NO	NR	Patients	July	Max: 30 day	followup	NO	Non-

2011{Huczek, 2011 239 /id} 21443410 Poland NR	e			undergoing percutaneous coronary intervention (PCI) for ACS	2008 until December 2009	followup	after intervention		industry (Polish Ministry of Science and Higher Education [No. N402 4400 33])
Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	RCT	NO	Consecutive	patients with typical angina, not on statins and without elevated levels of cardiac enzymes scheduled for drug-eluting stent (DES) implantation in de novo coronary artery lesions	June 2007-May 2009	Total 6 mo	Outpatient visits and inpatient during PCI	YES [YES]	Partly industry
Lee, 2009{Lee, 2009 230 /id} 20049136 South Korea NR	Prospective	NO	Consecutive	ACS patients undergoing DES stenting	Jan. 2006-Dec. 2007	Total 6 mo	In hospital for those who were continually hospitalized or outpatient followup for those who were discharged	NO	NR
Mangiacapra, 2010{Mangiacapra, 2010 83 /id} 20298992 Italy NR	Prospective observational study	NO	NR	Patients undergoing elective PCI	NR	NR	followup after intervention	YES; Accrual >80%	NR
Mangiacapra, 2010{Mangiacapra, 2010 94 /id} 20129566 Belgium NR	Prospective observational study	NO	NR	Patients undergoing angiography for stable angina or have stenotic coronary artery	NR	NR	Followup after intervention	YES Accrual > 80%	NR
Mangiacapra, 2010{Man	Prospective observatio	NO	NR	Patients undergoing	NR	NR	followup after interventi	YES; Accrual >80%	NR

giacapra, 2010 65 /id} 20723634 Italy NR	nal study			elective PCI for stable angina or non–ST-elevation acute coronary syndromes			on		
Marcucci, 2009{Marcucci, 2009 144 /id} 19118249 Italy NR	Prospective cohort	NO	NR	Patients with ACS who underwent PCI	January 2005 to March 2006	12 months	Followup after intervention	NO	Non-industry (grant to the FiorGen Foundation by Ente Cassa di Risparmio Florence, Italy)
Patti, 2008{Patti, 2011 22 /id} 18804738 Italy ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome)	Prospective observational study	NO	NR (appears to be a consecutive study)	Patients undergoing PCI for ACS, including those who have had a myocardial infarction	NR	6 month followup for each patient	Followup after intervention	YES; accrual >80%	Not supported by external sources of funding
Patti, 2011{Patti, 2011 22 /id} 21256470 Italy Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA) –Bleeding Study (ARMYDA-BLEEDS)	Prospective	NO	Consecutive	clopidogrel-treated patients who underwent PCI	April 1-Dec. 31, 2009	Total 1 month	Inpatient for PCI, then followup for 1 mo as outpatient	NO	NR
Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging	Prospective cohort with comparison being made between	YES	Consecutive	PCI for ACS and MI	July 2008 – Apr 2010	6 months	Followup after intervention	Yes; Accrual>80%	Industry (Accumetrics & study drug was provided by an

Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS)	one of the randomized arm of an RCT and a parallel observation cohort								investigator-initiated grant from Bristol-Myers Squibb/ sanofi-aventis)
Price, 2008{Price, 2008 174 /id} 18263931 USA NR	prospective Cohort	No	Patients with one lesion ≥50% diameter stenosis requiring PCI.	Patients with one lesion ≥50% diameter stenosis requiring PCI.	July 2005-Aug 2006	6 months	Hospital inpatient	YES	Industry
Saw, 2008{Saw, 2008 242 /id} 19463380 Canada BRIEF-PCI	Sub-study of RCT	No	Sub-study of RCT	Patients underwent PCI	March 2005-May 2007	24 hours	Vancouver General Hospital	Yes. A sample size of 204 was determined to be required—assuming clopidogrel low-responder prevalence of 25% and myonecrosis prevalence of 40% after PCI in responders—to detect an absolute difference of 20% from low-responders, with 5% alpha and 80% power.	Non-industry only
Valgimigli, 2009{Valgimigli, 2009 244 /id} 19528337 10 sites in Europe (Italy, Belgium, France, Spain) Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study	Prospective	YES	Consecutive	Adults with stable or troponin-negative non-STEMI ACS undergoing (elective ?) coronary angiography or PCI	Feb. 2006-June 2008	Total 30 days	Inpatient and then followup after discharge for 30 days	YES (YES—90%)	Partly industry
Vavuranakis, 2011{Vavu	Prospective observatio	NO	NR	Patients undergoing PCI	NR	Mean ± sd: 203±152 days	followup after interventi	YES [accrual > 80%; Min required:	Reported as None

ranakis, 2011 245 /id} 21712606 Greece NR	nal study			for ACS (NSTEMI)			on	64; recruited 74]	
Breet, 2011{Breet , 2011 15 /id} 21478385 The Netherland s POPular	Observatio nal study	NR	Consecut ive	Patients schedule d for PCI with stent implantat ion	NR	1 year	Hospital	NR	NR
Suh, 2011{Suh, 2011 33 /id} 21232664 Korea CILON-T	prospectiv e RCT	yes	patients had angina pectoris or native coronary artery lesions	patients had angina pectoris or native coronary artery lesions	Sep 2006 and June 2009	6 months	5 hospitals	yes. 80%	Non-industry

Appendix Table E26: Study design characteristics of studies assessing the predictive ability of VerifyNow in patients with cerebrovascular disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Ryu, 2010{Ryu, 2010 229 /id} 21113358 South Korea NR	Prospective	NO	NR	Patients receiving a neurointervention	Jan. 2007 to July 2008	18.2 ± 7.84 months mean/SD	In hospital at baseline, outpatient followup at 6 mo	NR	Non-industry only
Drazin, 2011{Drazin, 2011 238 /id} 21990814 US NR	Prospective	NR	Consecutive	Patients undergoing neurovascular stenting and receiving clopidogrel and aspirin	2007-2009	Mean 12 mo (range, 0-34 mo)	Intraoperative + in- and outpatient followup	NO	NR but one author has consulting fees, and one has grants, from industry
Kang, 2010{Kang, 2010 1 /id} 20223886 South Korea NR	observational study	NO	NR	patients undergoing coil embolization for intracranial aneurysms	Since Mar 2008	Max 60 days	followup after intervention	NO	NR

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-elevation; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; DES=drug eluting stent; CABG=coronary artery bypass grafting; AA= arachidonic acid; SD=standard deviation; RCT=randomized controlled trial; NR=not reported;

Appendix Table E27: Phenotypic test details in studies assessing the predictive ability of VerifyNow in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer *	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	VerifyNow VerifyNow Accumetrics, San Diego, CA, USA)	ADP	After discarding 5 mL, arterial sheath blood was drawn into vacutainer R tubes and analyzed using the Verify-Now system containing sodium citrate 0.109 M NR NR	PRU≤240 PRU >240	Based on previous literature	PRU≤240 PRU >240
Angiolillo, 2007{Angiolillo, 2008 180 /id} 18312754 USA OPTIMUS	VerifyNow P2Y12 VerifyNow P2Y12	ADP	2 to 4 hours after antiplatelet therapy intake NR 2 to 4 hours after antiplatelet therapy intake NR	P2Y12 inhibition ≥50% P2Y12 inhibition <50%	Not explicitly reported.	P2Y12 inhibition ≥50%: n=17 (50%) P2Y12 inhibition <50%: n=17 (50%)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	VerifyNowP2Y12assay Accumetrics, SanDiego,California	ADP	NR Greiner tubes NR Within 2 hours after blood collection.	Verify now P2Y12 <236 Verify now P2Y12 ≥ 236	Based on ROC curves	Verify now P2Y12 <236: n=646 Verify now P2Y12 ≥236: n=406
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	turbidimetry-based optical detection device VerifyNowP2Y12assay NR	20 µmol/L ADP	Blood was drawn into a Greiner Bio-One 3.2% citrate Vacuette tube sodium citrate 3.2% clopidogrel- naı¨ve patients received a 300-mg loading-dose (LD) of clopidogrel at least 12 h before procedure, and blood sampling was	PRU<240 PRU≥240	Based on literature	PRU<240 n=512 PRU≥240 n=546

			performed after insertion of the arterial sheath. In the case of patients who were already on chronic clopidogrel therapy, blood sampling was performed at the catheterization lab without clopidogrel LD 60 minutes			
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	turbidimetric-based optical detection system VerifyNow P2Y12 Assay Accumetrics	ADP	Before PCI; 8 and 24 hrs after PCI lepirudin (25 µg/mL) 5 days (clopidogrel came first) 0.125 days (Within 3 hrs)	Hyporesponsiveness to clopidogrel (PRU≥ 274) Normal responsiveness to clopidogrel (PRU<274)	For identification of PRU cutoff, ROC curve analysis that presented the highest sum of sensitivity and specificity was used	Hyporesponsiveness to clopidogrel (PRU≥ 274): 121 (54.5) Normal responsiveness to clopidogrel (PRU<274): 101 (45.5)
Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial	VerifyNowP2Y12assay NR Accumetrics, SanDiego,California	NR	NR NR NR NR	Full responder (%PI≥40% full responder) Poor responder (%PI<40 poor responder)	Based on literature	Full responder (%PI≥40% full responder): N=289 Poor responder (%PI<40 poor responder): N=179
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	VerifyNowP2Y12assay NR Accumetrics, SanDiego,California	NR	NR NR All samples obrtained after clopidogrel started; Blood samples were drawn at baseline (just before PCI and administration of interventional therapy) and at 1 and 6 months after PCI. NR	Clopidogrel poor response (PRU value ≥235) at baseline Clopidogrel full response (PRU <235) at baseline Enhanced response (PRU ≤85) at 1 mo Normal response (PRU 86-238) at 1 mo Poor response (≥239) at 1 month	For PRU≥235 vs <235: Based on literature For enhanced, normal, poor: best cutoffs from ROC curves done in current study	Clopidogrel poor response (PRU value ≥235) at baseline, 107 (36%) Clopidogrel full response (PRU <235) at baseline, 193 (64%) Enhanced response (PRU ≤85) at 1 mo, 75 (25%) Normal response (PRU 86-238) at 1 mo, 185 (62%) Poor response (≥239) at 1 mo, 40 (13%)
Cuisset, 2008{Cuisset, 2008 168 /id} 18549843 Belgium NR	VerifyNow P2Y12 VerifyNow P2Y12 NR	PGE1+ADP	Before PCI NR 0.5 days (≥12 hrs) Clopidogrel came first	Quartile 1 (nonresponders) percent inhibition P2Y12 <15% Quartile 2-4 (responders) percent inhibition P2Y12 ≥15%	Not explicitly reported.	Quartile 1 (nonresponders) percent inhibition P2Y12 <15%: 32 (25%) Quartile 2-4 (responders) percent

			NR			inhibition P2Y12 ≥15%: 90 (75%)
de_Miguel_Castro, 2009{de Miguel, 2009 136 /id} 19232185 Spain NR	VerifyNow VerifyNow® analyzer Accumetrics Inc., San Diego, California	NR	Before angiography 3.2% sodium citrate NR [clopidogrel came first] 0.04 (1 hr)	Post treatment platelet reactivity ≤ 175 Post treatment platelet reactivity >175 Quartile 1 (<115 PRU) Quartile 2 (115 -164 PRU) Quartile 3 (165 - 206 PRU) Quartile 4 (>206 PRU)	Not explicitly reported.	Post treatment platelet reactivity ≤ 175: 97 (60.2%) Post treatment platelet reactivity >175: 64 (39.8%) Quartile 1 (<115 PRU): 40 (25%) Quartile 2 (115 -164 PRU): 40 (25%) Quartile 3 (165 -206 PRU): 40 (25%) Quartile 4 (>206 PRU):41 (25%)
Gladding, 2008{Gladding, 2008 149 /id} 19463375 New Zealand Secondary (but not subgroup) analysis of PRINC (Plavix Response in Coronary Intervention) Trial	Agglutination plus light transmittance VerifyNow point-of-care rapid platelet function analyzer (RPFA) and its P2Y12 cartridge Accumetrics Ltd., San Diego, California	ADP, 20 mmol/l [published as mmol but must be umol?]	Arterial blood was sampled through a 6-F femoral sheath and transferred immediately; collection tubes were inverted 4 times to mix the anticoagulant and left at ambient temperature (24°C) 3.2% citrate Platelet function was tested at baseline, 2, 4, and 7 h from 10 mins	600 mg Clopidogrel: Nonresponse (inhibition <10%) at 7 hr Response (inhibition >=10%) at 7 hr 1200 mg Clopidogrel Nonresponse (inhibition <10%) at 7 hr Response (inhibition >=10%) at 7 hr	Not explicitly reported.	600 mg Clopidogrel Nonresponse (inhibition <10%) at 7 hr: 6/26 (26%) Response (inhibition >=10%) at 7 hr: 20/26 (77%) 1200 mg Clopidogrel Nonresponse (inhibition <10%) at 7 hr:2/37 (5%) Response (inhibition >=10%) at 7 hr:35/37 (95%)
Huczek, 2011{Huczek, 2011 239 /id} 21443410 Poland NR	VerifyNow/ turbidoaggregometry VerifyNow P2Y12 assay Accumetrics Inc., San Diego, CA	ADP (with prostaglandin E1 to reduce the nonspecific binding for ADP to P2Y1 receptor)	Venous blood sample after clopidogrel 3.2% sodium citrate 0.5 ± 0.1 days (12± 2 hours); Clopidogrel came first NR	low platelet reactivity (PRU≤150) - first Medium platelet reactivity (PRU = 151-209 High platelet reactivity (PRU ≥210) – Third tertile	Not explicitly reported.	low platelet reactivity (PRU≤150) - first tertile - 124 (33.2%) Medium platelet reactivity (PRU = 151-209) - Second tertile - 124 (33.2%) High platelet reactivity (PRU ≥210) – Third tertile-124 (33.2%)
Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol	VerifyNow P2Y12 NR Accumetrics	NR	Samples were obtained by antecubital venipunture using a 23-gauge syringe, and the initial 3 to 4 mm of blood was discarded. The second samples were collected in 4.5-mL plastic tubes for rapid	clopidogrel resistance (% inhibition <20%) normal response to clopidogrel (% inhibition ≥20%)	Based on literature	clopidogrel resistance (% inhibition <20%): 37/110 (34%) normal response to clopidogrel (%

administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	Inc., San Diego, CA		platelet-function assay 3.2% citrate Venous blood samples were drawn immediately after randomization (baseline, before clopidogrel), before PCI (7 days later after pre-treatment with clopidogrel), and 6 and 24 hours after PCI. NR			inhibition ≥20%): 73/110 (66%)
Lee, 2009{Lee, 2009 230 /id} 20049136 South Korea NR	VerifyNow P2Y12 assay NR NR	NR	samples were collected from the vein following PCI. Sampling was done in the hospital for patients who were continually hospitalized during this period or during the first follow-up for patients who had been discharged. 3.2% citrate samples were collected after PCI and 5 days after initiating regular administration of clopidogrel (75 mg) Within 8 hours	Clopidogrel low response (<20% inhibition) Clopidogrel normal response (≥20% inhibition)	Based on literature	Clopidogrel low response (<20% inhibition): 95 (40%) Clopidogrel normal response (≥20% inhibition):142 (60%)
Mangiacapra, 2010{Mangiacapra, 2010 83 /id} 20298992 Italy NR	VerifyNow/optical turbidimetry VerifyNow P2Y12 assay Accumetrics, San Diego, California	20-µmol adenosine diphosphate,	Before PCI 3.2% sodium citrate NR [Clopidogrel came first] NR	high platelet reactivity PRU value ≥240 not high platelet reactivity	Based on literature	high platelet reactivity PRU value ≥240: 78 (31.2%) Not high platelet reactivity: 172 (68.8%)
Mangiacapra, 2010{Mangiacapra, 2010 94 /id} 20129566 Belgium NR	VerifyNow/optical turbidimetry VerifyNow P2Y12 assay Accumetrics, San Diego, California	20-µmol adenosine diphosphate,	Before PCI 3.2% sodium citrate NR [Clopidogrel came first] NR	High platelet reactivity (HPR) - PRU value ≥240 units Normal platelet reactivity - PRU value <240 units	Not explicitly reported.	High platelet reactivity (HPR) - PRU value ≥240 units: 101 (30%) Normal platelet reactivity - PRU value <240 units: 237 (70%)
Mangiacapra,	VerifyNow/opti	20-µmol adenosine	Before PCI	high platelet reactivity	Based on literature	high platelet reactivity

2010{Mangiacapra, 2010 65 /id} 20723634 Italy NR	cal turbidimetry VerifyNow P2Y12 assay Accumetrics, San Diego, California	diphosphate,	3.2% sodium citrate NR [Clopidogrel came first] NR	PRU value ≥240 not high platelet reactivity		PRU value ≥240: 77 (27%) not high platelet reactivity: 208 (73%)
Marcucci, 2009{Marcucci, 2009 144 /id} 19118249 Italy NR	VerifyNow/optical turbidimetry VerifyNow P2Y12 assay Accumetrics, San Diego, California	ADP	24 hours after 600-mg clopidogrel loading sodium citrate 0.109 mol/L 1 day [clopidogrel came first] NR	high residual platelet reactivity (PRU ≥ 240) No residual platelet reactivity (PRU < 240) high residual platelet reactivity (PRU ≥ 235) No residual platelet reactivity (PRU < 235) PRU quartiles Quartile 1 ≤129 Quartile 2 130-195 Quartile 3 196-257 Quartile 4 ≥258	ROC analysis; posttreatment PRU that provided the greatest sum of sensitivity and specificity.	high residual platelet reactivity (PRU ≥ 240): 219 (32.1%) No residual platelet reactivity (PRU < 240): 464 (67.9%) high residual platelet reactivity (PRU ≥ 235): 231 (33.8%) No residual platelet reactivity (PRU < 235): 452 (66.2%) PRU quartiles Quartile 1 ≤129: 171 (25%) Quartile 2 130-195: 171 (25%) Quartile 3 196-257: 171 (25%) Quartile 4 ≥258: 170 (25%)
Patti, 2008{Patti, 2011 22 /id} 18804738 Italy ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome)	VerifyNow/optical turbidimetry VerifyNow P2Y12 assay Accumetrics, San Diego, California	NR (ADP and PGE1 as per Ref 8)	Before PCI & 8 and 24 hrs after intervention NR 0.25 days between clopidogrel dose & sampling in 120 pts; the other 40 were on chronic clopidogrel therapy NR	First Quartile Second Quartile Third Quartile Fourth Quartile	Not explicitly reported for quartile classification; For identification of PRU cutoff, ROC curve analysis that presented the highest sum of sensitivity and specificity was used.	First Quartile: 40 (25) Second Quartile:40 (25) Third Quartile: 40 (25) Fourth Quartile: 40 (25)
Patti, 2011{Patti, 2011	VerifyNow P2Y12 assay	NR	NR	PRU quartiles at baseline (before PCI):	Not explicitly reported for quartiles; for cutoff	PRU quartiles at baseline (before PCI):

22 /id} 21256470 Italy Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)–Bleeding Study (ARMYDA-BLEEDS)	NR Accumetrics, Inc., San Diego, California		NR Dose came first; reactivity tested immediately before PCI and at 8 and 24 hours after intervention NR	1 (lowest PRU, which = highest inhibtion) 2 3 4 Also ROC-curve-based threshold PRU>189 (low inhibition) PRU< or = 189 (high inhibition)	at 187, authors did an ROC analysis in this study	1 (lowest PRU, which = highest inhibtion): 77 (25%) 2: 77 (25%) 3: 77 (25%) 4: 79 (25%) Also ROC-curve-based threshold PRU>189 (low inhibition): NR PRU< or = 189 (high inhibition): NR
Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS)	VerifyNow P2Y12 test/turbidoaggregometry VerifyNow P2Y12 test Accumetrics, San Diego, California	NR	12 to 24 hours after PCI; outcomes and repeat measurements at 30 days and 6 months NR 0.5-1 day (12-24 hrs) Clopidogrel came first NR	High on-treatment reactivity (PRU≥230) Not High On-Treatment Reactivity (PRU<230)	Based on literature	High on-treatment reactivity (PRU≥230): 1105 (65.3%) Not High On-Treatment Reactivity (PRU<230): 586 (34.7%)
Price, 2008{Price, 2008 174 /id} 18263931 USA NR	VerifyNow P2Y12 assay NR Accumetrics Inc	20-µmol adenosine diphosphate,	Whole blood was obtained at the time of catheterization prior to anticoagulant therapy in patients on previous clopidogrel therapy and by phlebotomy 12 h after PCI 3.2% sodium Whole blood was obtained by phlebotomy 12 h after PCI and a 600 mg clopidogrel loading dose in patients who were clopidogrel naive NR	Low reactivity (PRU<235) High reactivity (PRU≥235)	ROC analysis	Low reactivity (PRU<235): 258 High reactivity (PRU≥235): 122
Saw, 2008{Saw, 2008 242 /id} 19463380 Canada BRIEF-PCI	VerifyNow P2Y12 assay NR Accumetrics Inc	ADP	Whole blood samples 3.2% sodium citrate NR NR	Low-responder (Clopidogrel low-responders were defined as those belonging to the lowest quartile of platelet inhibition)- <19% Responder ≥19%	Not explicitly reported.	Low-responder (Clopidogrel low-responders were defined as those belonging to the lowest quartile of platelet inhibition): 51 (24.4)

						responder: 147 (70.3)
Valgimigli, 2009{Valgimigli, 2009 244 /id} 19528337 10 sites in Europe (Italy, Belgium, France, Spain) Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study	VerifyNow P2Y12 assay NR Accumetrics Inc	NR	NR NR Clopidogrel loading dose (300 or 600 mg) 2-6 hr before PCI except in those who'd been on clopidogrel for at least 7 days previously at a dose of 75 mg/day NR	Clopidogrel nonresponders (<40% inhibition) Dual (clopidogrel and aspirin) nonresponders Aspirin nonresponder	Not explicitly reported	Clopidogrel nonresponders (<40% inhibition): 147 Dual (clopidogrel and aspirin) nonresponders: 26 Aspirin nonresponder: 136 For groups above, denominator unclear no % not given. The Ns sum to 309 patients but 54 were withdrawn—group affiliation not given. Total of 263 enrolled in the end.
Vavuranakis, 2011{Vavuranakis, 2011 245 /id} 21712606 Greece NR	VerifyNow system/turbido aggregometry VerifyNow P2Y12 system Accumetrics, SanDiego, CA, USA	NR	Whole blood ; prior to catheterization 0.2 ml buffered 3.2% sodium citrate solution NR[clopidogrel came first] 0.01 ± 0.007 (15±1 min after collection)	NR	ROC analysis to predicts the presence of Large Thrombus Burden	NR
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	VerifyNow NR NR	ADP	NR K3-EDTA NR 2h	No HCPR (VerifyNow) With HCPR and Dual HCPR (VerifyNow) Cutoff: 236 P2Y12 reaction units	Based on literature	No HCPR (VerifyNow): 280 With HCPR and dual HPR (VerifyNow): 168
Suh, 2011{Suh, 2011 33 /id} 21232664 Korea CILON-T	VerifyNow/ turbidometric aggregation NR NR	20uM ADP and 22nM PGE1	NR NR NR 2h	low PRU 0-164 Middle PRU 165-264 High PRU ≥ 265	by ROC analysis	low PRU 0-164:<16% Middle PRU 165-264:16-36% High PRU ≥ 265:>36%

*If more than one test, use separate rows
**E.g., nonresponsive vs. responsive to clopidogrel, high vs. low platelet reactivity,

Appendix Table E28: Phenotypic test details in studies assessing the predictive ability of VerifyNow in patients with cerebrovascular disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer *	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Ryu, 2010{Ryu, 2010 229 /id} 21113358 South Korea NR	VerifyNow P2Y12 assay NR Accumetrics Inc	NR	NR NR Test conducted after taking the medicine for 3 days NR	platelet inhibition < 40% (clopidogrel resistance) platelet inhibition >/= 40% (clopidogrel nonresistance)	Not explicitly reported.	platelet inhibition < 40% (clopidogrel resistance): 33/53 (62.3%) platelet inhibition >/= 40% (clopidogrel nonresistance): 20/53 (37.7%)
Kang, 2010{Kang, 2010 1 /id} 20223886 South Korea NR	VerifyNow P2Y12 assay/Turbidimetric based optical detection system VerifyNow P2Y12 assay Accumetrics, San Diego, California	20 µmol of ADP	Whole blood was obtained before the coil embolization 3.2% sodium citrate NR [Clopidogrel came first] NR	First quartile (<240 PRU) Second quartile (240-284 PRU) Third quartile (285-332 PRU) Fourth quartile (>332 PRU)	Not explicitly reported.	First quartile (<240 PRU): 47 (25.3%) Second quartile (240-284 PRU): 46 (24.7%) Third quartile (285-332 PRU): 46 (24.7%) Fourth quartile (>332 PRU): 47 (25.3%)
Drazin, 2011{Drazin, 2011 238 /id} 21990814 US NR	VerifyNowP2Y12assay NR Accumetrics	ADP	NR Heparin Clopidogrel given at least 12 hr before stenting and measurements taken intraoperatively NR	Suboptimal clopidogrel response (<20% P2Y12 platelet inhibition), measured intraoperatively Optimal responders, measured intraoperatively	Not explicitly reported.	Suboptimal clopidogrel response (<20% P2Y12 platelet inhibition), measured intraoperatively: 19/52 (37%) Optimal responders, measured intraoperatively: 33/52 (63%)

ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity;

NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E29: Results from studies assessing the ability of VerifyNow to predict death in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	VerifyNow P2Y12	Death	death,	1-year	High OTPR	Death	9/406 (2.2)	OR=1.60	0.63-4.08	0.32 (high OTPR vs Normal OTPR) [logistic regression]	No	NR	
						Normal OTPR		9/646 (1.4)						
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	VerifyNow P2Y12 (PRU)	cardiac death	cardiac death	6 months	<240	cardiac death	0.2%	OR=3.85	0.46-32.12	0.258 (≥240 vs <240) [logistic regression]	NR	NR	
						≥240		0.9%						
Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	Death	Death	1-year	Full responder	Death	5/289 (1.7)	NR	NR	0.4 (poor vs full responder) [log rank]	NR	NR	Figure 4 and figure 5, KM curve for 1-year primary end point

						Poor responder		4/179 (2.2)	OR (calculate) =1.30		P=0.737 (poor responder vs full responder) [Fisher's exact test]			
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	Clopidogrel + aspirin	VerifyNow	Death	NR	1 yr	Poor response at baseline (N=107)	Death	3	OR (calculated)=1.83		P=0.67 (poor responder at baseline vs full responder) [Fisher's exact test]	NR	NR	NO
						Full response at baseline (n=193)		3						
	Clopidogrel + aspirin	VerifyNow	Death	Death	1 yr	Poor response at 1 mo (n=40)		5	OR (calculated)=37		P=0.0002 (poor responder at 1 month vs full responder) [Fisher's exact test]			
						Full response at 1 mo (n=260)		1						

Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	Clopidogrel+aspirin	VerifyNow	Cardiac death		6 months	Clopidogrel resistance		0/37 (0%)			NS (resistance vs normal response) [chi-square statistics or Fisher 's exact test]			
						Normal response		1/73 (1%)						
Lee, 2009{Lee, 2009 230 /id} 20049136 South Korea NR	600 mg clopidogrel + 300 mg aspirinLD & in pts with DES, 100 mg aspirin +75 mg clopidogrel	VerifyNow	Cardiac death	Cardiac death		Normal response		1 (0.7%)			0.344 (low vs normal response) [chi-square or Fisher's exact]			
						Low response		2 (2.1%)						
Marcucci, 2009{Marcucci, 2009 144 /id} 19118249 Italy NR	clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD	VerifyNow	Cardiovascular death	Cardiovascular death	12 months	high residual platelet reactivity (PRU≥240)	Cardiovascular death	13 (5.9)	HR=2.38	1.15 –5.2	P=0.031 (RPR vs no RPR) [cox regression]	NO	NR	

						No residual platelet reactivity (PRU<240)		11 (2.4)						
					12 months	high residual platelet reactivity (PRU≥240)	Cardiovascular death	13 (5.9)	HR=2.55	1.08 – 6.07	P=0.034 (RPR vs no RPR) [cos regression]	YES; cardiovascular risk factors, renal failure, left ventricular ejection fraction <40%, multivessel disease, total stent length, bifurcation lesions, number of lesions treated, type of stent used, and use of glycoprotein IIb/IIIa inhibitors	NR	
						No residual platelet reactivity (PRU<240)		11 (2.4)						
			Survival free from Cardiovascular death	Survival free from Cardiovascular death	12 months	high residual platelet reactivity (PRU≥240)	Survival free from Cardiovascular death	NR	NR	NR	P=0.02 (RPR vs no RPR) Log rank test	NO	NR	
						No residual platelet reactivity (PRU<240)		NR						
			Cardiovascular death	Cardiovascular death	12 months	high residual platelet reactivity (PRU≥235)	Cardiovascular death	NR	HR=2.37	1.06 –5.3	P=0.035 (RPR vs no RPR) [cox regression]	NO	NR	

						No residual platelet reactivity (PRU<235)		NR						
			Cardiovascular death	Cardiovascular death**Error! Bookmark not defined.**	12 months	high residual platelet reactivity (PRU≥235)	Cardiovascular death	NR	HR=2.41	1.01 – 5.72	P=0.046 (RPR vs no RPR) [cox regression]	YES; cardiovascular risk factors, renal failure, left ventricular ejection fraction <40%, multivessel disease, total stent length, bifurcation lesions, number of lesions treated, type of stent used, and use of glycoprotein IIb/IIIa inhibitors	NR	
						No residual platelet reactivity (PRU<235)		NR						
Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS)	Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD	VerifyNow	Cardiovascular death	Cardiovascular death23	6 months	High on-treatment reactivity was defined (PRU≥230)	Cardiovascular death	8 (0.7%)	HR=1.42	0.38-5.36	P=0.60 (high vs not high) [log-rank test stratified by acute coronary syndromes status]	NO	NR	Secondary analysis

						Not High On-Treatment Reactivity (PRU<230)		3 (0.5%)						
	Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD	VerifyNow	All cause death	All cause death	6 months	High on-treatment reactivity was defined (PRU≥230)	All cause death	10 (0.9%)	HR=1.34	0.42-4.28	P=0.62 (high vs not high) [log-rank test stratified by acute coronary syndromes status]	NO	NR	Secondary analysis
						Not High On-Treatment Reactivity (PRU<230)		4 (0.7%)						
Price, 2008{Price, 2008 174 /id} 18263931 USA NR	Clopidogrel LD 600 mg and maintaining 75mg daily	VerifyNow P2Y12 assay	CV death	Cardiovascular death	6-months	Lower reactivity	CV death	0/209	NR	NR	0.04 comparing with the following row	NR	NR	
						High reactivity		3/108 (2.8)						
	Clopidogrel LD 600 mg and maintaining 75mg daily	VerifyNow P2Y12 assay	CV death	Cardiovascular death	6-months follow-up with a minimal of 3 months post-procedure	Lower reactivity	CV death	0/252	NR	NR	0.04 comparing with the following row	NR	NR	
						High reactivity		3/121 (2.5)						
						Total		3/373 (0.8)						

Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	VerifyNow	Death	Death	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	Death,	6/168	OR (calculate) =3.6		P=0.07 (HCPR(high on-clopidogrel platelet reactivity) or dual HPR vsLow CPR+ or low PR) [Fisher's exact test]	NR	NR	
						Low CPR + Low PR		3/280						

Appendix Table E30: Results from studies assessing the ability of VerifyNow to predict myocardial infarction in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	VerifyNow P2Y12	MI	MI	1-year	High OTPR	MI	40/406 (9.9)	OR=2.96	1.74-5.02	<0.001	No	NR	
						Normal OTPR		23/646 (3.6)						
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	VerifyNow P2Y12 (PRU)	non-fatal myocardial infarction	non-fatal myocardial infarction	6 months	<240	non-fatal myocardial infarction	1.7%	OR=2.62	1.13-6.06	0.019	NR	NR	
						≥240		4.3%						
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	75 mg/d clopidogrel & 100 mg/d aspirin	VerifyNow P2Y12 Assay	Periprocedural MI	Postprocedural ↑ of troponin or CK-MB >3 times the 99th percentile of the ULN in patients with normal	From PCI to 30 days	Hyporesponsiveness (PRU>274)	MI+	NR	Sens=0.923 Spec=0.479	NR	NR	NR	NR	Prev. of CKMB>3x and moderate/severe bleeding were reported by clopidogrel response; These were not

				baseline levels (or >3 times in pts with elevated baseline levels)										extracted
	75 mg/d clopidogrel & 100 mg/d aspirin	VerifyNow P2Y12 Assay	Periprocedural MI	Postprocedural ↑ of troponin or CK-MB >3 times the 99th percentile of the ULN in patients with normal baseline levels (or >3 times in pts with elevated baseline levels).	From PCI to 30 days	NR	MI+	NR	NR	NR	NR	NR	NR	AUC=0.680; P=0.024 (Fig2d)
Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	Myocardial infarction	Myocardial infarction	1-year	Full responder	Myocardial infarction	13/289 (4.5)	NR	NR	0.001	NR	NR	
						Poor responder		29/179 (16.2)						
	Clopidogrel LD 300 or 600 mg or maintaining	VerifyNowP2Y12	MI by CK-MB	55 MIs, 6.6% using≥3x ULN of CK-MB definition	0-3 days	Full responder	MI by CK-MB	55	HR=1.19	1.09-1.28	<0.01	NR	NR	

	75mg daily													
	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	MI by CK-MB	55 MIs, 6.6% using≥3x ULN of CK-MB definition	0-3 days	Full responder	MI by CK-MB	NR	HR=1.15	1.05-1.35	0.01	Yes, variables with p-value>0.2	NR	
	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	MI by troponin I/T	114 MIs, 6.6% using≥3x ULN of troponin I/T definition	0-3 days	Full responder	MI by troponin I/T	NR	HR=1.39	1.28-1.5	<0.01	NR	NR	
	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	MI by troponin I/T	114 MIs, 6.6% using≥3x ULN of troponin I/T definition	0-3 days	Full responder	MI by troponin I/T	NR	HR=1.30	1.07-1.56	0.01	Yes, variables with p-value>0.2	NR	
Cuisset, 2008{Cuisset, 2008 168 /id} 18549843 Belgium NR	clopidogrel 600 mg + aspirin 500 mg LD	VerifyNow P2Y12	Periprocedural MI	postprocedural increase in troponin T 3 times the 99th percentile (>0.03 ng/ml).	NR	nonresponder (Quartile 1)	Periprocedural MI	14/32 (44%)	OR=4.6 OR=3.9	1.9-11.5 1.6-8.7	P=0.001 (Q1 vs Q2-4) P<0.01 (Q1 vs Q2-4)	NO YES; For confounding variable (list NR)	NR NR	
						responder (Quartile 2)		4/30 (13%)						
						responder (Quartile 3)		5/30 (17%)						

						responder (Quartile 4)		4/30 (13%)						
Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	Clopidogrel+aspirin	VerifyNow	MI		6 mo	Clopidogrel resistance		1/37 (1%)			NS vs. next row (chi-square statistics or Fisher 's exact test)			
						Normal response		0/73 (0%)						
			periprocedural MI	CK-MK elevation >/=3 times UNL	6 mo	Clopidogrel resistance	YES event	2/37 (5%)	NR	NR	NS vs. next row (chi-square statistics or Fisher 's exact test)	NR	NR	NONE
						Normal response		4/73 (5%)						
			large periprocedural MI	CK-MK elevation >/=10 times UNL		Clopidogrel resistance		1/37 (3%)			NS vs. next row (chi-square statistics or Fisher 's exact test)			
						Normal response		2/73 (3%)						
			cTnI elevation >/=3 times UNL			Clopidogrel resistance		5/37 (14%)			NS vs. next row (chi-square statistics or Fisher 's exact test)			

						Normal response		14/73 (19%)						
			cTnI elevation >/=10 times UNL			Clopidogrel resistance		3/37 (8%)			NS vs. next row (chi-square statistics or Fisher 's exact test)			
						Normal response		7/73 (10%)						
Mangiacapra 2010{Mangiacapra, 2010 83 /id} 20298992 Italy NR	Clopidogrel 300 mg LD, 75 mg MD with aspirin	verifyNow	Periprocedural myocardial infarction	periprocedural myocardial infacrction as per CPK-MB: increases of biomarkers >3x ULN	NR	HPR	periprocedural MI by CK-MB	10/78 (13%)	OR= 3.47	1.27-9.48	p=0.011 (HPR vs no HPR) [logistic regression]	No	NR	Secondary outcome
						No HPR		7/172 (4%)						
	Clopidogrel 300 mg LD, 75 mg MD with aspirin	verifyNow	Periprocedural myocardial infarction	periprocedural myocardial infacrction as per Tropinin I increases of biomarkers >3x ULN	NR	HPR	periprocedural MI by Troponin I	25/78 (32%)	OR= 2.06	1.12-3.80	p=0.019 (HPR vs no HPR) [logistic regression]	No	NR	Secondary outcome
						No HPR		33/172 (19%)						
	Clopidogrel 300 mg LD, 75 mg MD with aspirin	verifyNow	Periprocedural myocardial infarction	periprocedural myocardial infacrction as per CPK-MB: increase	NR	HPR	periprocedural MI by CK-MB	10/78 (13%)	OR= 3.21	1.11-9.32	p=0.032 (HPR vs no HPR) [logistic regression]	YES; multivessel intervention, lesion type B2/C, multivessel disease,	NR	Secondary outcome

				s of biomarkers >3x ULN								diabetes, total stent length, left ventricle ejection fraction <40%		
						No HPR		7/172 (4%)						
	Clopidogrel 300 mg LD, 75 mg MD with aspirin	verifyNow	Periprocedural myocardial infarction	periprocedural myocardial infacrction as per Tropinin I increases of biomarkers >3x ULN	NR	HPR	periprocedural MI by Troponin I	25/78 (32%)	OR= 2.25	1.24-4.13	p=0.019 (HPR vs no HPR) [logistic regression]	YES; multivessel intervention, lesion type B2/C, multivessel disease, diabetes, total stent length, left ventricle ejection fraction <40%	NR	Secondary outcome
						No HPR		33/172 (19%)						
Mangiacapra, 2010{Mangiacapra, 2010 94 /id} 20129566 Belgium NR	clopidogrel 600 mg and aspirin 500 mg	VerifyNow	Periprocedural MI	post-procedural Troponin-T increase more than 3 times the 99th percentile of the upper reference limit	NR	HPR	Periproicedural MI	42 (41.2%)	1.92	1.18-3.13	P=0.008	NO	Bonferroni	
						Normal platelet reactivity		63 (26.7%)						
	clopidogrel 600 mg and aspirin	VerifyNow	Periprocedural MI	post-procedural Troponin	NR	HPR	Periproicedural MI	42 (41.2%)	1.684	1.016-2.789	P=0.043 (high PR vs normal PR) [multivariab	YES; All clinical and procedural	Bonferroni	

	500 mg			-T increase more than 3 times the 99th percentile of the upper reference limit							le logistic regression model]	variables that showed a significant univariate association with periprocedural MI (p<0.05)		
Mangiacapra, 2010{Mangiacapra, 2010 65 /id} 20723634 Italy NR	Clopidogrel 600 mg LD + 75 mg MD + aspirin 100 mg LD & MD	VerifyNow	Periprocedural MI	postprocedural increase in creatine kinase-MB x3 times the 99th percentile of the upper reference limit (with baseline negative myocardial necrosis markers) or subsequent increase ≥50% the baseline value (in patients with increased baseline levels of creatine kinase MB)	NR	HPR	Periprocedural MI	11/77 (14%)	NR	NR	P=0.0008 (P for trend) [chi square test]	NO	NR	Data calculated from Fig 3 and Fig 1
						No HPR		16/208 (7.7%)						

	Clopidogrel 600 mg LD + 75 mg MD + aspirin 100 mg LD & MD	VerifyNow	Periprocedural MI	postprocedural increase in creatine kinase-MB x3 times the 99th percentile of the upper reference limit (with baseline negative myocardial necrosis markers) or subsequent increase ≥50% the baseline value (in patients with increased baseline levels of creatine kinase MB)	NR	HPR	Periprocedural MI	11/77 (14%)	OR=8.34	2.6-26.76	P=0.0003 (HPR vs no HPR) [multivariate logistic regression]	YES; All variables listed in Tables 1 and 2 showing a significant univariate association with periprocedural MI (p<0.05) and HPR	NR	Data calculated from Fig 3 and Fig 1
Marcucci, 2009{Marcucci, 2009 144 /id} 19118249 Italy NR	clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD	VerifyNow	Nonfatal MI	Nonfatal MI **Error! Bookmark not defined.**	12 months	high residual platelet reactivity (PRU≥240)	Nonfatal MI	16 (7.3)	HR=2.73	1.54 – 5.01	P=0.006 (RPR vs no RPR)	NO	NR	
						No residual platelet reactivity (PRU<240)		11 (2.4)						

	clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD	VerifyNow	Nonfatal MI	Nonfatal MI **Error! Bookmark not defined.**	12 months	high residual platelet reactivity (PRU≥240)	Nonfatal MI	16 (7.3)	HR=3.36	1.49 – 7.58	P=0.034 (RPR vs no RPR)	YES; cardiovascular risk factors, renal failure, left ventricular ejection fraction <40%, multivessel disease, total stent length, bifurcation lesions, number of lesions treated, type of stent used, and use of glycoprotein IIb/IIIa inhibitors	NR	
						No residual platelet reactivity (PRU<240)		11 (2.4)						
	clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD	VerifyNow	Nonfatal MI	Nonfatal MI **Error! Bookmark not defined.**	12 months	high residual platelet reactivity (PRU≥235)	Nonfatal MI	NR	HR=2.94	1.37 – 6.34	P=0.006 (RPR vs no RPR)	NO	NR	
						No residual platelet reactivity (PRU<235)		NR						
	clopidogrel 600 mg LD + 75 mg MD & ASA 500	VerifyNow	Nonfatal MI	Nonfatal MI **Error! Bookmark not**	12 months	high residual platelet reactivity (PRU≥235)	Nonfatal MI	NR	HR=3.12	1.38 – 7.02	P=0.006 (RPR vs no RPR)	YES; cardiovascular risk factors, renal failure, left	NR	

	mg IV LD + 100-325 mg MD			**defined.**								ventricular ejection fraction <40%, multivessel disease, total stent length, bifurcation lesions, number of lesions treated, type of stent used, and use of glycoprotein IIb/IIIa inhibitors		
						No residual platelet reactivity (PRU<235)		NR						
Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS)	Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD	VerifyNow	Nonfatal MI	Nonfatal MI23	6 months	High on-treatment reactivity was defined (PRU≥230)	Nonfatal MI	18 (1.6%)	HR=1.93	0.72-5.21	P=0.19 (high vs not high) [log-rank test stratified by acute coronary syndromes status]	NO	NR	Secondary analysis
						Not High On-Treatment Reactivity (PRU<230)		5 (0.9%)						
Price, 2008{Price, 2008 174 /id} 18263931 USA NR	Clopidogrel LD 600 mg and maintaining 75mg daily	VerifyNow P2Y12 assay	Non-fatal MI	Non-fatal MI	6-months	Lower reactivity	Non-fatal MI	2/209 (1.0)	NR	NR	0.6 comparing with the following row	NR	NR	

						High reactivity		2/108 (1.9)						
						Total		4/317 (1.3)						
	Clopidogrel LD 600 mg and maintaining 75mg daily	VerifyNow P2Y12 assay	Non-fatal MI	Non-fatal MI	6-months follow-up with a minimal of 3 months post-procedure	Lower reactivity	Non-fatal MI	2/252 (0.8)	NR	NR	0.6 comparing with the following row	NR	NR	
						High reactivity		2/121 (1.7)						
						Total		4/373 (1.1)						
Valgimigli , 2009{Valgimigli, 2009 244 /id} 19528337 10 sites in Europe (Italy, Belgium, France, Spain) Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study	Clopidogrel	VerifyNow	periprocedural MI	elevation of troponin I/T ratio >/=3xULN	48 hr after PCI	Clopidogrel nonresponders, 21% to <40% inhibition		NR	NR	NR	0.35 for interaction between tirofiban or placebo for this and next row	NR	NR	Risk ratios and CIs are in Fig. 4 (all are <1)
						Clopidogrel nonresponders, <21% inhibition		NR	NR	NR	0.78 for interaction between tirofiban and	NR	NR	Risk ratios and CIs are in Fig. 4 (all

											placebo and clopidogrel vs. aspirin nonresponder			are <1)
						Dual (clopidogrel and aspirin) nonresponders		NR	NR	NR	NR	NR	NR	Risk ratios and CIs are in Fig. 4 (all are <1)
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	VerifyNow	MI	MI	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual PR	MI	12/168	NR	NR	0.0033comparing with NPR(normal on-treatment platelet reactivity)	NR	NR	
Saw, 2008{Saw, 2008 242 /id} 19463380 Canada BRIEF-PCI	Clopidogrel LD 600 mg and maintaining 75mg daily	VerifyNow P2Y12	MI	Tr-I > 3x ULN with normal baseline Tr-I	30 day	Low-responder (n=51)	30-day death, MI, urgent TVR	12 (24%)	NR	NR	0.433 (low vs normal responder) [Fisher's exact]	NR	NR	
						Responder (n=147)		43 (29.3%)	NR					
			MI	CK-MB > 3x ULN with high baseline Tr-I	30 day	Low-responder (n=51)	30-day death, MI, urgent TVR	2 (3.9%)	NR	NR	0.467 (low vs normal responder) [Fisher's exact]	NR	NR	
						Responder (n=147)		3 (2%)	NR					

Appendix Table E31: Results from studies assessing the ability of VerifyNow to predict stent thrombosis in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	VerifyNow P2Y12	Stent thrombosis	Stent thrombosis	1-year	High OTPR	Stent thrombosis	8/406 (2.0)	OR=2.58	0.84-7.93	<0.09	No	NR	
						Normal OTPR		5/646 (0.8)						
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	VerifyNow P2Y12 (PRU)	stent thrombosis	stent thrombosis	6 months	<240	stent thrombosis	1.0%	OR=2.92	0.98-8.7	0.044	NR	NR	
						≥240		2.8%						
Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNow P2Y12	Definite ST	Definite ST	1-year	Full responder	Definite ST	2/289 (0.6)	NR	NR	0.3	NR	NR	
						Poor responder		3/179 (1.7)						

	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	Verify Now P2Y12	Definite/probable ST	Definite/probable ST	1-year	Full responder	Definite/probable ST	3/289 (1)	NR	NR	0.1	NR	NR	
						Poor responder		5/179 (2.8)						
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	Clopidogrel + aspirin	Verify Now	Stent thrombosis			Poor response at baseline (N=107)		2	OR (calculate)= 1.82	NR	P=0.62 (poor response vs full response) [Fisher's exact test]			
						Full response at baseline (n=193)		2						
	Clopidogrel + aspirin	Verify Now	Stent thrombosis	xx		Poor response at 1 mo (n=40)		3	OR (calculate)= 21	NR	P=0.008 (poor response vs full response) [Fisher's exact test]			
						Full response at 1 mo (n=260)		1						

Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	Clopidogrel+aspirin	Verify Now	Stent thrombosis		6 mo	Clopidogrel resistance		1/37 (3%)			NS vs. next row (chi-square statistics or Fisher 's exact test)			
						Normal response		1/73 (1%)						
Lee, 2009{Lee, 2009 230 /id} 20049136 South Korea NR	600 mg clopidogrel + 300 mg aspirinLD & in pts with DES, 100 mg aspirin +75 mg clopidogrel	Verify Now	Definitie stent thrombosis	in-stent thrombosis on coronary angiography	6 mo after stenting	Normal response	YES event	0 (0%)	NR	NR	0.014 vs. next row (chi-square or Fisher's exact)	NR	NR	NONE
						Low response		4 (4.2%)						

			Probable stent thrombosis	MI confirmed around the area of stent insertion or in cases in which death due to an unknown cause occurred within 30 days post-PCI		Normal response		0 (0%)						
						Low response		0 (0%)						
			Possible stent thrombosis	idiopathic sudden death within 30 days post-PCI		Normal response		0 (0%)						
						Low response		0 (0%)						
			Acute stent thrombosis		within 24 hours after stenting	Normal response		0 (0%)						
						Low response		1 (1.0%)						
			Subacute stent thrombosis		Within 1 day after stenting	Normal response		0 (0%)						
						Low response		1 (1.0%)						
			Late stent thrombosis		Within 1 mo after stenting	Normal response		0 (0%)						
						Low response		2 (2.1%)						

Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS)	Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD	Verify Now	Stent thrombosis	Stent thrombosis	6 months	High on-treatment reactivity was defined (PRU≥230)	Stent thrombosis	8 (0.7%)	HR=2.16	0.46-10.19	P=0.31 (high vs not high) [log-rank test stratified by acute coronary syndromes status]	NO	NR	Secondary analysis
						Not High On-Treatment Reactivity (PRU<230)		2 (0.3%)						
Price, 2008{Price, 2008 174 /id} 18263931 USA NR	Clopidogrel LD 600 mg and maintaining 75mg daily	Verify Now P2Y12 assay	Stent thrombosis	Stent thrombosis	6-months	Lower reactivity	Stent thrombosis	0/209	NR	NR	0.004 comparing with the following row	NR	NR	
						High reactivity		5/108 (4.6)						
						Total		5/317 (1.6)						
	Clopidogrel LD 600 mg and maintaining 75mg daily	Verify Now P2Y12 assay	Stent thrombosis	Stent thrombosis	6-months follow-up with a minimal of 3 months post-procedure	Lower reactivity	Stent thrombosis	0/252	NR	NR	0.004 comparing with the following row	NR	NR	
						High reactivity		5/121 (4.1)						

						Total		5/373 (1.3)						
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	Verify Now	ST	ST	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	ST	2/168	OR (calculate)= 3.53	NR	P=0.3 (HCPR(high on-clopidogrel platelet reactivity) or dual HPR vsLow CPR+ or low PR) [Fisher's exact test]	NR	NR	
						Low CPR + normal PR		1/280						

Appendix Table E32: Results from studies assessing the ability of VerifyNow to predict major adverse cardiovascular events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	300 mg or 600 mg LD Clopidogrel and maintaining 75 mg+ Aspirin	VerifyNow	MACE	MI+revascularization+cardiovascular admissions	1 year	PRU<240 (n=19)	MACE	0	NR	NR	P<0.02 (high PRU vs low PRU) [Fisher's exact]	NR	NR	
						PRU>240 (n=29)		5						
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	VerifyNow P2Y12	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR >236 PRU (n=406)	Death combined	54 (13.3)	OR=2.53	1.63-3.91	<0.001 (high OTPR vs low OTPR) [Fisher's exact]	No	NR	
						Normal OTPR ≤236 PRU (n=646)		37 (5.7)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	VerifyNow P2Y12	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR >236 PRU (n=406)	Death combined	54(406) (13.3)	AUC: 0.62 Sens: 0.604 Spec: 0.631	0.57-0.67 0.502-0.699 0.6-0.661	NR	No	NR	
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	VerifyNow P2Y12 (PRU)	composite	composite	6 months	<240 (n=512)	composite	1.7%	OR=2.82	1.23-6.48	0.011	NR	NR	
						≥240 (n=546)		4.6%						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	75 mg/d clopidogrel & 100 mg/d aspirin	VerifyNow P2Y12 Assay	Major adverse cardiovascular events (MACE)	Death, MI, stroke, and target vessel revascularization	30 days	Hyporesponsiveness (PRU>274) (n=121)	MACE+	NR	OR=5.95	1.26-28.1)	P=0.024 between hyporesponsive vs normal responsive	YES; All Only variables with p <0.15 were entered into final model; final list is NR; only reported variables include: total stent length, hyporesponsiveness to clopidogrel, and no previous use of statin	NR	
	75 mg/d clopidogrel & 100 mg/d aspirin	VerifyNow P2Y12 Assay	Major adverse cardiovascular events (MACE)	Death, MI, stroke, and target vessel revascularization	From PCI to 30 days	Hyporesponsiveness (PRU>274) (n=101)	MACE +	NR	Sens=0.833 Spec=0.481	NR	NR	NR	NR	NR
	75 mg/d clopidogrel & 100 mg/d aspirin	VerifyNow P2Y12 Assay	Major adverse cardiovascular events (MACE)	Death, MI, stroke, and target vessel revascularization	From PCI to 30 days	NR	MACE +	NR	NR	NR	NR	NR	NR	NR	AUC=0.649; P=0.032 (Fig 2b)

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	Composite primary end point	death, MI, and stroke	1-year	Full responder (n=289)	Composite primary end point	17 (5.9)	HR=1.20	1.1-1.3	<0.01	NR	NR	
						Poor responder (n=179)		31 (17.3)						
	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	Composite primary end point	death, MI, and stroke	1-year	Full responder (n=289)	death, MI, and stroke	17 (5.9)	HR=1.3	1.07-1.56	0.01	Yes, variables with p-value>0.2	NR	
						Poor responder (n=179)		31 (17.3)						
	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	Composite primary end point	death, MI, and stroke	0-3 days	Full responder (n=289)	death, MI, and stroke	8 (2.8)	NR	NR	0.004	NR	NR	
						Poor responder (n=179)		20 (11.1)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	Composite primary end point	death, MI, and stroke	3-365 days	Full responder (n=289)	death, MI, and stroke	11 (3.8)	HR=1.15	1.05-1.29	0.01	NR	NR	
						Poor responder (n=179)		17 (9.5)						
	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	Composite primary end point	death, MI, and stroke	3-365 days	Full responder (n=289)	death, MI, and stroke		HR=1.12	1.06-1.25	0.03	Yes, variables with p-value>0.2	NR	
						Poor responder (n=179)								

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	Clopidogrel + aspirin	VerifyNow	Death, MI, or stroke			Poor response at baseline (N=107)		14	HR 3.1	1.3-7.3	Table 3 gives <0.01 but text gives 0.02 vs. next row (t-test)			May be HR not for composite endpoint but rather any AE? Text unclear
						Full response at baseline (n=193)		7						
	Clopidogrel + aspirin	VerifyNow	Death, MI, or stroke			Poor response at 1 mo (n=40)		17	HR 28.5	8-104	<0.01 vs. next row (t-test)			
						Full response at 1 mo (n=260)		4						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel + aspirin	VerifyNow	Death, MI, or stroke			Full response at baseline but poor response at 1 mo (n=8)					<0.01vs. next row (1-way ANOVA)			Kaplan-Meier curves given in Fig 3
						Poor response at baseline and at 1 mo (n=32)								
						Poor response at baseline but full response at 1 mo (n=75)								
						Full response at baseline but poor response at 1 mo (n=185)								

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel + aspirin	VerifyNow	Death, MI, or stroke			Enhanced response (PRU ≤85) at 1 mo (n=75)		1						This and rest of data in table from Fig 5
						Normal response (PRU 86-238) at 1 mo (N=185)		3						
						Poor response (PRU ≥239) at 1 mo (n=40)		17						
	Clopidogrel + aspirin	VerifyNow	Ischemic endpoints (details NR)						Difference in AUC for 1 mo vs baseline, 0.21	0.05-0.33	<0.01			
					Baseline	>/=214 PRU cutoff			AUC 0.69	0.63-0.74				
									Sensitivity 78%, specificity 63%, PPV 14%, NPV 97%					

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
					1 mo	>/=239 PRU cutoff			AUC 0.87	0.63-0.74				
									Sensitivity 81%, specificity 92%, PPV 43%, NPV 98%					
de_Miguel_Castro, 2009{de Miguel, 2009 136 /id} 19232185 Spain NR	clopidogrel 300 mg LD + 75 mg/d MD w/ aspirin250 mg LD + 100 mg MD	VerifyNow	MACE	Death from any cause, nonfatal acute myocardial infarction, new revascularization (CABG or PCI) after readmission for NSTEACS, and ischemic stroke	1 year	PRU>175	MACE	13 (20%)	Sensitivity 0.75 Specificity 0.64	NR	NR	NR	NR	
						PRU≤175		5 (5%)						
	clopidogrel 300 mg LD + 75 mg/d MD w/ aspirin250 mg LD + 100 mg MD	VerifyNow	MACE	Death from any cause, nonfatal acute myocardial infarction, new revascularization (CABG or PCI) after readmission for NSTEACS, and ischemic stroke	1 year	PRU>175	MACE	13 (20%)			P=0.0013 (Between PRU>175 and PRU ≤175) [Event free survival by kaplan meir method and Log rank test]	NR	NR	
						PRU≤175		5 (5%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel 300 mg LD + 75 mg/d MD w/ aspirin250 mg LD + 100 mg MD	VerifyNow	MACE	Death from any cause, nonfatal acute myocardial infarction, new revascularization (CABG or PCI) after readmission for NSTEACS, and ischemic stroke	1 year	PRU>175	MACE	13 (20%)	OR=3.9	1.2-15.4	P=0.024 (Between PRU>175 and PRU ≤175) [logistic regression]	Yes; not listed - All variables (demographic, clinical, and angiographic) that had shown an association with PPR, percentage of IPA, or MACE with a probability value of P≤.20 in the univariate models	NR	
	clopidogrel 300 mg LD + 75 mg/d MD w/ aspirin250 mg LD + 100 mg MD	VerifyNow	MACE	Death from any cause, nonfatal acute myocardial infarction, new revascularization (CABG or PCI) after readmission for NSTEACS, and ischemic stroke	1 year	Quartile 1 (<115 PRU)	MACE	1 (2.7%)			P=0.009 (Between quartiles) [Chi square or Fishers exact test]	NO	NR	
						Quartile 2 (115 -164 PRU)		3 (7.9%)						
						Quartile 3 (165 -206 PRU)		4 (10.5%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Quartile 4 (>206 PRU)		9 (21.6%)						
Huczek, 2011{Huczek, 2011 239 /id} 21443410 Poland NR	Clopidogrel 600mg LD and 75mg MD Aspirin: 300 mg LD & 75 mg MD	VerifyNow P2Y12 assay	Composite ischemic end point	CV death (defined as death from cardiac causes or stroke) and non-fatal myocardial infarction (defined as rise in CK-MB of at least twice the upper limit of normal with either ischemic symptoms or typical ECG changes);	30 days	Low PR	Ischemic events	7 (Non-fatal MI:4 Cardiovascular death:3Early stent thrombosis[16]: 2)	Ref group vs high	Ref group vs high	Ref group vs high			
						Medium PR	Ischemic events	2 (Non-fatal MI:1 Cardiovascular death:1 Early stent thrombosis[16]: 0)	Ref group vs high	Ref group vs high	Ref group vs high			

[16] Each case of stent thrombosis resulted in MI

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						High PR	Ischemic events	17 (Non-fatal MI:8 Cardiovascular death:9 Early stent thrombosis16: 5)	7.26 1.51	1.67-31.6 0.96-2.36	0.008 (High vs medium) 0.074 (High vs Low)	YES female sex, BMI, diabetes, ejection fraction	NR	Kaplan–Meier time-to-event curves in Fig 4
	Clopidogrel 600mg LD and 75mg MD Aspirin: 300 mg LD & 75 mg MD	VerifyNow P2Y12 assay	Composite ischemic end point	CV death (defined as death from cardiac causes or stroke) and non-fatal myocardial infarction (defined as rise in CK-MB of at least twice the upper limit of normal with either ischemic symptoms or typical ECG changes);	30 days	PRU ≥225	Ischemic events	NR	Sensitivity: 61.5% specificity: 77% Area under the curve (AUC): 0.64	sensitivity of (40.6-79.8) specificity (72.3-81.3) 0.59 – 0.69	P=0.038	NR	NR	ROC curve Fig 5

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel 600mg LD and 75mg MD Aspirin: 300 mg LD & 75 mg MD	VerifyNow P2Y12 assay	Combined end point of ischemic events and bleeding	CV death (defined as death from cardiac causes or stroke) and non-fatal myocardial infarction (defined as rise in CK-MB of at least twice the upper limit of normal with either ischemic symptoms or typical ECG changes);	30 days	Low PR	Ischemic events + bleeding	20	Ref group vs medium	Ref group vs medium	Ref group vs medium			
						Medium PR	Ischemic events	6	0.3 0.31	0.12-0.75 0.12-0.77	0.01 (Medium vs low) 0.012 (Medium vs High)	YES female sex, BMI, diabetes, ejection fraction	NR	Kaplan–Meier time-to-event curves in Fig 6
						High PR	Ischemic events	19	Ref group vs medium	Ref group vs medium	Ref group vs medium			

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel 600mg LD and 75mg MD Aspirin: 300 mg LD & 75 mg MD	VerifyNow P2Y12 assay	Composite ischemic end point	CV death (defined as death from cardiac causes or stroke) and non-fatal myocardial infarction (defined as rise in CK-MB of at least twice the upper limit of normal with either ischemic symptoms or typical ECG changes);	30 days	Medium PR defined with a different range than before (≥161 to <225 PRU)	Ischemic events + bleeding	NR	0.14 0.42	0.05-0.4 0.24-0.73	0.0003 (Medium vs low) 0.002 (Medium vs High)	YES female sex, BMI, diabetes, ejection fraction	NR	Kaplan–Meier time-to-event curves in Fig 6

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	Clopidogrel+aspirin	VerifyNow	Cardiac death, MI, target-lesion revascularization, or cerebrovascular accident		6 mo	Clopidogrel resistance		4/37 (11%)			NS vs. next row (chi-square statistics or Fisher 's exact test)			
						Normal response		2/73 (3%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Lee, 2009{Lee, 2009 230 /id} 20049136 South Korea NR	600 mg clopidogrel + 300 mg aspirinLD & in pts with DES, 100 mg aspirin +75 mg clopidogrel	VerifyNow	Any stent thrombosis or cardiac death		6 months	Normal response		1 (0.7%)			0.012 vs. next row (chi-square or Fisher's exact)			
						Low response		6 (6.3%)	vs previous row: OR (also stated as relative risk), 12.074 (multivariate logistic regression) Relative risk, 9.646 (univariate logistic regression)	1.205-120.992 for mutivariate OR 1.139-81.679 for univariate RR	0.034 for multivariate OR 0.038 for univariate RR	YES age and sex for OR/RR		

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Marcucci, 2009{Marcucci, 2009 144 /id} 19118249 Italy NR	clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD	VerifyNow	MACE	Cardiovascular death and nonfatal MI	12 months	high residual platelet reactivity (PRU≥240)	MACE	27 (12.3)	HR=2.52	1.30 – 5.13	P=0.011 (RPR vs no RPR)	NO	NR	
						No residual platelet reactivity (PRU<240)		17 (3.6)						
	clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD	VerifyNow	MACE	Cardiovascular death and nonfatal MI	12 months	high residual platelet reactivity (PRU≥240)	MACE	27 (12.3)	Sens: 0.61 Spec: 0.7 AUC 0.66	0.47-0.758 0.664-0.735 0.57-0.78	P<0.001	NO	NR	
						No residual platelet reactivity (PRU<240)		17 (3.6)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD	VerifyNow	MACE	Cardiovascular death and nonfatal MI**Error! Bookmark not defined.**	12 months	Quartile 1 ≤129	MACE	NR	HR=1.1 HR=1.6 HR=3.6	0.4-3.4 0.6-4.5 1.5-9.1	P>0.05 (Quartile II vs 1) P>0.05 (Quartile III vs 1) P<0.05 (Quartile IV vs 1)	NO	NR	
						Quartile 2 130-195		NR						
						Quartile 3 196-257		NR						
						Quartile 4 ≥258		NR						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Patti, 2008{Patti, 2011 22 /id} 18804738 Italy ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome)	Clopidogrel 75 mg/day	VerifyNow P2Y12	major adverse cardiac events (MACE)	Cardiac death, myocardial infarction (MI)17, target vessel revascularization 18	30 days	1st quartile	MACE+	1 (3 %)	Ref group	Ref Group	Ref group	NO	NR	
						2nd quartile	MACE+	2 (5%)	NR	NR	NR	NR	NR	
						3rd quartile	MACE+	4 (10%)	NR	NR	NR	NR	NR	

[17] Myocardial infarction was defined as post-procedural increase of cardiac biomarkers (Tn or CK-MB) >3 x 99th percentile of the upper reference limit
[18] Target vessel revascularization included by-pass surgery or repeat PCI of the target vessel(s).

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						4th quartile	MACE+	8 (20%)	OR=12.67 (4th vs. 1st)[19]	1.49-107.7	P=0.034 (between 4th and 1st quartile); Fisher's exact/Chi square	NO	NR	
					6 months	1st quartile	MACE+	4 (10%)	Ref group	Ref Group	Ref group	NO	NR	
						2nd quartile	MACE+	5 (13%)	NR	NR	NR	NR	NR	
						3rd quartile	MACE+	7 (17%)	NR	NR	NR	NR	NR	
						4th quartile	MACE+	12 (30%)	OR=6 (4th vs. 1st)[20]	1.67-21.6	P=0.05 (between 4th and 1st quartile); Fisher's exact/Chi square	NO	NR	
					30 days	1st quartile	MACE+	1 (3 %)	Ref group	Ref Group	Ref group	YES	NR	
						2nd quartile	MACE+	2 (5%)			P=0.71(between 1st and 2nd quartile); Logistic regression	YES		

[19] Calculated; P value only reported for 1st vs 4th
[20] Calculated; P value only reported for 1st vs 4th

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						3rd quartile	MACE+	4 (10%)			P=0.68 (between 1st and 3rd quartile); Logistic regression	YES		
						4th quartile	MACE+	8 (20%)	OR=6.1 (4th vs. 1st)	1.1-18.3	P=0.033 (between 4th and 1st quartile); Logistic regression	YES; All Only variables with p <0.15 were entered into final model; final list is NR; only reported variables include: Age >70 years, left ventricular dysfunction, and use of glycoprotein IIb/IIIa inhibitors, statin therapy		

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel 75 mg/day	VerifyNow P2Y12	major adverse cardiac events (MACE)	Cardiac death, myocardial infarction (MI)21, target vessel revascularization 22	30 days	PRU≥ 240 units	MACE+	NR	Sens=0.81; spec=0.53	NR	NR	NR	NR	AUC= 0.69 (95% CI: 0.56 to 0.81; p= 0.016)

[21] Myocardial infarction was defined as post-procedural increase of cardiac biomarkers (Tn or CK-MB) >3 x 99th percentile of the upper reference limit
[22] Target vessel revascularization included by-pass surgery or repeat PCI of the target vessel(s).

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS)	Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD	VerifyNow	MACE	Death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis[23]	6 months	High on-treatment reactivity was defined (PRU≥230) n=586	MACE	25 (2.3%)	HR=1.68	0.76-3.72	P=0.20 (high vs not high) [log-rank test stratified by acute coronary syndromes status]	NO	NR	Secondary analysis
						Not High On-Treatment Reactivity (PRU<230) n=1109		8 (1.4%)						

[23] All deaths were considered cardiovascular unless an unequivocal noncardiovascular cause could be established; hemorrhagic deaths were also considered to be cardiovascular. Myocardial infarction followed the American College of Cardiology definition. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium definitions.

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD	VerifyNow	MACE	Death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis23	30 days	High on-treatment reactivity was defined (PRU≥230) n=586	MACE	17 (1.6%)	HR=2.27	0.76-6.74	P=0.13 (high vs not high) [log-rank test stratified by acute coronary syndromes status]	NO	NR	Landmark analysis
						Not High On-Treatment Reactivity (PRU<230) n=1109		4 (0.7%)						
Price, 2008{Price, 2008 174 /id} 18263931 USA NR	Clopidogrel LD 600 mg and maintaining 75mg daily	VerifyNow P2Y12 assay	CV death, non-fatal MI, Stent thrombosis	CV death, non-fatal MI, Stent thrombosis	6-months	Lower reactivity	CV death, non-fatal MI, Stent thrombosis	2/209 (1)	NR	NR	0.008 comparing with the following row	NR	NR	
						High reactivity		7/108 (6.5)						
						Total		9/317 (2.8)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel LD 600 mg and maintaining 75mg daily	VerifyNow P2Y12 assay	CV death, non-fatal MI, Stent thrombosis	CV death, non-fatal MI, Stent thrombosis	6-months follow-up with a minimal of 3 months post-procedure	Lower reactivity	CV death, non-fatal MI, Stent thrombosis	2/252 (2)	NR	NR	0.008 comparing with the following row	NR	NR	
						High reactivity		7/121 (5.8)						
						Total		9/373 (2.4)						
Saw, 2008{Saw, 2008 242 /id} 19463380 Canada BRIEF-PCI	Clopidogrel LD 600 mg and maintaining 75mg daily	VerifyNow P2Y12	30-day death, MI, urgent TVR	30-day death, MI, urgent TVR	30 day	Low-responder (n=51)	30-day death, MI, urgent TVR	1 (2%)	NR	NR	0.766 (low vs normal responder) [Fisher's exact]	NR	NR	
						Responder (n=147)		4 (2.7%)	NR					

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Vavuranakis, 2011{Vavuranakis, 2011 245 /id} 21712606 Greece NR	300-600 mg LD + 75 mg MD; Aspirin 325 mg X 7 days then 100 mg MD	VerifyNow P2Y12	MACE	death; myocardial infarction; stroke	Mean followup: 203±152	NR	MACE	4 (death: 2; myocardial infarction: 2; stroke: 0)	NR	NR	NR [Cox regression (stepwise backward conditional method)]	NR	NR	"Multivariate analysis did not revealed any significant relationship between PRU and MACE."
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	VerifyNow	Death, MI, ST, stroke	Death, MI, ST, stroke	1 year	HCPR(high on-clopidogrel platelet reactivity or dual HPR) N=168	Death, MI, ST, stroke	21	OR (calculate) = 3.16	NR	P=0.003 (HCPR or Dual HPR vs NPR) [Fisher's exact]	NR	NR	

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						NPR(normal on-clopidogrel platelet reactivity or only high aspirin PR) N=254		11						
Suh, 2011{Suh, 2011 33 /id} 21232664 Korea CILON-T	Aspirin (100 mg daily) and clopidogrel (75 mg daily	VeryfyNow	primary end point	composite of cardiac death, non fatoal MI, ischemic stroke and TLR	6 months	PRU 0-184	primary end point	NR	NR	NR	0.077	NR	NR	figure 4A showed bar graphs
						PRU 185-264								
						PRU 265-438								
	Aspirin (100 mg daily) and clopidogrel (75 mg daily	VeryfyNow	atherothrombotic complications	composite of cardiac death, non fatoal MI, ischemic stroke	6 months	PRU 0-184	atherothrombotic complications	0%	NR	NR	0.037	NR	NR	figure 4A showed bar graphs
						PRU 185-264		2%						
						PRU 265-438		2.9%						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Aspirin (100 mg daily) and clopidogrel (75 mg daily	VeryfyNow	target lesion revascularization	composite of cardiac death, non fatoal MI, ischemic stroke	6 months	PRU 0-184	target lesion revascularization	NR	NR	NR	0.486	NR	NR	figure 4A showed bar graphs
						PRU 185-264								
						PRU 265-438								
	Aspirin (100 mg daily) and clopidogrel (75 mg daily	VeryfyNow	composite clinical outcomes	composite of cardiac death, non fatoal MI, ischemic stroke	6 months	high PRU level (every increase of tertile)	composite clinical outcomes	NR	HR=1.42	1.04-1.93	NR	NR	NR	

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Aspirin (100 mg daily) and clopidogrel (75 mg daily	VeryfyNow	composite clinical outcomes	composite of cardiac death, non fatoal MI, ischemic stroke	6 months	high PRU level (every increase of tertile)	composite clinical outcomes	NR	HR=1.61	1.16-2.25	NR	yes (age, sex, Diabetes, HTN, hypercholesterolemia, previous MI, cnilical diagnosis, lesion length, reference vessel diameter, multivessel intervention, type of DES, the use of cilostazol, PRU level at discharge)	NR	

Appendix Table E33: Results from studies assessing the ability of VerifyNow to predict stroke in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	VerifyNow P2Y12	stroke	Stroke	1-year	High OTPR	Stroke	7/406 (1.7)	OR=1.87	0.62-5.61	<0.26	No	NR	
						Normal OTPR		6/646 (0.9)						
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	VerifyNow P2Y12 (PRU)	ischemic stroke	ischemic stroke	6 months	<240	ischemic stroke	0%	OR=1.0	0.99-1.01	0.524	NR	NR	
						≥240		0.3%						
Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	Stroke	Stroke	1-year	Full responder	Stroke	0/289 (0)	NR	NR	0.2	NR	NR	
						Poor responder		2/179 (1.1)						

Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	Clopidogrel+aspirin	VerifyNow	Cerebrovascular accident		6 months	Clopidogrel resistance		1/37 (1%)			NS vs. next row (chi-square statistics or Fisher's exact test)			
						Normal response		0/73 (0%)						
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Clopidogrel LD 300 or 600mg or maintaining 75 mg daily	VerifyNow	Stroke	Stroke	1 year	HCPR(high on-clopidogrel platelet reactivity) or dual HPR	Stroke	3/168	NR	NR	NR	NR	NR	

Appendix Table E34: Results from studies assessing the ability of VerifyNow to predict bleeding events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Kim, 2010{Kim, 2010 241 /id}20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	PRU≥240	TIMI bleeding	TIMI bleeding (major, minor)	6 months	HPPR-PRU≥240 (n=546)	TIMI bleeding	5.6% (major 3.7%, minor 1.9%)	NR	NR	0.628 (HPPR vs no HPPR) [chi-square test]	NR	NR	
						no HPPR (n=512)		5.1% (major 1.7%, minor 3.4%)						
Campo, 2010{Campo, 2010 58 /id}20951320 10 sites in Italy, Belgium, France, Sprain 3T/2R trial	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	TIMI major bleeding	TIMI major bleeding	1-year	Full responder (n=289)	TIMI major bleeding	2 (0.6)	NR	NR	0.8 (full vs poor responder) [chi-square test]	NR	NR	
						Poor responder (n=179)		1 (0.5)						
	Clopidogrel LD 300 or 600 mg or maintaining 75mg daily	VerifyNowP2Y12	TIMI minor bleeding	TIMI minor bleeding	1-year	Full responder (n=289)	TIMI minor bleeding	9 (3.1)	NR	NR	0.4 (full vs poor responder) [chi-square test]	NR	NR	

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Poor responder (n=179)		4 (2.2)						
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	Clopidogrel + aspirin	VerifyNow	Major or minor TIMI bleeding		1 year	Poor response at baseline (N=107)		6			0.8 (poor vs fuill responders) [Fisher's exact]			
						Full response at baseline (n=193)		13						
	Clopidogrel + aspirin	VerifyNow	Superficial bleeding according to BleedScore			Poor response at baseline (N=107)		9	OR (calculated)= 0.75		P= 0.495 (poor vs full responder) [Fisher's exact]			
						Full response at baseline (n=193)		21						
	Clopidogrel + aspirin	VerifyNow	Internal or alarming bleeding according to BleedScore	intracranial, needing transfusion, melema, hematuria, hematemesis, or epistaxis		Poor response at baseline (N=107)		8			0.3 (poor vs full responder) [Fisher's exact]			
						Full response at baseline (n=193)		18						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel + aspirin	VerifyNow	Major or minor TIMI bleeding			Poor response at 1 mo (n=40)		1			0.5 (poor vs full responder) [Fisher's exact]			
						Full response at 1 mo (n=260)		18						
	Clopidogrel + aspirin	VerifyNow	Superficial bleeding according to BleedScore			Poor response at 1 mo (n=40)		3			NR			
						Full response at 1 mo (n=260)		27						
	Clopidogrel + aspirin	VerifyNow	Internal or alarming bleeding according to BleedScore	intracranial, needing transfusion, melema, hematuria, hematemesis, or epistaxis		Poor response at 1 mo (n=40)		1			0.2 (poor vs full responder) [Fisher's exact]			
						Full response at 1 mo (n=260)		25						
	Clopidogrel + aspirin	VerifyNow	Bleeding			Enhanced response (PRU ≤85) at 1 mo (n=75)		15			?			

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Normal response (PRU 86-238) at 1 mo (N=185)		3						
						Poor response (PRU ≥239) at 1 mo (n=40)		1						
	Clopidogrel + aspirin	VerifyNow	Bleeding endpoints (details NR)						Difference in AUC for 1 mo vs baseline, 0.2	0.1-0.3	<0.01			
					Baseline	</=95 PRU cutoff (n=NR)			AUC 0.63	0.58-0.69				
									Sensitivity 46%, specificity 85%, PPV 17%, NPV 96%					
					1 mo	</=85 PRU cutoff (n=NR)			AUC 0.84	0.79-0.88				
									Sensitivity 81%, specificity 80%, PPV 21%, NPV 98%					

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Huczek, 2011{Huczek, 2011 239 /id} 21443410 Poland NR	Clopidogrel 600mg LD and 75mg MD Aspirin: 300 mg LD & 75 mg MD	VerifyNow P2Y12 assay	Bleeding events	Bleeding defined as the occurrence of either TIMI major or TIMI minor bleeding	30 days	Low PR (n=124)	Bleeding	18	3.5 2.78	1.3-9.42 1.5-5.15	0.014 (Low vs medium) 0.001 (Low vs High) []	YES female sex, BMI, diabetes, ejection fraction	NR	Kaplan–Meier time-to-event curves in Fig 2
						Medium PR (n=124)	Bleeding	5	Ref group vs low	Ref group vs low	Ref group vs low			
						High PR (n=126)	Bleeding	3	Ref group vs low	Ref group vs low	Ref group vs low			
	Clopidogrel 600mg LD and 75mg MD Aspirin: 300 mg LD & 75 mg MD	VerifyNow P2Y12 assay	Bleeding events	Bleeding defined as the occurrence of either TIMI major or TIMI minor bleeding	30 days	PRU ≤161 (n=NR)	Bleeding	NR	Sensitivity: 88.5% specificity: 65.8% Area under the curve (AUC): 0.77	sensitivity of (69.8 – 97.6) specificity (60.6 – 70.8) 0.72 – 0.81	P<0.0001	NR	NR	ROC curve Fig 3

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Mangiacapra 2010{Mangiacapra, 2010 83 /id} 20298992 Italy NR	Clopidogrel 300 mg LD, 75 mg MD with aspirin	verifyNow	major bleeding	NR	NR	HPR (n=78)	major bleeding	0 (0%)	NR	NR	NR	NO	NR	Secondary outcome
						No HPR (n=172)		0 (0%)						
Patti 2011{Patti, 2011 22 /id} 21256470 Italy Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)–Bleeding Study (ARMYDA-BLEEDS)	Clopidogrel + aspirin	VerifyNow	30-day incidence of major TIMI bleeding			PRU</=189 (high inhibition) (n=NR)		11.6%	AUC 0.76 Sensitivity 87% Specificity 70%	For AUC, 0.66-0.87	For AUC, P=0.001 For incidence, <0.001 vs. next row	NR	NR	
						PRU>189 (low inhibition) (n=NR)		1.9%	NR	NR	NR	NR	NR	
			30-day incidence of minor TIMI bleeding			PRU</=189 (high inhibition) (n=NR)		13.7%	NR	NR	<0.001 (high vs low inhibition) []	NR	NR	
						PRU>189 (low inhibition) (n=NR)		5.1%	NR	NR	NR	NR	NR	

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS)	Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD	VerifyNow	Severe or moderate bleeding	As per Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definition	6 months	High on-treatment reactivity was defined (PRU≥230) (n= 1092)	Severe or moderate bleeding	25 (2.3%)	HR=0.51	0.22-1.19	P=0.12 (high vs not high) [log-rank test stratified by acute coronary syndromes status]	NO	NR	Secondary analysis
						Not High On-Treatment Reactivity (PRU<230) (n=586)		7 (1.2%)						
	Clopidogrel 75 mg/d MD+ Aspirin 75-162 mg/d MD	VerifyNow	Any bleeding	As per Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definition	6 months	High on-treatment reactivity was defined (PRU≥230) (n=1105)	Any bleeding	113/1105 (10.2%)	HR=1.02	0.75-1.39	P=0.87 (high vs not high) [log-rank test stratified by acute coronary syndromes status]	NO	NR	Secondary analysis
						Not High On-Treatment Reactivity (PRU<230) (n=586)		62/586 (10.6%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Saw, 2008{Saw, 2008 242 /id} 19463380 Canada BRIEF-PCI	Clopidogrel 300 or 600 mg LD and maintaining 75 mg daily	VerifyNow P2Y12	Major bleeding	REPLACE-2 major bleeding	30 day	Low-responder (n=51)	Major bleeding	2 (3.9%)	NR	NR	0.667 (low vs normal responder) [chi square]	NR	NR	
						responder (n=147)		4 (2.7)	NR					
	Clopidogrel 300 or 600 mg LD and maintaining 75 mg daily	VerifyNow P2Y12	Minor bleeding	REPLACE-2 minor bleeding	30 day	Low-responder (n=51)	Minor bleeding	9 (17.6)	NR	NR	0.125 (low vs normal responder) [chi square]	NR	NR	
						responder (n=147)		43 (29.3)	NR					

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Valgimigli 2009{Valgimigli, 2009 244 /id} 19528337 10 sites in Europe (Italy, Belgium, France, Spain) Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study	Clopidogrel	VerifyNow	Major TIMI bleeding	NR	30 days	Clopidogrel nonresponders (<40% inhibition) (n=147)	Major bleeding	0	OR (calculated)= 0.18	NR	P= 0.39 (<40% vs ≥ 40%) [Fisher's exact]	NR	NR	NONE
						Dual (clopidogrel and aspirin) nonresponders (n=26)		0	NR	NR	NR	NR	NR	NONE

Appendix Table E35: Results from studies assessing the ability of VerifyNow to predict other clinical events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for Reduction of periprocedural myonecrosis trial (CLEAR trial)	Clopidogrel+aspirin	VerifyNow	Target-lesion revascularization		6 months	Clopidogrel resistance		2/37 (5%)			NS vs. next row (chi-square statistics or Fisher 's exact test)			
						Normal response		1/73 (1%)						

Marcucci, 2009{Marcucci, 2009 144 /id} 19118249 Italy NR	clopidogrel 600 mg LD + 75 mg MD & ASA 500 mg IV LD + 100-325 mg MD	VerifyNow	Target-lesion revascularization	by repeat PCI or CABG	12 months	high residual platelet reactivity (PRU≥240)	Target-lesion revascularization	16 (7.3)	HR=1.48	0.78 – 2.78	P=0.225 (RPR vs no RPR)	NO	NR	
						No residual platelet reactivity (PRU<240)		24 (5.2)						
Patti, 2011{Patti, 2011 22 /id} 21256470 Italy Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)–Bleeding Study (ARMYDA-BLEEDS)	Clopidogrel + aspirin	VerifyNow	30-day incidence of major TIMI bleeding or significant entry-site complications (hematoma > 10 cm in diameter, pseudoaneurysm, or arteriovenous fistula)	NR	Within 1 mo	PRU Q1 (highest inhibition) (n=77)	Yes bleeding	10.1%	OR, 4.5 (NR whether this is vs. Q4 or vs. Q2-4)	1.9-25.9	For incidence, 0.043 vs. next row (Fisher's exact or chi-square) For OR, 0.01	NR for incidence YES for OR: age, sex, BMI, DM, stable angina vs ACS, chronic renal failure, hemoglobin levels, previous TIA or stroke, previous major bleeding, use of bivalirudin vs. unfractionated heparin, and use of glycoprotein IIb/IIIa inhibitors	NR	NONE
						PRUQ4 (n=79)		1.3%	NR	NR	NR	NR	NR	

						PRU Q3 (n=77)		1.4%	NR	NR	0.05 vs. first row (Fisher's exact or chi-square)	NR	NR	
						PRU Q2 (n=77)		6.3%	NR	NR	NR	NR	NR	

Appendix Table E36: Results from studies assessing the ability of VerifyNow to predict other clinical events in patients with cerebrovascular disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Drazin, 2011{Drazin, 2011 238 /id} 21990814 US NR	Clopidogrel+aspirin	VerifyNow	Intraprocedural thrombosis	NR	Intraprocedural	Suboptimal response	Yes event	1 (2%)	NR	NR	NR	NR	NR	NONE
						Optimal response		0 (0%)	NR	NR	NR	NR	NR	NONE
			Thromboembolic event		At followup	Suboptimal response		0 (0%)	NR	NR	NR	NR	NR	NONE
						Optimal response		0 (0%)	NR	NR	NR	NR	NR	NONE
			Good function score on modified Ranking Scale	score </=2	At discharge	Suboptimal response	Yes good function	16/19	OR for poor function among suboptimals vs. optimals, 1.55	0.54-4.44	0.41 Ordinal repeated measures model (GEEs)	YES age, sex, DM status, smoking, PPI)	NR	Table 2 has raw data
						Optimal response		32/33 (97%)	NR	NR	NR	NR	NR	Table 2 has raw data
					At followup	Suboptimal response		16/19 (84%)	NR	NR	NR	NR	NR	Table 2 has raw data

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Optimal response		31/33 (94%)	NR	NR	NR	NR	NR	Table 2 has raw data
			Good function Glasgow Outcome Score	Score >/=4	At discharge	Suboptimal response		17/19 (89%)	OR for poor function among suboptimals vs. optimals, 1.19	0.25-5.67	0.83 Ordinal repeated measures model (GEEs)	YES age, sex, DM status, smoking, PPI)		Table 2 has raw data
						Optimal response		33/33 (100%)	NR	NR	NR	NR	NR	Table 2 has raw data
					At followup	Suboptimal response		17/19 (89%)	NR	NR	NR	NR	NR	Table 2 has raw data
						Optimal response		31/33 (94%)	NR	NR	NR	NR	NR	Table 2 has raw data

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Kang, 2010{Kang, 2010 1 /id} 20223886 South Korea NR	Clopidogrel 300 mg LD	VerifyNow P2Y12 assay	procedure-related thromboembolism	Thrombus formation and/or a distal embolism observed during procedure or clinically recognized ischemic deficits that occurred within 60 days of the procedure	60 days	PRU>295	Thromboembolic event	NR	Sensitivity: 75% Specificity: 57% AUC: 0.675	0.526-0.825	P=0.043	NO	NR	
	Clopidogrel 300 mg LD	VerifyNow P2Y12 assay	procedure-related thromboembolism	Thrombus formation and/or a distal embolism observed during procedure or clinically recognized ischemic deficits that occurred within 60 days of the procedure	60 days	1st quartile	Thromboembolic event	2	NR	NR	0.013 (between quartiles, Chi-square for trends)	NO	Tukey-Kramer multiple comparison test	
						2nd quartile		1						
						3rd quartile		3						
						4th quartile		8						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel 300 mg LD	VerifyNow P2Y12 assay	procedure-related aneurysm perforation	Perforation ("leak" [demonstration of extra-aneurysmal contrast material] and "nonleak" [device extrusion from an aneurysm without contrast leakage])	60 days	1st quartile	Perforation	1	NR	NR	0.605 (between quartiles, Chi-square for trends)	NO	Tukey-Kramer multiple comparison test	
						2nd quartile		0						
						3rd quartile		0						
						4th quartile		2						
	Clopidogrel 300 mg LD	VerifyNow P2Y12 assay	All procedure related adverse events	Combination of thromboembolic and perforation events	60 days	1st quartile	thromboembolic and perforation events	3	NR	NR	0.605 (between quartiles, Chi-square for trends)	NO	Tukey-Kramer multiple comparison test	
						2nd quartile		1						
						3rd quartile		3						
						4th quartile		10						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Ryu, 2010{Ryu, 2010 229 /id} 21113358 South Korea NR	Clopidogrel+aspirin	VerifyNow	thromboembolic compli-cations	Emboloic or thrombotic	6 mo after stenting/ clinical intervention	Resistance	YES event	5	NR	NR	NR	NR	NR	NONE
						Nonresistance		0						

Appendix Table E37: Results from studies assessing the ability of VerifyNow to predict platelet reactivity during followup (when used as a continuous measurement) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	300 mg or 600 mg LD Clopidogrel and maintaining 75 mg+ Aspirin	VerifyNow	PRU	PRU mean AUC15	NR	PRU≤240	19	Mean 493	SD 238	t-test	NR	NR	0.0001 comparing the lower group	NR	NR	
						PRU>240	29	Mean 911	SD195							

Appendix Table E38: Results from studies assessing the ability of VerifyNow to predict platelet reactivity during followup (when used as a discrete outcome) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	Clopidogrel + aspirin	VerifyNow	Clopidogrel response category	NR	1 mo after PCI	Poor at baseline (n=107)	Poor (no change)	32	>=235 PRU (poor)	NR	NR	< 0.01 across this and next 4 rows (exact version of McNemar test	NR	NR	NO
							Full (change)	75							
						Full at baseline (n=196)	Poor (change)	8							
							Full (no change)	185							

Gladding, 2008{Gladding, 2008 149 /id} 19463375 New Zealand Secondary (but not subgroup) analysis of PRINC (Plavix Response in Coronary Intervention) Trial	Clopidogrel	VerifyNow	Nonresponse at 7 hr			<2% at 2 hr				AUC 0.90, sensitivity 100%, specificity 88%		0.02			Scatterplots are in Fig 2

Appendix Table E39: Quality Assessment of studies assessing the predictive ability of VerifyNow in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	no	yes	yes	low	low	NR	No	high	low	yes	NR	yes	low	yes	yes	yes	yes	low
Angiolillo, 2007{Angiolillo, 2008 180 /id} 18312754 USA OPTIMUS	NO	yes	yes	low	low	NR	NR	unclear	unclear	No	NR	unclear	high	no [1 month]	yes	yes	yes	low
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	yes	yes	yes	low	low	NR	no	high	low	yes	yes	low	low	yes	yes	yes	yes	low
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	yes	yes	yes	low	low	NR	yes	unclear	Low	Yes	NR	unclean	Low	no [6 months]	yes	yes	yes	low
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	YES	YES	YES	LOW	LOW	YES	NO	HIGH	LOW	YES	NR	UNCLEAR	LOW	NO [30 days]	YES	YES	YES	LOW
Campo, 2010{Campo, 2010 58 /id} 20951320 10 sites in Italy, Belgium, France,	No	YES	YES	LOW	LOW	NR	yes	unclear	Low	YES	NR	UNCLEAR	LOW	yes [1 year]	yes	yes	yes	low

Sprain 3T/2R trial																		
Campo, 2011{Campo, 2011 13 /id} 21679849 Italy NR	Yes	YES	YES	LOW	LOW	NR	yes	Low	Low	YES	NR	UNCLEAR	LOW	yes [12 months]	yes	yes	yes	low
Cuisset, 2008{Cuisset, 2008 168 /id} 18549843 Belgium NR	Yes	YES	YES	LOW	LOW	NR	No	High	Low	YES	Yes	Low	LOW	NO [followup NR]	yes	yes	yes	low
de_Miguel_Castro, 2009{de Miguel, 2009 136 /id} 19232185 Spain NR	No	YES	YES	LOW	LOW	Yes	No	High	Low	YES	Yes	Low	LOW	yes [1 year]	yes	yes	yes	low
Gladding, 2008{Gladding, 2008 149 /id} 19463375 New Zealand Secondary (but not subgroup) analysis of PRINC (Plavix Response in Coronary Intervention) Trial	Yes	YES	YES	LOW	LOW	NR [double-blind trial but details related to genotyping unclear]	yes	Unclear	Low	No	NR [double-blind trial but details related to genotyping unclear]	High	Low	No [7 days]	yes	yes	yes	low
Huczek, 2011{Huczek, 2011 239 /id} 21443410 Poland NR	NR	YES	No	Unclear	LOW	NR	No	High	Low	YES	NR	UNCLEAR	LOW	NO [30 days]	YES	YES	YES	LOW
Kim, 2011{Kim, 2011 5 /id} 21786434 South Korea CiLostazol administration before pErcutaneous coronAry intervention for	Ye (RCT)s	YES	YES	LOW	LOW	NR	yes	Unclear	Low	YES	NR	UNCLEAR	LOW	NO [6 months]	YES	YES	YES	LOW

Reduction of periprocedural myonecrosis trial (CLEAR trial)																		
Lee, 2009{Lee, 2009 230 /id} 20049136 South Korea NR	Yes	YES	YES	LOW	LOW	NR	yes	Unclear	Low	YES	NR	UNCLEAR	LOW	NO [6 months]	YES	YES	YES	LOW
Mangiacapra, 2010{Mangiacapra, 2010 83 /id} 20298992 Italy NR	No	YES	YES	LOW	LOW	NR	yes	Unclear	Low	YES	NR	UNCLEAR	LOW	NO [followup NR]	yes	yes	yes	low
Mangiacapra, 2010{Mangiacapra, 2010 94 /id} 20129566 Belgium NR	No	YES	YES	LOW	LOW	NR	No	High	Low	YES	NR	UNCLEAR	LOW	NO [followup NR]	yes	yes	yes	low
Mangiacapra, 2010{Mangiacapra, 2010 65 /id} 20723634 Italy NR	Yes	YES	YES	LOW	LOW	NR	yes	Unclear	Low	YES	NR	UNCLEAR	LOW	NO [followup NR]	yes	yes	yes	low
Marcucci, 2009{Marcucci, 2009 144 /id} 19118249 Italy NR	No	YES	YES	LOW	LOW	Yes	No	Unclear	Low	YES	NR	UNCLEAR	LOW	yes [12 months]	yes	yes	yes	low
Patti, 2008{Patti, 2011 22 /id} 18804738 Italy ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome)	NR	YES	YES	LOW	LOW	NR	No	High	Low	YES	NR	UNCLEAR	LOW	NO; 1 MONTH & 6 MONTH	yes	yes	yes	low

Patti, 2011{Patti, 2011 22 /id} 21256470 Italy Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)–Bleeding Study (ARMYDA-BLEEDS)	Yes	YES	YES	LOW	LOW	NR	yes	Unclear	Low	YES	NR	UNCLEAR	LOW	NO (1 month)	yes	yes	yes	low
Price, 2011{Price, 2011 23 /id} 21406646 USA Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS)	Yes	YES	YES	LOW	LOW	Yes	yes	Low	Low	Yes	yes	Low	Low	NO (6 months)	yes	yes	yes	low
Price, 2008{Price, 2008 174 /id} 18263931 USA NR	No	YES	YES	LOW	LOW	NR	NR	Unclear	Low	YES	NR	UNCLEAR	LOW	NO (6 months)	yes	yes	yes	low
Saw, 2008{Saw, 2008 242 /id} 19463380 Canada BRIEF-PCI	No	YES	YES	LOW	LOW	Yes	No	Unclear	Low	YES	NR	UNCLEAR	LOW	NO (6 months)	yes	yes	yes	low
Valgimigli, 2009{Valgimigli, 2009 244 /id} 19528337 10 sites in Europe (Italy, Belgium, France, Spain) Tailoring Treatment With Tirofiban in Patients Showing	No	YES	YES	LOW	LOW	NR	No	High	Low	YES	NR	UNCLEAR	LOW	NO (2-30 days)	yes	yes	yes	low

Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study																		
Vavuranakis, 2011{Vavuranakis, 2011 245 /id} 21712606 Greece NR	No	YES	No	HIgh	LOW	NR	No	High	Low	Yes	yes	Low	Low	NO (Mean 203 days)	yes	yes	yes	low
Breet, 2011{Breet, 2011 15 /id} 21478385 The Netherlands POPular	Yes	yes	yes	low	low	NR	Yes	Unclear	Unclear	Yes	Yes	Low	low	Yes [1 year]	yes	yes	yes	low
Suh, 2011{Suh, 2011 33 /id} 21232664 Korea CILON-T	NR	YES	YES	LOW	LOW	Yes	No	High	Low	Yes	NR	Unclear	low	NO (6 months)	yes	yes	yes	low

Appendix Table E40: Quality Assessment of studies assessing the predictive ability of VerifyNow in patients with cerebrovascular disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	**2**	**3**	**ROB (selection)**	**Applicability (selection)**	**4**	**5**	**ROB (index)**	**Applicability (index)**	**6**	**7**	**ROB (reference)**	**Applicability (reference)**	**8**	**9**	**10**	**11**	**ROB (flow & timing)**
Drazin 2011{Drazin, 2011 238 /id} 21990814 US NR	Yes	YES	YES	LOW	LOW	NR	No	High	Low	YES	NR	UNCLEAR	LOW	yes [12 months]	yes	yes	yes	low
Kang 2010{Kang, 2010 1 /id} 20223886 South Korea NR	NR	YES	No	Unclear	LOW	NR	No	High	Low	YES	NR	UNCLEAR	LOW	NO [60 days]	YES	YES	YES	LOW
Ryu 2010{Ryu, 2010 229 /id} 21113358 South Korea NR	NR	YES	YES	LOW	LOW	NR	No	High	Low	YES	NR	UNCLEAR	LOW	NO (6 months)	yes	yes	YES (but 4 pts [7%] did not have data available and reason NR)	low

Appendix Table E41: Baseline characteristics of patients with ischemic heart disease in studies assessing the predictive ability of VASP

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	Total N Enrolled Race (% by group) Male (%) Age[24]	Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)	Stent implantation(%) Type of stent(%) Multi-or single vessel(%)			
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 NR 205 62±16	43.3 NR NR PCI 24.3 NR see UA/NSTEMI 10 22.7 29.7/34.3	hyper 69.3 27.3 HTN 74.7 27.3	NR 100 100 81.3	100 DES 65.3 multi-vessel 58.7	PCI and coronary stenting	Clopidogrel-naïve patients received a 300 or 600 mg loading dose (LD). Patients on chronic clopidogrel therapy with 75 mg clopidogrel of at least seven consecutive days did not receive an additional LD.	According to actual evidence, all patients received in parallel ASA (100 mg daily dose). The use of GP-IIb/IIIa-blockers during PCI as well as the choice of the anticoagulant depended on the individual situation and the thrombus load at angiography, and was left to the discretion of the operator
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria	30 NR 63±10	100 NR CVD 7 PCI 43 NR	hyper 77 57 HTN 77 33	NR 100 100 NR	NR NR NR	Patients undergoing PCI for coronary artery disease	Patients had been on chronic aspirin (100 mg/day) and clopidogrel (75 mg/day) treatment for three months on average.	All patients received unfractionated heparin and 250 mg of injectable acetyl-salicylic acid during PCI

[24] Mean (standard deviation), unless otherwise stated.

NR		NR 10 37 NR						
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	99 NR 74 (74.7) 63.7±11.2	NR NR NR PCI 47 (47.5) 35 (35.4) NR NR 47 (47.5) 22(22.2)/29 (29.3)	58 (58.6) 42 (42.4) 70 (70.1) 16 (16.2)	NR 100 100 NR	NR DES 65 (65.7); BMS 34 (34.3) NR	Patients with an elevated risk to develop ST acute MI within 48 hours undergoing emergency or elective PCI	All patients were given 75 mg clopidogrel and 100 mg aspirin once a day at least five days prior to PCI. Only in case of emergency PCI, patients received a loading dose of 600 mg before the intervention. Dual antiplatelets for 6 months.	
Kalantzi, 2011{Kalantzi, 2011 19 /id} 21255245 Greece NR	61 NR 47 (77) 58.8 ± 11.5	NR NR NR NR NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR	Patients with acute coronary syndromes (ACS), including those who have had a NSTEMI or have unstable angina)	Loading dose of 325 mg aspirin followed by 100 mg per day Loading dose of 600 mg clopidogrel, followed by 75 mg per day	Low-molecular-weight heparin (enoxaparin) given sc at 1 mg/kg x12 h until discharge Atorvastatin (40 mg/d) started at admission & continued on discharge
Siller-Matula, 2010{Siller-Matula,	416 NR 76	100 NR NR	hyper 76 55 85	NR 100 100	99 NR NR	PCI with stenting	Clopidogrel loading dose at least 2 hr before PCI (600 mg);	Also all patients received unfractionated heparin (100 IU per kg) during

2010 89 /id} 19943879 Austria NR	64±12	47 NR NR 13 33 NR	32	77			thereafter, a daily dose of 75 mg, with planned treatment with clopidogrel and aspirin for at least 6 months.	PCI and 250 mg aspirin intravenously immediately after stent placement (and daily dose of 100 mg thereafter).
Bjelland, 2010{Bjelland, 2010 42 /id} 20727659 Norway NR	25 NR 19 (76%) 59.7 ± 14.6	8% 8% NR PCI: 52% NR NR NR 56% STEMI: 40%; NSTEMI: 16%	NR NR NR 8%	NR 0% 88% 64%	NR NR NR	Patients with suspected ACS treated with therapeutic hypothermia	Clopidogrel: enteral LD 300mg (600mg if urgent coronary angiography planned); MD of 75 mg/day	NR
Bonello, 2007{Bonello, 2007 199 /id} 17488353 France NR	144 NR 114 (79) 68±10	56 (39) NR NR NR NR NR NR NR	76 (53) 94 (50) 72 (50) 58 (40)	NR 100 100 NR	NR NR NR	Patients admitted for PCI	pretreatment with a loading dose of clopidogrel (300-mg initial oral bolus) 24 h before the procedure, followed by 75 mg per day for at least 6 months + aspirin 160 mg daily, starting at least 12 h	

							before stenting.	
Djukanovic, 2008{Djukanovic, 2008 163 /id} 18719318 Serbia NR	32 (only 17 included in final analysis as others were not given clopidogrel) NR 27 (84.3%) 57.1 ±8.5	Previous vascular event: 81.3% NR NR NR NR NR NR 68.8% NR	NR NR NR NR	NR NR NR NR	NR NR NR	Patients with ischemic heart disease, undergoing elective PCI	Aspirin 100 mg x 3 days followed by aspirin (100 mg/day) + clopidogrel (75 mg/day) from 7 days before stent implantation up to 12 months after the intervention	All patients received unfractioned heparin (5000 – 6000 IU or 700 IU/kg, i.v.) and antibiotic (1 g ceftazidim or 1.5 g cefuroxim, i.v.) before PCI The use of other cardiovascular drugs (beta-blockers, ACE inhibitors, Ca2+-channel blockers, diuretics) was allowed.
El Ghannudi, 2011{El, 2011 3 /id} 21524751 France NR	436 NR NR Mean/SD 65.0/12.4 yr	NR NR Prior stroke 4.6% Prior CABG 8.3% Stable angina or silent ischemia, 25.5% 8.5% Peripheral vascular disease 6.9% NR 32.8%/33.3%	Hyperlipidemia 51.6% 48.9 HTN 54.6% 32.4%	NR 100% 100% 72.2%	100% DES 47.9% Three vessel 31.0%	Patients undergoing PCI with stenting	Everyone received a loading dose (300 or 600 mg) of clopidogrel and aspirin	
El Ghannudi, 2010{El, 2010 74 /id} 20630458	461 NR NR 65.4(55.8-75.4)	NR NR Stroke 20 (4.3) CABG 40 (8.7); PCI 130 (28.2)	NR NR Stroke 20 (4.3) CABG 40 (8.7); PCI 130 (28.2)	NR 100 100 314 (83.7)	NR NR NR	Patients undergoing PCI for ACS or stable CAD	loading dose (300 or 600 mg) of clopidogrel.	

France NR		NR NR NR NR 81 (17.6) / 27 (5.9)	NR NR NR NR 81 (17.6) / 27 (5.9)					
Morel, 2011{Morel, 2011 187 /id} 21251579 France NR	440 NR 333 (75.7%) mean: 65.3	NR NR Stroke: 4.5% NR NR 9.3 NR NR STEMI: 16.8%	Hyperlipidemia: 52.5% Current: 40.3% HTN: 54.3% 37.5%	oral anticoagulants: 6.1% clopidogrel & aspirin: 100% clopidogrel & aspirin: 100% 69.8%	NR NR NR	Patients undergoing percutaneous coronary intervention (PCI) for ACS & CAD	clopidogrel. loading dose (300 or 600 mg)	
Palmerini, 2010{Palmerini, 2010 81 /id} 19604542 Italy DOUBLE	48 NR 43 (90%) 63	NR NR NR NR NR NR 100% STEMI: 100%	hyperlipidemia: 44% present or previous: 67% HTN: 48% 17%	NR NR 100% 46%	NR NR Multivessel; 59%	Patients with STEMI	Clopidogrel: LD 300 mg; MD – 75 or 150 mg	Abciximab in the periprocedural period
Schafer, 2011{Schafer, 2011 11 /id}	54 NR 46 (85%)	NR NR NR	NR 37% HTN 64%	NR NR NR	93% DES 13%; BMS 80% NR	patients with acute STEMI admitted for coronary intervention	loading dose, 600 mg clopidogrel	

21655677 Germany NR	64 ± 1 years (mean/SD)	NR NR NR NR 100% AMI; Family history of MI, 28% NR	17%	NR				
Frere, 2007{Frere, 2007 193 /id} 17938809 France NR	195 NR 158 (81) 63.4±11.1	NR NR NR NR NR NR NR NR NR	107 (54.9) 96 (49.2) 111(56.9) 68 (34.9)	NR 100 100 NR	NR NR NR	Patients had undergone successful coronary stenting	All patients received a 600 mg loading dose of clopidogrel and a 250 mg loading dose of aspirin administered at least 12 h before stenting. After PCI, patients received clopidogrel and aspirin 75 mg daily during one-month follow-up.	Anticoagulation was performed with low-molecular-weight heparin (enoxaparin), or unfractionated heparin if age over 75 years or in case of renal insufficiency (creatinin clearance < 60 ml/min).

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;

Appendix Table E42: Study design characteristics of studies assessing the predictive ability of VASP in patients with ischemic heart disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enroment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	Prospective, registry data	NO	Consecutive	Adults undergoing PCI and coronary stenting with no contraindication for dual antiplatelet therapy for up to one year	May 2009 to February 2010	Total 6 month, mean/SD 189/68 days	Inpatient, then outpatient visits after discharge, at 1 mo and 6 mo	YES [YES]	Non-industry only
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Prospective observational study	NO	NR	Patients undergoing PCI for coronary artery disease	Aug 2007-Apr 2008	1 day	followup after intervention	YES Accrual=100%	Non-industry [grant from the Jubiläums fond of the Austrian National Bank (Nr. 12565)]
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	prospective Cohort	No	Selected sample?	Patients with an elevated risk to develop ST acute MI within 48 hours undergoing emergency or elective PCI	NR	6 months	Department of cardiology in University Hospital Aachen inpatient	NR	NR
Kalantzi, 2011{Kalantzi, 2011 19 /id} 21255245 Greece NR	prospective observational study	NO	NR	Patients with acute coronary syndromes (ACS), including those who have had a NSTEMI or have unstable angina)	NR	30 days f/u after discharge	Inpatient	NO	NR
Siller-Matula, 2010{Siller-Matula, 2010 89	Prospective observational	NO	Consecutive	Adults with CAD undergoing PCI with stenting (most elective) with clopidogrel	NR	Total, 6 months	Inpatient with followup after discharge	YES (YES—80%)	Nonindustry only

/id} 19943879 Austria NR				and aspirin therapy			(contacted patients at 3 and 6 mo after)		
Bjelland, 2010{Bjelland, 2010 42 /id} 20727659 Norway NR	Prospective observational study	YES	Other (Patients were recruited through screening for participation in an RCT comparing two protocols for sedation analgesia in patients treated with therapeutic hypothermia)	Patients with suspected ACS treated with therapeutic hypothermia	Apr 2008 – May 2009	Max 3 days	Inpatient (Emergency room)	NO	Non-industry (Grant from the medical student research programme at the Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Norway & grant from Trondheim University Hospital, Trondheim, Norway.)
Bonello, 2007{Bonello, 2007 199 /id} 17488353 France NR	prospective cohort	No	Consecutive	Patients admitted for PCI	Nov 2004-Nov 2005	6-month	Cardiology department of the university hospital	NR	NR
Djukanovic, 2008{Djukanovic, 2008 163 /id} 18719318 Serbia NR	Prospective observational study	NO	NR	Patients with ischemic heart disease, undergoing elective PCI	NR	I year	NR	NR	non-industry (Ministry of Science, Republic of Serbia)
El Ghannudi,	Prospective	NO	Consecutive	Patients undergoing PCI	Sept 2007-Dec 2008	Mean/SD 9/2 mo	Inpatient for	NR	NR

2011{El, 2011 3 /id} 21524751 France NR				with stenting		Range 6-14 mo (end of study June 30, 2009)	stenting and then outpatient followup via questionnaire and phone		
El Ghannudi, 2010{El, 2010 74 /id} 20630458 France NR	prospective Cohort	No	Consecutive patients	Patients undergoing PCI for ACS or stable CAD	Sep 2007, Dec 2008	Mean 9 months	Hospital inpatient	NR	NR
Morel, 2011{Morel, 2011 187 /id} 21251579 France NR	Prospective	NO	Consecutive	Patients undergoing percutaneous coronary intervention (PCI) for ACS & CAD	Sep 2007 – dec 2008	mean:9± 2 months	followup after intervention	NR	NR [Authors report no conflict]
Palmerini, 2010{Palmerini, 2010 81 /id} 19604542 Italy DOUBLE	Prospective; 2 arms of an RCT are separate cohorts	NO	RCT	Patients with STEMI	NR	Max 1 month	Followup after intervention	YES; Accrual > 80%	Non-industry [Fondazione Fanti Melloni, Bologna, Italy]
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	Prospective	NO	Consecutive	patients with acute STEMI admitted for coronary intervention	November 2008 and May 2009	Total 12 months	Inpatient for PCI; outpatient followup for 1 yr afterward	NO	NR but one author has a COI from funding from industry
Frere, 2007{Frere, 2007 193 /id} 17938809 France NR	Prospective observational	No	Selected patients with coronary stenting	Patients had undergone successful coronary stenting	March 2005-may 2006	1 month follow up	Department of Cardiology	NR	NR

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-elevation; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; DES=drug eluting stent; CABG=coronary artery bypass grafting; AA= arachidonic acid; SD=standard deviation; RCT=randomized controlled trial; NR=not reported;

Appendix Table E43: Phenotypic test details in studies assessing the predictive ability of VASP in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer *	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	Flow cytometric analysis of VASP phosphorylation Platelet VASP kit Biocytex, Marseille, France	ADP	Venous blood samples along with the routine blood samples were collected via atraumatic venipuncture of the forearm into coagulation tubes buffered sodium citrate 3.2% 6-24 h (morning) after PCI 48 hours after blood collection	VASP result: PRI≤60.2% (low reactivity, good response) VASP result: PRI>60.2% (high reactivity, poor response)	ROC curve (area under the ROC-curve was 0.683 (p=0.014) for the platelet reactivity index (PRI) calculated from median fluorescence intensities (FI) with an optimal cut-off at 60.2% PRI.)	VASP result: PRI≤60.2% (low reactivity, good response): 114/300 (38%) VASP result: PRI>60.2% (high reactivity, poor response): 186/300 (62%)
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Flow cytometric analysis of VASP phosphorylation Platelet VASP kit Biocytex, Marseille, France	Adenosine diphosphate (ADP), prostaglandin (PGE1)	1st blood sample: in catheterization laboratory, after PCI and after 250 mg IV aspirin ; 2nd blood sample: 20-24 hours after PCI 3.8% citrate NR; Clopidogrel came first 0.04 days (1 hour)	Platelet reactivity index ≥ 69% by VASP (? Low efficiency) Platelet reactivity index <69% by VASP	Based on normal ranges as reported by manufacturer	Platelet reactivity index ≥ 69% by VASP (? Low efficiency): 8 (27%) Platelet reactivity index <69% by VASP: 22 (63%)
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	Flow cytometric analysis of VASP phosphorylation NR Biocytex, Marseille, France	10 µM ADP	blood samples were obtained 72–96 h after stent placement Citrate Interval at least 8 days. NR	VASP-platelet reactivity indices (VASP-PRI) > 48% VASP-platelet reactivity indices (VASP-PRI) < 48%	ROC curve revealed VASP PRI <48% be the best cut-off	VASP-platelet reactivity indices (VASP-PRI) > 48%: NR VASP-platelet reactivity indices (VASP-PRI) < 48%: NR
Kalantzi,	Flow	ADP	Pre-clopidogrel, 5 days after	Non-responders (VASP	Based on literature;	Non-responders (VASP

2011{Kalantzi, 2011 19 /id} 21255245 Greece NR	cytometric analysis of VASP phosphorylation NR Biocytex, Marseille, France		clopidogrel, 30 days after clopidogrel Citrate 5 days; the pre-clopidogrel sampling was not used for estimation of responder status NR	platelet reactivity index [PRI] ≥50%) Responders (VASP PRI < 50%)	Proposed previously [Ref #6] and also associated with adverse clinical outcome [ref #4]	platelet reactivity index [PRI] ≥50%): 46 (75.4%) Responders (VASP PRI < 50%): 15 (24.6%)
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	Flow cytometric analysis of VASP phosphorylation NR Biocytex, Marseille, France	ADP	Blood samples obtained from arterial sheath 3.8% citrate Dose first (clopidogrel loading dose given at least 2 hr before PCI); Samples taken directly after PCI and at least 5 min after IV aspirin dose (250 mg). NR	Clopidogrel responders (PRI<42%) Clopidogrel nonresponders (PRI≥42%)	ROC optimal cutoffs for prediction of definite stent thrombosis at 6 m, as done in this study	Clopidogrel responders (PRI<42%): 154 (37%) Clopidogrel nonresponders (PRI≥42%): 262 (64%)
Bjelland, 2010{Bjelland, 2010 42 /id} 20727659 Norway NR	Dual flow cytometry PLT VASP/P2Y12 Biocytex, France	ADP	Whole blood; Day 1 and Day 3 after clopidogrel administration citrate Day 1: Median 21 hrs [IQR: 17.5-27.5] Day 1: Median 68 hrs [IQR: 63-72] NR	Satisfactory clopidogrel effect (Platelet reactivity index <0.5) Unsatisfactory clopidogrel effect (Platelet reactivity index ≥0.5)	Based on literature	Satisfactory clopidogrel effect (Platelet reactivity index <0.5): 0 (0%) Unsatisfactory clopidogrel effect (Platelet reactivity index ≥0.5): 25 (100%)
Bonello, 2007{Bonello, 2007 199 /id} 17488353 France NR	VASP Platelet VASP kits Diagnostica Stago,Asnieres, France	ADP and/or prostaglandin E1 (PGE1)	Blood samples for PRI testing were drawn before PCI and at least 24 h after clopidogrel loading dose and aspirin 3.8% trisodium citrate 24 hours 24 hours	Quintile 1 (<47%) vs Quintile 2-4	70% is normal range using ROC curve.	Quintile 1 (<47%) : 29 vs Quintile 2-4: 115
Djukanovic, 2008{Djukanovic, 2008 163 /id} 18719318 Serbia NR	Flow cytometric analysis of VASP phosphorylation	PGE1 and ADP	Whole blood; Collection time NR 0.129 M sodium citrate NR NR	At Day 2: Rapid response (Platelet reactivity index ≤50% at 2 days) Not rapid response (Platelet reactivity index >50% at 2 days)	Based on literature	Rapid response (Platelet reactivity index ≤50% at 2 days): 7/17 (41.2%) Not rapid response (Platelet reactivity

	Platelet VASP kit Diagnostica Stago (Biocytex), Asnières, France			At Day 7: Good responders (Platelet reactivity index ≤50% at Day 7): NR (Difficult to extract from Fig 2B) Bad responders (Platelet reactivity index >50% at Day 7)		index >50% at 2 days): 10/17 (58.8%) Good responders (Platelet reactivity index ≤50% at Day 7): NR (Difficult to extract from Fig 2B) Bad responders (Platelet reactivity index >50% at Day 7): NR (Difficult to extract from Fig 2B)
El Ghannudi, 2011{El, 2011 3 /id} 21524751 France NR	Flow cytometric analysis of VASP phosphorylation Platelet VASP kit Diagnostica Stago (Biocytex), Asnières, France	ADP	Whole blood samples were drawn by venous puncture 0.129 M sodium citrate Blood taken at least 6 h after clopidogrel, mean interval ~24 h, and range 12-120 h Sent to Alsace laboratory for VASP immediately after sample obtained but interval NR	Non-diabetic responders (NDM-R) (PRI <61%) Non-diabetic low responders (NDM-LR) (PRI≥61%) Diabetic responders (DM-R) (PRI<61%) Diabetic low responders (DM-LR) (PRI≥61%) [NB outcome data available for only 429 of the 436 (98.4%) but NR why] Also some data reported for groups with cutoff at 60%, not 61%, but no explanation given	Based on literature (Ref 7)	Non-diabetic responders (NDM-R) (PRI <61%) 177 (64.8%) Non-diabetic low responders (NDM-LR) (PRI≥61%) 96 (35.2%) Diabetic responders (DM-R) (PRI<61%) 85 (52.1%) Diabetic low responders (DM-LR) (PRI≥61%) 78 (47.9%)
El Ghannudi, 2010{El, 2010 74 /id} 20630458 France NR	Flow cytometric analysis of VASP phosphorylation Platelet VASP kit Diagnostica Stago (Biocytex), Asnières, France	ADP	Blood samples drawn at least 6 h after a loading dose (300 or 600 mg) of clopidogrel. 0.129 mol/L sodium Citrate 6 h after a loading dose (300 or 600 mg) of clopidogrel. NR	Low responder (PRI≥61%) Responder (PRI≥61%)	Based on an ROC curve from data on subjects in this study	Low responder (PRI≥61%): N=184 Responder (PRI≥61%): N=277

Morel, 2011{Morel, 2011 187 /id} 21251579 France NR	Flow cytometric analysis of VASP phosphorylation Platelet VASP kit Diagnostica Stago (Biocytex), Asnières, France	prostaglandin E1 (PGE1) or ADP	after PCI 0.129 M sodium citrate 0.25 (6 hours after loading dose) NR [It is reported that the samples were sent off immediately for analysis]	Low responders (PRI≥ 61%) Normal responders (PRI<61%) By Quartile: Quartile 1 (<40.30%) Quartile 2 (40.30%–55.83%) Quartile 3 (55.84%–70.25%) Quartile 4 (>70.25%)	Single PRI cutoff based on literature; quartile cutoffs not explicitly reported	Low responders (PRI≥ 61%): 173 (40%) Normal responders (PRI<61%): 260 (60%) Quartile 1 (<40.30%): 108 (25%) Quartile 2 (40.30%–55.83%): 108 (25%) Quartile 3 (55.84%–70.25%):108 (25%) Quartile 4 (>70.25%): 109 (25%)
Palmerini, 2010{Palmerini, 2010 81 /id} 19604542 Italy DOUBLE	VASP Phosprylation VASP kit Biocytex, Marseille, France	ADP 20 µmol/L	1-2 hrs after ingestion of last clopidogrel dose done at baseline, 1 week and 1 month Citrate NR [clopidogrel] 0.02 [30 minutes]	Poor responders (PRI>50%) in clopidogrel 75 mg group Normal responders (PRI between 30-50%) in clopidogrel 75 mg group Poor responders (PRI>50%) in clopidogrel 150 mg group Normal responders (PRI between 30-50%) in clopidogrel 150 mg group	Based on literature	Poor responders (PRI>50%) in clopidogrel 75 mg group: 21 (87.5%) Normal responders (PRI between 30-50%) in clopidogrel 75 mg group : 3 (12.5%) Poor responders (PRI>50%) in clopidogrel 150 mg group: 20 (83.3%) Normal responders (PRI between 30-50%) in clopidogrel 150 mg group: 4 (16.7%)
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	Flow cytometric analysis of VASP phosphorylation Platelet VASP/P2Y12 kit Biocytex, Marseille, France	ADP	NR NR 24 hours after loading with 600 mg clopidogrel NR	PRI >50% (suboptimal inhibition; impaired clopidogrel responsiveness) PRI≤ 50%14 (26%) PRI quartiles: <51%, 51-58%, 59-71%, and >71% PRI >57% PRI ≤57%	>50% vs. </=50% was based on literature 57% threshold based on ROC analysis in present study	PRI >50% (suboptimal inhibition; impaired clopidogrel responsiveness): 40 (74%) PRI≤50%: 14 (26%) PRI quartiles: <51%, 51-58%, 59-71%, and >71%: Frequency NR PRI >57%: 40 (74%) PRI ≤57%: 14 (26%)
Frere, 2007{Frere,	Flow cytometric	PGE1 and ADP	before the PCI at least 12 h after the loading dose of clopidogrel and	VASP PRI ≥ 53% VASP PRI < 53%	As per the ROC curve created using data	VASP PRI ≥ 53%: 13/106 (12.3%)

2007 193 /id} 17938809 France NR	analysis of VASP phosphorylation Platelet VASP/P2Y12 kit Biocytex, Marseille, France		aspirin, and before administration of tirofiban if needed. 3.8% trisodium citrate After 12hours after the loading dose of clopidogrel With 1 hour		from study subjects	VASP PRI < 53%: 1/89 (1.1%)

*If more than one test, use separate rows
**E.g., nonresponsive vs. responsive to clopidogrel, high vs. low platelet reactivity,
ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E44: Results from studies assessing the ability of VASP to predict death in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	Clopidogrel+aspirin	VASP	CV death		6-month	PRI>60.2% (high reactivity, poor response) N=186		7	OR (calculated)=4.41	NR	P=0.167 (poor vs good response) [Fisher's exact]	NR	NR	Get n's from Fig 1 (pasted in on last page of this form)
						VASP result: PRI≤60.2% (low reactivity, good response) N=114		1						Get n's from Fig 1 (pasted in on last page of this form)
Bonello, 2007{Bonello, 2007 199 /id} 17488353 France NR	clopidogrel LD 300-mg followed by 75 mg daily	VASP	Death of cardiovascular origin	Death of cardiovascular origin	6-month	Quintile 1 N=28	Death of cardiovascular origin	0	OR (calculated)= 0.57	NR	P=0.711 (Q1 vs Q2-5) [Fisher's exact]	NR	NR	
						Quintiles 2-4 N=116		3(2.6%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
El Ghannudi, 2011{El, 2011 3 /id} 21524751 France NR	Clopidogrel + aspirin	VASP	Cardiac death	any death with a demonstrable cardiovascular cause or any death which was not clearly attributable to a non-cardiovascular cause	Any point during study period	non-diabetic responders (NDM-R) (PRI <61%)	Cardiac death	4 (4.2%)	HR 1.74	0.43 – 7.00)	0.43 (univariate analysis) 0.004 across all 4 phenotypic groups with 61% cutoff (log-rank test)	NR	NR	Get survival curves from Fig 2 for each of the 4 phenotypic groups
						non-diabetic low responders (NDM-LR) (PRI≥61%)		4 (2.3%)						
						PRI > 50% (LR to clopidogrel) in patients without diabetes			HR 1.38	0.33 – 5.81	0.66 (univariate analysis)			
						diabetic responders (DM-R) (PRI<61%)		2 (2.4%)						
						diabetic low responders (DM-LR) (PRI≥61%)		9 (12.2%)	HR 5.798	1.25 – 26.86	0.025 (univariate analysis)			
						Same as just above except multivariate			HR 6.09	1.27 – 29.08	0.02 (MULTIvariate analysis)			

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						PRI > 50% (LR to clopidogrel) in patients with diabetes			HR 2.81	0.60 – 13.02	0.19 (univariate analysis)			
			Total death			non-diabetic responders (NDM-R) (PRI <61%)		5 (5.3%)			0.003 across all 4 phenotypic groups with 61% cutoff (log-rank test)			
						non-diabetic low responders (NDM-LR) (PRI≥61%)		6 (3.4%)	HR 1.53	0.47 – 5.04	0.48 (univariate analysis)			
						diabetic responders (DM-R) (PRI<61%)		3 (3.5%)						
						diabetic low responders (DM-LR) (PRI≥61%)		11 (14.9%)	HR 3.84	1.04 – 14.23	0.04 (univariate analysis)			
						Same as just above but multivariate analysis			4.42	1.12 – 17.40	0.03 (MULTIvariate analysis)			
						PRI > 50% (LR to clopidogrel) in patients without diabetes			HR 1.56	0.45 – 5.37	0.48 (univariate analysis)			
						PRI > 50% (LR to clopidogrel) in patients with diabetes			HR 1.86	0.50 – 6.89	0.35 (univariate analysis)			

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
El Ghannudi, 2010{El, 2010 74 /id} 20630458 France NR	Clopidogrel LD 300 or 600mg	VASP	Total death	Total death	9 months	Low responders N=178	Total death	17 (9.6%)	NR	NR	0.005 (low responder vs responder)	NR	NR	
						Responders N=275		9 (3.3%)						
	Clopidogrel LD 300 or 600mg	VASP	Cardiac death	Cardiac death	9 months	Low responders N=178	Cardiac death	14 (7.9%)	NR	NR	0.004 (low responder vs responder)	NR	NR	
						Responders N=275		6 (2.2%)						
	Clopidogrel LD 300 or 600mg	VASP PRI	Cardiac death	Cardiac death	9 months	PRI≥61%	Cardiac death	NR	HR=3.65	1.40-9.50	0.008 (≥61% vs <61%) [Cox regression]	No	NR	Figure 2 and figure 3Kaplan-Meier analysis for cardiac survival
						PRI≥50%	Cardiac death	NR	HR=2.22	0.80-6.12	0.12 (≥50% vs <50%) [Cox regression]	No	NR	
						PRI≥69%	Cardiac death	NR	HR=2.42	1.00-5.85	0.049 (≥69% vs <69%) [Cox regression]	No	NR	

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel LD 300 or 600mg	VASP PRI	Cardiac death	Cardiac death	9 months	PRI≥61%	Cardiac death	NR	HR=4.0	1.08-14.8	0.037 (≥61% vs <61%) [Cox regression]	Yes, variables with p<0.1 in univariate analysis were entered into a stepwise ascending multivariate analysis	NR	
	Clopidogrel LD 300 or 600mg	VASP PRI	Total death	Total death	9 months	PRI≥61%	Total death	NR	HR=2.71	1.18-6.2	0.02 (≥61% vs <61%) [Cox regression]	No	NR	
					9 months	PRI≥50%	Total death	NR	HR=1.86	0.77-4.51	0.17	No	NR	
					9 months	PRI≥69%	Total death	NR	HR=1.85	0.8-4.24	0.15	No	NR	
Morel, 2011{Morel, 2011 187 /id} 21251579 France NR	clopidogrel 300-600 mg LD	VASP	Cardiac death	any death with demonstrable cardiovascular cause or any death that was not clearly attributable to a noncardiovascular cause	mean 9±2 months	low responders (PRI≥ 61%)	Cardiac death	14 (8.1%)	HR=3.66	1.4-9.53	P=0.008 (low vs normal) [Cox regression]	NO	NR	Primary

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						normal responders (PRI<61%)		6 (2.3%)						
	clopidogrel 300-600 mg LD	VASP	Cardiac death	any death with demonstrable cardiovascular cause or any death that was not clearly attributable to a noncardiovascular cause	mean 9±2 months	low responders (PRI≥ 61%)	Cardiac death	14 (8.1%)	HR=11.96	1.22-116.82	P=0.033 (low vs normal) [Cox regression]	YES; Killip class III–IV; Drug-eluting stent; PRI ≥61%; CKD	NR	Primary PRI>61% is entered twice in the model; could explain the large se
					mean 9±2 months	normal responders (PRI<61%)		6 (2.3%)						
	clopidogrel 300-600 mg LD	VASP	Cardiac death	any death with demonstrable cardiovascular cause or any death that was not clearly attributable to a noncardiovascular cause		Quartile 1 (<40.30%)	Cardiac death	1 (3%)	NR	NR	P=0.023 (Q4 vs Q1-3) fishers exact	NO	NR	primary

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Quartile 2 (40.30%–55.83%)		1 (3.3%)						
						Quartile 3 (55.84%–70.25%)		5 (15.6%)						
						Quartile 4 (>70.25%)		7 (24.1%)						
	clopidogrel 300-600 mg LD	VASP	all-cause mortality	all-cause mortality	mean 9±2 months	low responders (PRI≥ 61%)	all-cause mortality	16 (9.2%)	NR	NR	P=0.019 (low vs normal) chi square	NO	NR	primary
						normal responders (PRI<61%)		9 (3.5%)						
	clopidogrel 300-600 mg LD	VASP	all-cause mortality	all-cause mortality	mean 9±2 months	Quartile 1 (<40.30%)	all-cause mortality	1 (3%)	NR	NR	P=0.019 (low vs normal) fishers exact	NO	NR	primary
						Quartile 2 (40.30%–55.83%)		1 (3.3%)						
						Quartile 3 (55.84%–70.25%)		5 (15.6%)						
						Quartile 4 (>70.25%)		8 (27.6%)						
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	Clopidogrel	VASP	cardiac death			>57% N=40		1	OR (calculated)=1.1	NR	P=0.95 (>57 vs ≤ 57%) [Fisher's exact]	NR	NR	NR

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						</=57% N=14		0	NR	NR	NR	NR	NR	NR

Appendix Table E45: Results from studies assessing the ability of VASP to predict myocardial infarction in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	Clopidogrel+aspirin	VASP	STEMI	STEMI	6 months	PRI>60.2% (high reactivity, poor response) N=186	STEMI	3	OR (calculated)=4.37	NR	P=0.33 (>60.2 vs ≤ 60.2) [Fisher's exact]			Getn's from Fig 1 (pasted in on last page of this form)
						VASP result: PRI≤60.2% (low reactivity, good response) N=114		0						Getn's from Fig 1 (pasted in on last page of this form)
Djukanovic, 2008{Djukanovic, 2008 163 /id} 18719318 Serbia NR	clopidogrel 75 mg + Aspirin 100 mg	VASP phosphorylation	Periprocedural MI	NR	1 year	Bad responder N=17	Periprocedural MI	0	OR(calculated)= 1	NR	P= 1.0 (bad vs good responder) [Fisher's exact]	NR	NR	NR
						Good responder N=17		0	NR	NR	NR	NR	NR	NR
	clopidogrel 75 mg + Aspirin 100 mg	VASP phosphorylation	Myocardial Infarction	NR	1 year	Bad responder N=17	Myocardial Infarction	0	OR(calculated)= 1	NR	P= 1.0 (bad vs good responder) [Fisher's exact]	NR	NR	NR

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Good responder N=17		0	NR	NR	NR	NR	NR	NR
El Ghannudii, 2011{El, 2011 3 /id} 21524751 France NR	Clopidogrel + aspirin	VASP	STEMI			non-diabetic responders (NDM-R) (PRI <61%)		1 (1.1%)			0.86 across this and next 3 rows (log rank)			
						non-diabetic low responders (NDM-LR) (PRI≥61%)		3 (1.7%)						
						diabetic responders (DM-R) (PRI<61%)		2 (2.4%)						
						diabetic low responders (DM-LR) (PRI≥61%)		2 (2.7%)						
			NSTEMI			non-diabetic responders (NDM-R) (PRI <61%)		6 (6.3%)			0.41 across this and next three rows (log rank)			
						non-diabetic low responders (NDM-LR) (PRI≥61%)		5 (2.9%)						
						diabetic responders (DM-R) (PRI<61%)		6 (7.1%)						
						diabetic low responders (DM-LR) (PRI≥61%)		5 (5.4%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
El Ghannudi, 2010{El, 2010 74 /id} 20630458 France NR	Clopidogrel LD 300 or 600mg	VASP	STEMI	STEMI	9 months	Low responders N=178	STEMI	3 (1.7%)	NR	NR	1.00 (low responder vs responder)	NR	NR	
						Responders N=275		5 (1.8%)						
	Clopidogrel LD 300 or 600mg	VASP	NSTEMI	NSTEMI	9 months	Low responders N=178	NSTEMI	11(6.2%)	NR	NR	0.39 (low responder vs responder)	NR	NR	
						Responders N=275		12 (4.4%)						
Morel, 2011{Morel, 2011 187 /id} 21251579 France NR	clopidogrel 300-600 mg LD	VASP	STEMI	new or presumably new ST-segment elevation in 2 consecutive leads associated with an increase in biochemical markers of myocardial necrosis	mean 9±2 months	low responders (PRI≥ 61%)	STEMI	3 (1.7%)	NR	NR	P=1 (low vs normal) chi square	NO	NR	primary
						normal responders (PRI<61%)		5 (1.9%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel 300-600 mg LD	VASP	STEMI	new or presumably new ST-segment elevation in 2 consecutive leads associated with an increase in biochemical markers of myocardial necrosis	mean 9±2 months	Quartile 1 (<40.30%)	STEMI	1 (3%)	NR	NR	P=1 (low vs normal) fishers exact	NO	NR	primary
						Quartile 2 (40.30%–55.83%)		1 (3.3%)						
						Quartile 3 (55.84%–70.25%)		1 (3.1%)						
						Quartile 4 (>70.25%)		1 (3.4%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel 300-600 mg LD	VASP	NSTEMI	occurrence of ischemic symptoms, STsegment depression and/or T-wave abnormalities, and an increase of biochemical markers of myocardial necrosis	mean 9±2 months	low responders (PRI≥ 61%)	NSTEMI	11 (6.4%)	NR	NR	P=0.513 (low vs normal) chi square	NO	NR	primary
						normal responders (PRI<61%)		12 (4.6%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel 300-600 mg LD	VASP	NSTEMI	occurrence of ischemic symptoms, STsegment depression and/or T-wave abnormalities, and an increase of biochemical markers of myocardial necrosis	mean 9±2 months	Quartile 1 (<40.30%)	NSTEMI	1 (3%)	NR	NR	P=0.906 (low vs normal) fishers exact	NO	NR	primary
						Quartile 2 (40.30%–55.83%)		1 (3.3%)						
						Quartile 3 (55.84%–70.25%)		2 (6.3%)						
						Quartile 4 (>70.25%)		1 (3.4%)						
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	Clopidogrel	VASP	nonfatal myocardial infarction			>57%		3	OR (calculate) = 2.71	NR	P=0.52 (>57% vs ≤57%) [Fisher's exact]	NR	NR	NR

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						</=57%		0	NR	NR	NR	NR	NR	NR

Appendix Table E46: Results from studies assessing the ability of VASP to predict stent thrombosis in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	Clopidogrel+aspirin	VASP	Definite or probable stent thrombosis	Definite or probable stent thrombosis		PRI>60.2% (high reactivity, poor response) n=186	Stent thrombosis	5	OR (calculated) = 6.94	NR	P=0.19 (>60.2% vs ≤60.2) [Fisher's exact]			Get n's from Fig 1 (pasted in on last page of this form)
						VASP result: PRI≤60.2% (low reactivity, good response) n=114		0						Get n's from Fig 1 (pasted in on last page of this form)
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	75 mg clopidogrel	VASP-PRI	Stent thrombosis	Stent thrombosis	6 months	NR	Stent thrombosis	NR	OR=1.112	1.041-1.188	0.002	No	NR	
	75 mg clopidogrel	VASP-PRI	Stent thrombosis	Stent thrombosis	6 months	NR	Stent thrombosis	NR	OR=1.164	1.008-1.334	0.039	Yes, variables with P<0.01 in the univariable analysis	NR	

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	Clopidogrel+aspirin	VASP	Definite stent thrombosis	Defined by ARC as ACS with angiographic or pathologic confirmation of thrombosis	Within 6 mo after stenting	Response vs. nonresponse to clopidogrel	Definite Stent thrombosis	NR	AUC, 0 .60 (SE 0.10) ROC cutoff, 42% Sensitivity 100% and specificity 37%; PPV 1%, NPV 100%; positive likelihood ratio,.1.6	For AUC, 0.39-0.80	0.547	NR	NR	NONE
						Response to clopidogrel N=145	Definite Stent thrombosis	0	OR (calculated) = 4.00	NR	P=0.36 (nonresponse vs response) [Fisher's exact test]]	NR	NR	Data also given for MEA+VASP in Fig 3
						Nonresponse to clopidogrel N=257		3						Data also given for MEA+VASP in Fig 3

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	Clopidogrel+aspirin	VASP	Composite of definite or probable stent thrombosis	Probable defined any unexplained death within 30 days or target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion		Response vs. nonresponse to clopidogrel	Composite of definite or probable stent thrombosis	--	AUC, 0 .53 (SE 0.94) ROC cutoff, 23% Sensitivity 100% and specificity 17%; PPV 2%, NPV 100%; positive likelihood ratio, 1.2	For AUC, 0.34-0.71	0.811	NR	NR	NONE
						Response to clopidogrel N=145	Composite of definite or probable stent thrombosis	2	OR (calculated) =1.42	NR	P=0.68 (nonresponse vs response) [Fisher's exact test]]	NR	NR	Data also given for MEA+VASP in Fig 3
						Nonresponse to clopidogrel N=257		5	NR	NR	NR	NR	NR	Data also given for MEA+VASP in Fig 3

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	Clopidogrel+aspirin	VASP	Probable stent thrombosis	Probable stent thrombosis		Response to clopidogrel N=145	Probable stent thrombosis	2	OR (calculated) =0.56	NR	P=0.57 (nonresponse vs response) [Fisher's exact test]]	NR	NR	Data also given for MEA+VASP in Fig 3
						Nonresponse to clopidogrel N=257		2	NR	NR	NR	NR	NR	Data also given for MEA+VASP in Fig 3
El Ghannudi, 2011{El, 2011 3 /id} 21524751 France NR	Clopidogrel + aspirin	VASP	Stent thrombosis definite	Stent thrombosis definite	9 months	non-diabetic responders (NDM-R) (PRI <61%)		2 (2.1%)			0.09 across this and next 3 rows (log rank)			
						non-diabetic low responders (NDM-LR) (PRI≥61 %)		0 (0%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						diabetic responders (DM-R) (PRI<61%)		3 (3.5%)						
						diabetic low responders (DM-LR) (PRI≥61%)		3 (3.9%)						
			Stent thrombosis probable			non-diabetic responders (NDM-R) (PRI <61%)		3 (3.2%)			0.61 across this and next 3 rows (log rank)			
						non-diabetic low responders (NDM-LR) (PRI≥61%)		2 (1.1%)						
						diabetic responders (DM-R) (PRI<61%)		1 (1.2%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						diabetic low responders (DM-LR) (PRI≥61%)		2 (2.6%)						
			Stent thrombosis possible			non-diabetic responders (NDM-R) (PRI <61%)		0 (0%)			0.0001 across this and next 3 rows (log rank)			
						non-diabetic low responders (NDM-LR) (PRI≥61%)		0 (0%)						
						diabetic responders (DM-R) (PRI<61%)		1 (1.2%)						
						diabetic low responders (DM-LR) (PRI≥61%)		5 (6.6%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			Stent thrombosis any			non-diabetic responders (NDM-R) (PRI <61%)		4 (4.2%)			0.002 across this and next 3 rows (log rank)			
						non-diabetic low responders (NDM-LR) (PRI≥61 %)		3 (1.7%)						
						diabetic responders (DM-R) (PRI<61 %)		5 (5.9%)						
						diabetic low responders (DM-LR) (PRI≥61 %)		10 (13.3%)						
El Ghannudi, 2010{El, 2010 74 /id} 20630458 France NR	Clopidogrel LD 300 or 600mg	VASP	Definite stent thrombosis	Definite stent thrombosis	9 months	Low responders N=178	Definite stent thrombosis	5 (2.8%)	NR	NR	0.49 (low responder vs responder) [chi square]	NR	NR	

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Responders N=275		4 (1.5%)						
	Clopidogrel LD 300 or 600mgl	VASP	Probable stent thrombosis	Probable stent thrombosis	9 months	Low responders N=178	Probable stent thrombosis	5 (2.8%)	NR	NR	0.27 (low responder vs responder) [chi square]	NR	NR	
						Responders N=275		3 (1.1%)						
	Clopidogrel LD 300 or 600mg	VASP	Possible stent thrombosis	Possible stent thrombosis	9 months	Low responders N=178	Possible stent thrombosis	6 (3.3%)	NR	NR	0.017 (low responder vs responder) [chi square]	NR	NR	
						Responders N=275		1 (0.4%)						
	Clopidogrel LD 300 or 600mg	VASP	All stent thrombosis	All stent thrombosis	9 months	Low responders N=178	All stent thrombosis	15 (8.3%)	NR	NR	0.018 (low responder vs responder) [chi square]	NR	NR	
						Responders N=275		9 (3.3%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Morel, 2011{Morel, 2011187 /id}21251579 France NR	clopidogrel 300-600 mg LD	VASP	All stent thrombosis	According to the Academic Research Consortium criteria	mean 9±2 months	low responders (PRI≥ 61%)	All stent thrombosis	15 (8.7%)	NR	NR	P=0.086 (low vs normal) chi square	NO	NR	Secondary
						normal responders (PRI<61 %)		8 (3.1%)						
	clopidogrel 300-600 mg LD	VASP	All stent thrombosis	According to the Academic Research Consortium criteria	mean 9±2 months	Quartile 1 (<40.30 %)	All stent thrombosis	1 (3%)	NR	NR	P=0.906 (low vs normal) fishers exact	NO	NR	Secondary
						Quartile 2 (40.30% – 55.83%)		1 (3.3%)						
						Quartile 3 (55.84% – 70.25%)		4 (12.6%)						
						Quartile 4 (>70.25 %)		6 (20.6%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel 300-600 mg LD	VASP	Definite stent thrombosis	acute coronary syndrome and angiographic or pathologic evidence of stent thrombosis	mean 9±2 months	low responders (PRI≥ 61%)	Definite stent thrombosis	5 (2.9%)	NR	NR	P=0.494 (low vs normal) chi square	NO	NR	Secondary
						normal responders (PRI<61 %)		4 (1.5%)						
	clopidogrel 300-600 mg LD	VASP	Definite stent thrombosis	acute coronary syndrome and angiographic or pathologic evidence of stent thrombosis	mean 9±2 months	Quartile 1 (<40.30 %)	Definite stent thrombosis	1 (3%)	NR	NR	P=0.562 (low vs normal) fishers exact	NO	NR	Secondary
						Quartile 2 (40.30% – 55.83%)		0						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Quartile 3 (55.84% – 70.25%)		0						
						Quartile 4 (>70.25 %)		1 (3.4%)						
	clopidogrel 300-600 mg LD	VASP	Probable stent thrombosis	unexplained death within 30 days or target vessel infarction without angiographic information	mean 9±2 months	low responders (PRI≥ 61%)	Probable stent thrombosis	5 (2.9%)	NR	NR	P=0.275 (low vs normal) chi square	NO	NR	Secondary
						normal responders (PRI<61 %)		3 (1.2%)						
	clopidogrel 300-600 mg LD	VASP	Probable stent thrombosis	unexplained death within 30 days or target vessel infarction without angiographic information	mean 9±2 months	Quartile 1 (<40.30 %)	Probable stent thrombosis	0	NR	NR	P=0.04 (low vs normal) fishers exact	NO	NR	Secondary

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Quartile 2 (40.30% – 55.83%)		1 (3.3%)						
						Quartile 3 (55.84% – 70.25%)		2 (6.3%)						
						Quartile 4 (>70.25 %)		2 (6.9%)						
	clopidogrel 300-600 mg LD	VASP	Possible stent thrombosis	unexplained death within 30 days or target vessel infarction without angiographic information	mean 9±2 months	low responders (PRI≥ 61%)	Possible stent thrombosis	5 (2.9%)	NR	NR	P=0.110 (low vs normal) chi square	NO	NR	Secondary
						normal responders (PRI<61 %)		1 (0.4%)						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel 300-600 mg LD	VASP	Possible stent thrombosis	unexplained death within 30 days or target vessel infarction without angiographic information	mean 9±2 months	Quartile 1 (<40.30 %)	Possible stent thrombosis	0	NR	NR	P=0.485 (low vs normal) fishers exact	NO	NR	Secondary
						Quartile 2 (40.30% – 55.83%)		0						
						Quartile 3 (55.84% – 70.25%)		2 (6.3%)						
						Quartile 4 (>70.25 %)		3 (10.3%)						
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	Clopidogrel	VASP	stent thrombosis	stent thrombosis	12 months	>57% N=40		0	OR (calculated) =0.35	NR	P=0.61 (>57% vs ≤ 57%)) [Fisher's exact]	NR	NR	NR
						</=57% N=14		0	NR	NR	NR	NR	NR	NR

Appendix Table E47: Results from studies assessing the ability of VASP to predict major adverse cardiovascular events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	Clopidogrel+aspirin	VASP	MACE	MACE included: 1) definite and probable ST according to the ARC-definition; 2) cardiovascular death, defined as death associated with ACS, significant arrhythmia, or congestive heart failure; and 3) non-fatal STEMI (STEMI: acute onset of prolonged typical ischaemic chest pains,	6 mo	PRI>60.2% (high reactivity, poor response) N=186	MACE	8.1%	NR	NR	NR	NR	NR	Get n's from Fig 1 (pasted in on last page of this form)

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
				ST-segment elevation of at least 1 mm in 2 or more contiguous electrocardiogram leads and increased biomarkers of myocardial necrosis)										
						VASP result: PRI≤60.2% (low reactivity, good response) N=114		0.9%	Relative risk reduction= 89%		0.007 (>60.2 vs ≤60.2)			Get n's from Fig 1 (pasted in on last page of this form)
						Cutoff 60.2%			AUC 0.683	NR	0.014			ROC curves in Fig 2

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Bonello, 2007{Bonello, 2007 199 /id} 17488353 France NR	clopidogrel LD 300-mg followed by 75 mg daily	VASP	MACE	Cardiovascular death, ischemic stroke, recurrent ACS, and repeated revascularization either by coronary angioplasty or bypass surgery	6-month	Quintile 1 N=28	MACE	0	NR	NR	NR	NR	NR	
						Quintiles 2-5 N=144		21(14.5)	OR (calculated)= 0.1	NR	P= 0.11 (Q2-5 vs Q1) [Fisher's exact]	NR	NR	
El Ghannudi 2011{El, 2011 3 /id} 21524751 France NR	Clopidogrel + aspirin	VASP	MACE	Not explicitly defined	9 months	non-diabetic responders (NDM-R) (PRI <61%)		15 (15.8%)			0.26 across all 4 phenotypic groups with 61% cutoff (log-rank test)			
						non-diabetic low responders (NDM-LR) (PRI≥61%)		23 (13.1%)	HR 1.06	0.55 – 2.03	0.87 (univariate analysis)			

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						PRI > 50% (LR to clopidogrel) in patients without diabetes			HR 1.15	0.60 – 2.21	0.67 (univariate analysis)			
						diabetic responders (DM-R) (PRI<61%)		12 (14.1%)						
						diabetic low responders (DM-LR) (PRI≥61%)		17 (23%)	HR 2.01	0.96 – 4.23	0.06 (univariate analysis)			
						Same as just above			HR 2.44	1.10 – 5.39	0.027 (multivariate analysis)			
						PRI > 50% (LR to clopidogrel) in patients with diabetes			HR 1.28	0.59 – 2.77	0.52 (univariate analysis)			
El Ghannudi, 2010{El, 2010 74 /id} 20630458 France NR	Clopidogrel LD 300 or 600mg	VASP	MACE	MACE	9 months	Low responders	MACE	35/178 (19.7)	NR	NR	0.06 (low responders vs responders)	NR	NR	
						responders		22/275 (13.1)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel LD 300 or 600mg	VASP PRI	MACE	MACE	9 months	PRI≥61%	MACE	NR	HR=1.54	0.97-2.46	0.07 (low responders vs responders) [Cox regression]	No	NR	
						PRI≥50%	MACE	NR	HR=1.36	0.83-2.22	0.22 (low responders vs responders) [Cox regression]	No	NR	
						PRI≥69%	MACE	NR	HR=1.14	0.67-1.92	0.64 (low responders vs responders) [Cox regression]	No	NR	
Morel, 2011{Morel, 2011 187 /id} 21251579 France NR	clopidogrel 300-600 mg LD	VASP	MACE	all-cause mortality, nonfatal myocardial infarction, or target lesion revascularization	mean 9±2 months	low responders (PRI≥ 61%)	MACE	35 (20.2%)	HR=1.54	0.96-2.45	P=0.069 (low vs normal) [Cox regression]	NO	NR	Secondary
						normal responders (PRI<61%)		36 (13.8%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	clopidogrel 300-600 mg LD	VASP	MACE	all-cause mortality, nonfatal myocardial infarction, or target lesion revascularization	mean 9±2 months	low responders (PRI≥ 61%)	MACE	35 (20.2%)	HR=2.36	1.35-4.15	P=0.003 (low vs normal) [Cox regression]	YES; Planned PCI; Drug-eluting stent;	NR	Secondary
						normal responders (PRI<61%)		36 (13.8%)						
	clopidogrel 300-600 mg LD	VASP	MACE	all-cause mortality, nonfatal myocardial infarction, or target lesion revascularization	mean 9±2 months	Quartile 1 (<40.30%)	MACE	5 (15.2%)	NR	NR	P=0.019 (low vs normal) fishers exact	NO	NR	Secondary
						Quartile 2 (40.30%–55.83%)		3 (10%)						
						Quartile 3 (55.84%–70.25%)		9 (31%)						
						Quartile 4 (>70.25%)		7 (24.1%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	Clopidogrel	VASP	combined cardiovascular endpoint consisting of cardiac death, nonfatal myocardial infarction, stent thrombosis, ischaemic stroke, and urgent target vessel revascularisation	NR	12 mo	<51% PRI (n is NR)	YES event	2	NR	NR	NR	NR	NR	NR
						51-58% PRI (n is NR)		2	NR	NR	NR	NR	NR	NR
						59-71% PRI (n is NR)		6	NR	NR	NR	NR	NR	NR
						>71% PRI (n is NR)		5	NR	NR	NR	NR	NR	NR

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						>57%		5/40 (12%) [per data in rest of table, s/b 12, not 5 [see Table 2 in paper])	HR = 4.3	1.3-9.9	0.0136 (>57% vs ≤ 57%) [log rank]	NR	NR	K-M curve given in Fig. 2B
						</=57%		6/14 (41.4%) [per data in rest of table, s/b 3, not 6 [see Table 2 in paper])	NR	NR	NR	NR	NR	K-M curve given in Fig. 2B
									AUC 0.69	0.53-0.86	0.027			ROC curve in Fig. 2A
Frere, 2007{Frere, 2007 193 /id} 17938809 France NR	600 mg loading dose of clopidogrel and maintaining 75mg daily	VASP	CV event	CV death, acute or subacute stent thrombosis, recurrent ACS and stroke	30 days after PCI	≥53% N=106	CV event	13 (12.3%)	AUC: 0.73±0.08 OR (calculated)= 12.3	NR	P= 0.017 (>53 vs ≤ 53%) [Fisher's exact]	NR	NR	NR
						<53% N=89	CV event	1 (1.1%)						

Appendix Table E48: Results from studies assessing the ability of VASP to predict stroke in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	Clopidogrel	VASP	ischaemic stroke	Ischemic stroke	1 year	>57% (n=40)	Suboptima inhibition	1	OR(calculated) =1.1	NR	P=0.953 (>57% vs ≤ 57%) [Fisher's exact]	NR	NR	NR
						</=57% (n=14)		0	NR	NR	NR	NR	NR	NR

Appendix Table E49: Results from studies assessing the ability of VASP to predict other clinical events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Djukanovic, 2008{Djukanovic, 2008 163 /id} 18719318 Serbia NR	clopidogrel 75 mg + Aspirin 100 mg	VASP phosphorylation	Revascularization	NR	1 year	Bad responder	Revascularization	0	OR (calculate)=1	NR	P=1.0 (bad vs good responder) [Fisher's exact test]	NR	NR	NR
						Good responder		0	NR	NR	NR	NR	NR	NR
Bonello, 2007{Bonello, 2007 199 /id} 17488353 France NR	clopidogrel LD 300-mg followed by 75 mg daily	VASP	ACS	defined according to the ACC/AHA guidelines	6-month	Quintile 1	ACS	0	OR (calculate)=410	NR	P<0.0001 (Q1 vs Q2-5) [Fisher's exact test]	NR	NR	
						Quintiles 2-4		18(15.6)						
	clopidogrel LD 300-mg followed by 75 mg daily	VASP	PCI	PCI	6-month	Quintile 1	PCI	0	OR (calculate)=410	NR	P<0.0001 (Q1 vs Q2-5) [Fisher's exact test]	NR	NR	
						Quintiles 2-5		16(13.9)						

	clopidogrel LD 300-mg followed by 75 mg daily	VASP	Bypass surgery	Bypass surgery	6-month	Quintile 1	Bypass surgery	0	OR (calculate)=307	NR	P<0.0001 (Q1 vs Q2-5) [Fisher's exact test]	NR	NR	
						Quintiles 2-5		2(1.7)						
El Ghannudi, 2011{El, 2011 3 /id} 21524751 France NR	Clopidogrel + aspirin	VASP	Target lesion revascularization		9 months	non-diabetic responders (NDM-R) (PRI <61%)		9 (9.5%)	OR (calculate)=22	NR	P=0.04 (nonresponders vs responder) [Fisher's exact test]			
						non-diabetic low responders (NDM-LR) (PRI≥61%)		17 (9.7%)						
						diabetic responders (DM-R) (PRI<61%)		6 (7.1%)						
						diabetic low responders (DM-LR) (PRI≥61%)		4 (5.4%)						
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	Clopidogrel	VASP	urgent target vessel revascularisation		1 year	>57%		7/40	OR (calculate)=0.78	NR	P=0.71 (>57% vs ≤57%) [Fisher's exact test]	NR	NR	NR
						</=57%		3/14						

Appendix Table E50: Results from studies assessing the ability of VASP to predict platelet reactivity during followup (when used as a continuous measurement) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Kalantzi, 2011{Kalantzi, 2011 19 /id} 21255245 Greece NR	Clopidogrel 300 mg loading & 75 mg/d	VASP at Day 5	Percent inhibition of maximum platelet aggregation (IPA,%)	Light transmittance aggregometry in platelet-rich plasm using 2.5 µM ADP & IPA achieved within 3 min	30 days	Nonresponder	15	51.8%	NR	NR	NR	NR	NR	NR	NR	NR	Value obtained from digitizing Fig1I One P value of 0.01 is reported between IPA values of 30 days vs 5 days but not specified for which ADP conc
					30 days	Responder	46	56.2%	NR	NR	NR	NR	NR	NR	NR	NR	
			Percent inhibition of maximum platelet aggregation (IPA,%)	Light transmittance aggregometry in platelet-rich plasm using 5 µM ADP & IPA achieved within 3 min	30 days	Nonresponder	15	40.9%	NR	NR	NR	NR	NR	NR	NR	NR	
					30 days	Responder	46	50.6%	NR	NR	NR	NR	NR	NR	NR	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			Percent inhibition of maximum platelet aggregation (IPA,%)	Light transmittance aggregometry in platelet-rich plasm using 10 µM ADP & IPA achieved within 3 min	30 days	Nonresponder	15	30.4%	NR	NR	NR	NR	NR	NR	NR	
					30 days	Responder	46	35.5%	NR	NR	NR	NR	NR	NR	NR	
			P-selectin expression (% positive cells)	Flow cytometry, using anti-CD62P-PE after activation with 100 µM of ADP (10 min, in static conditions at 37 °C)	30 days	Nonresponder who underwent PCI	8	Median=29	Range=24,35	NR	NR	NR	NR	NR	NR	
					30 days	Nonresponder who underwent conservative treatment	7	Median=27	Range=22,32	NR	NR	NR	NR	NR	NR	
					30 days	Responder	46	Median=27	Range=24,34	NR	NR	NR	NR	NR	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			Platelet/monocyte conjugates (% positive particles)	Flow cytometry, using anti-CD61-PerCP and anti-CD14-FITC after activation with 100 µM of ADP (10 min, in static conditions at 37 °C)	30 days	Nonresponder who underwent PCI	8	Median=49	Range=42,57	NR	NR	NR	NR	NR	NR	
					30 days	Nonresponder who underwent conservative treatment	7	Median=51	Range=45,60	NR	NR	NR	NR	NR	NR	
					30 days	Responder	46	Median=44	Range=37,49	NR	NR	NR	NR	NR	NR	
			Platelet/neutrophil conjugates (% positive particles)	Flow cytometry, using anti-CD41a-FITC and anti-CD45-PE after activation with 100 µM of ADP (10 min, in static conditions at 37 °C)	30 days	Nonresponder who underwent PCI	8	Median=25	Range=21,32	NR	NR	NR	NR	NR	NR	
					30 days	Nonresponder who underwent conservative treatment	7	Median=26	Range=21,32	NR	NR	NR	NR	NR	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	No. with given phenotype	Platelet reactivity measurement for the phenotype group [metric]	SD/SE (report value and metric)	Statistical method	Mean difference (state if other metric)	95% CI of mean difference (state if other metric)	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
					30 days	Responder	46	Median=23	Range=17,28	NR	NR	NR	NR	NR	NR	

Appendix Table E51: Results from studies assessing the ability of VASP to predict platelet reactivity during followup (when used as a discrete outcome) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Clopidogrel 75 mg MD	VASP	VASP	PRI as measured by VASP	24 hrs after PCI	Platelet reactivity index ≥ 69% by VASP (? Low efficiency)	Platelet reactivity index ≥ 69% by VASP (? Low efficiency)	1	NR	NR	NR	0.27 (fisher's exact calculated from data)	NR	NR	Fig 1B
						Platelet reactivity index ≥ 69% by VASP (? Low efficiency)	Platelet reactivity index <69%	7	NR	NR	NR	NR	NR	NR	
						Platelet reactivity index <69% by VASP	Platelet reactivity index ≥ 69%	0	NR	NR	NR	NR	NR	NR	
						Platelet reactivity index <69% by VASP	Platelet reactivity index <69% by VASP	22	NR	NR	NR	NR	NR	NR	

Kalantzi 2011{Kalantzi, 2011 19 /id} 21255245 Greece NR	Clopidogrel 300 mg loading & 75 mg/d	VASP at Day 5	Nonresponder by VASP	PRI ≥ 50%	30 days	Nonresponder	Nonresponder	3	PRI≤50%	NR	NR	0.01264 (fisher's exact calculated from data)	N	NO	
						Nonresponder	Responder	12	NR	NR	NR	NR	NR	NR	NR
						Responder	Nonresponder	0	NR	NR	NR	NR	NR	NR	NR
						Responder	Responder	46	NR	NR	NR	NR	NR	NR	NR
Bjelland, 2010{Bjelland, 2010 42 /id} 20727659 Norway NR	Clopidogrel 300-600 mg LD + 75 mg MD	VASP Platelet reactivity index < 0.5 at Day 1	Satisfactory Clopidogrel effect	Platelet reactivity index < 0.5	Day 3	Satisfactory (PRI <0.5) at day 1	Satisfactory (PRI <0.5) at day 3	0	0.5	NR	NR	Not calculable as no patients had PRI<50% at baseline	NR	NR	
						Satisfactory (PRI ≥0.5) at day 1	Unsatisfactory (PRI ≥0.5 at day 3)	0							
						Unsatisfactory (PRI ≥0.5) at day 1	Unsatisfactory (PRI ≥0.5) at day 3	20							
						Unsatisfactory (PRI ≥0.5) at day 1	Satisfactory (PRI <0.5 at day 3)	5							

Djukanovic, 2008{Djukanovic, 2008 163 /id} 18719318 Serbia NR	clopidogrel 75 mg + Aspirin 100 mg	VASP phosphorylation	Good response	PRI≤50 %	7 days	Rapid response	Good response	NR	NR	NR	NR	NR	NR	NR	Text mentions that "all the patients with rapid response still had PRI ≤50% (good responders) on day 7" but actual numbers in each outcome group can only be obtained from digitized Fig 2B which is not clear
							Bad response	NR	NR	NR	NR	NR	NR	NR	
						Not Rapid response	Good response	NR	NR	NR	NR	NR	NR	NR	
							Bad response	NR	NR	NR	NR	NR	NR	NR	
Palmerini, 2010{Palmerini, 2010 81 /id} 19604542 Italy DOUBLE	Clopidogrel 300 mg LD + 75 mg MD	VASP	VASP	PRI>50 % at 1 month	1 month	Poor responder	Poor responder	10	NR	NR	NR	1.0 (fisher's exact calculated from data)	NR	NR	
						Poor responder	Normal responder	11	NR	NR	NR	NR	NR	NR	
						Normal responder	Poor responder	2	NR	NR	NR	NR	NR	NR	

						Normal responder	Normal responder	1	NR	NR	NR	NR	NR	NR	
	Clopidogrel 300 mg LD + 150 mg MD	VASP	VASP	PRI>50 % at 1 month	1 month	Poor responder	Poor responder	3	NR	NR	NR	0.54 (fisher's exact calculated from data)	NR	NR	
						Poor responder	Normal responder	17	NR	NR	NR	NR	NR	NR	
						Normal responder	Poor responder	1	NR	NR	NR	NR	NR	NR	
						Normal responder	Normal responder	3	NR	NR	NR	NR	NR	NR	

Appendix Table E52: Quality Assessment of studies assessing the predictive ability of VASP in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	yes	yes	yes	low	low	NR	yes	unclear	low	yes	yes	low	low	no	yes	yes	yes	low
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	NR	yes	yes	low	low	NR	yes	unclear	high	No	NR	high	high	no	yes	yes	yes	low
Blindt, 2007{Blindt, 2007 189 /id} 18064332 Germany NR	NO	NO	yes	HIGH	LOW	NR	No	unclear	high	yes	NR	Unclear	low	no [6 months]	yes	yes	yes	low
Kalantzi 2011{Kalantzi, 2011 19 /id}	NR	Yes	No	UNCLEAR	LOW	NR	Yes	unclear	Low	No	NR	High	High	no [30 days]	yes	yes	yes	low

21255245 Greece NR																		
Siller-Matula 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	yes	yes	yes	low	low	NR	Yes	unclear	Low	yes	NR	Unclear	low	no [6 months]	yes	yes	yes	low
Bjelland, 2010{Bjelland, 2010 42 /id} 20727659 Norway NR	NO	Yes	No	HIGH	High	NR	Yes	unclear	Low	No	NR	High	High	no [2 days]	yes	yes	yes	low
Bonello, 2007{Bonello, 2007 199 /id} 17488353 France NR	yes	yes	yes	low	low	NR	NR	unclear	Low	yes	NR	Unclear	low	no [6 months]	yes	yes	yes	low
Djukanovic, 2008{Djukanovic, 2008 163 /id} 18719318 Serbia NR	No	yes	yes	low	low	NR	Yes	unclear	Low	yes	NR	Unclear	low	Yes [1 year]	yes	yes	yes	low
El Ghannudi, 2011{El, 2011 3 /id}	yes	yes	yes	low	low	NR	Yes	unclear	Low	yes	yes	low	low	No [Mean 9 months]	yes	yes	yes (<2% loss though it isn't	low

21524751 France NR																	explained)	
El Ghannudi, 2010{El, 2010 74 /id} 20630458 France NR	yes	yes	yes	low	low	NR	NR	unclear	Low	yes	NR	Unclear	low	No [9 months]	yes	yes	Yes	low
Morel, 2011{Morel, 2011 187 /id} 21251579 France NR	yes	yes	yes	low	low	Yes	Yes	Low	Low	yes	yes	low	low	No [Mean 9±2 months]	yes	yes	Yes	low
Palmerini, 2010{Palmerini, 2010 81 /id} 19604542 Italy DOUBLE	yes	yes	yes	low	low	NR	Yes	unclear	Low	NO	NR	High	High	No [1 month]	yes	yes	Yes	low
Schafer, 2011{Schafer, 2011 11 /id} 21655677 Germany NR	yes	YES (for clinicial; controls were included but not germane to data of interest)	yes	low	low	NR	Yes	unclear	Low	Yes	NR	unclear	Low	Yes [12 months]	yes	yes	yes	Low

Frere, 2007{Frere, 2007 193 /id} 17938809 France NR	yes	No	yes	low	low	NR	No	High	Low	yes	NR	Unclear	low	no [30 days]	yes	yes	yes	low

Appendix Table E53: Baseline characteristics of patients with ischemic heart disease in studies assessing the predictive ability of Multiplate Analyzer

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[25]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	30 NR 84 63±10	100 NR CVD 7 PCI 43 NR NR 10 37 NR	hyper 77 57 HTN 77 33	NR 100 100 NR	NR NR NR	not used	Patients had been on chronic aspirin (100 mg/day) and clopidogrel (75 mg/day) treatment for three months on average.	All patients received unfractionated heparin and 250 mg of injectable acetyl-salicylic acid during PCI
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	222 ?Asian 152 (69) 63.3 ± 10	100 NR CVA: 14.9 PCI: 37 (16.7); CABG: 1 (0.5) NR NR	Hypercholesterolemia: 46.8 Current: 12.2 HTN: 72.1 32	NR 72.1 89.6 NR	100 Drug eluting Multi-vessel; Stents/pt: 1.8±1	Patients undergoing percutaneous coronary intervention (PCI) for CAD	All patients were pretreated with aspirin (100 mg/d) and clopidogrel (75 mg/d) at least 5 days before PCI or received oral loading doses of 250	NR

[25] Mean (standard deviation), unless otherwise stated.

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[25]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR 5.9 NSTEMI: 10.1					mg aspirin and 300 mg clopidogrel 12 to 24 hours before PCI. Maintenance doses of 100 mg aspirin and 75 mg clopidogrel after PCI After PCI, dual antiplatelet therapy with 100 mg/d aspirin and 75 mg/d clopidogrel was continued for at least 6 months	
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	2533 NR 2034 (80.3%) mean: 67.8	NR NR NR CABG: 14.3% NR NR	Hypercholesterolemia: 68.4% Active: 13.2% Arterial HTN:90.6% 28.6%	10.9% Thienopyridine: 41.3% 74.3 NR	Stents per lesion: 1.3; Lesions per patient: 1.9 NR Multivessel disease: 85.5%	Patients undergoing PCI with stenting for ACS and CAD	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD Aspirin: 500 mg IV LD + 100 mg	PCI: Intravenous anticoagulant: unfractionated heparin or bivalirudin (140 U/kg body weight for unfractionated heparin and for bivalirudin with a dosing regimen of 0.75 mg/kg body

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[25]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR 31.4 NSTEMI/STEMI: 14.5%					aspirin (twice per day) MD	weight for bivalirudin before PCI, followed by an infusion of 1.75 mg/kg/h bivalirudin for the procedure); Some pts received glycoprotein IIb/IIIa inhibitor abciximab (0.25 mg/kg of body weight bolus, followed by a 0.125 µg/kg/min infusion for 12 h) with reduced heparin dose
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	1608 NR 1234 (77%) 67.5±40.5	NR NR NR CABG: 14% NR NR NR 32	Hypercholesterolemia: 70% Active: 13% HTN: 91.6% 29	NR NR 99.1 NR	NR NR NR	Patients undergoing PCI with stenting for ACS and CAD	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	PCI: Intravenous anticoagulant: unfractionated heparin or bivalirudin (140 U/kg body weight for unfractionated heparin and for bivalirudin with a dosing regimen of 0.75 mg/kg body weight for bivalirudin before PCI, followed by an infusion of 1.75 mg/kg/h bivalirudin for the

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[25]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR						procedure); Some pts received glycoprotein IIb/IIIa inhibitor abciximab (0.25 mg/kg of body weight bolus, followed by a 0.125 µg/kg/min infusion for 12 h) with reduced heparin dose
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	1608 NR 1234 (76.7%) 67.4	NR NR NR CABG: 14.4% 66.9 22.2 NR 31.5 STEMI: 2.5%; NSTEMI: 8.4%	Hypercholesterolemia: 69.8% Active: 13.4% HTN: 91% 28.7	NR NR NR NR	94.8% BMS: 2.2%; DES: 92.6% Multivessel: 85.1%	patients undergoing PCI	600 mg clopidogrel before PCI and 500 mg aspirin LD directly before the intervention; Postintervention therapy: clopidogrel 75 mg twice daily for 3 days, then 75 mg per day for 6 months with aspirin 100 mg twice daily	Periprocedural therapy: unfractionated heparin (as a bolus of 140 U/kg bodyweight) or bivalirudin (0.75 mg per kg bodyweight bolus, followed by an infusion of 1.75 mg per kg bodyweight per hour for the duration of the procedure) or abciximab (0.25-mg/kg bodyweight bolus, followed by an infusion of 0.125 µg/kg bodyweight per min for 12 hours)

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[25]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
								along with 70 U/kg bodyweight unfractionated heparin
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 NR 205 62±16	43.3 NR NR PCI 24.3 NR see UA/NSTEMI 10 22.7 29.7/34.3	hyper 69.3 27.3 HTN 74.7 27.3	NR 100 100 81.3	100 DES 65.3 multi-vessel 58.7	PCI and coronary stenting	Clopidogrel-naïve patients received a 300 or 600 mg loading dose (LD). Patients on chronic clopidogrel therapy with 75 mg clopidogrel of at least seven consecutive days did not receive an additional LD.	According to actual evidence, all patients received in parallel ASA (100 mg daily dose). The use of GP-IIb/IIIa-blockers during PCI as well as the choice of the anticoagulant depended on the individual situation and the thrombus load at angiography, and was left to the discretion of the operator
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	416 NR 76 64±12	100 NR NR 47	hyper 76 55 85 32	NR 100 100 77	99 NR NR	PCI with stenting	Clopidogrel loading dose at least 2 hr before PCI (600 mg); thereafter, a daily dose of	Also all patients received unfractionated heparin (100 IU per kg) during PCI and 250 mg aspirin

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[25]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR NR 13 33 NR					75 mg, with planned treatment with clopidogrel and aspirin for at least 6 months.	intravenously immediately after stent placement (and daily dose of 100 mg thereafter).
Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	219 NR 168 (77%) Mean/SD 66+/-9 yr	NR ACS 82 (37%) [not sure ACS=heart failure] NR PCI 70 (32%); CABG 26 (12%) 137 (63%) NR NR 60 (27%) NR	155 (71%) Current 57 (26%) Atrial HTN 163 (74%) 43 (20%)	NR 100%; (pretreatment in study) 100% (pretreatment in study) NR	NR 1 DES 164 (75%); BMS 55 (25%) Multi 77 (34%)	Patients with stable angina or ACS with an indication for PCI, undergoing PCI with stenting	500 mg ASA intravenously (unless if already on 100 mg daily); then 600 mg clopidogrel loading dose (unless already on 75 mg daily)	unfractionated heparin (70-100 U/kg body weight) before or at time of PCI
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	182 (163 full responders, 19 dual nonresponders) NR 130 (71%) Median age (95% CI); Nonresponders 68 (59–72); Responders 65 (67–72)	NR NR NR NR 78 (43%) 14 (8%) NR	Hypercholesterolemia 113 (82%) 61 (34%) HTN (arterial) 146 (80%) 57 (31%)	NR 100% 100% NR	100% DES only 77 (42%); BMS only 75 (41%); Both 23 (13%) 3-vessel 90 (49%)	CAD patients who underwent PCI	Emergency patients with ACS received 0.5 g ASA intravenously and an oral loading dose of 600 mg clopidogrel before PCI. Electively hospitalized patients with suspected	A single bolus of unfractionated heparin (10 000 U) was given immediately before PCI. The type of stent used for PCI was left at the discretion of the operator.

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[25]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR 40 (22%)/52 (29%)					CAD or suspected progression of CAD received 0.5 g ASA intravenously before and loading dose of 600 mg clopidogrel immediately after PCI and stenting. After PCI, all patients received maintenance doses of 100 mg ASA and 75 mg clopidogrel once daily.	

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DES=Drug eluting stent; HTN = hypertension, MI = myocardial infarction; NSTEMI = non-ST-elevation MI; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack;

Appendix Table E54: Baseline characteristics of patients with cerebrovascular disease in studies assessing the predictive ability of Multiplate Analyzer

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[26]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	50 NR 36(72) 65±8	NR NR Stroke 31 (63); TIA 19 (38) NR NR NR NR NR NR	NR NR NR NR	NR 100% NR NR	NR NR NR	Patients with extracranial or intracranial stenosis	All 50 of the patients received a loading dose of 300 mg of clopidogrel at least 12 hours before the intervention and after loading were treated with 75 mg/day continuously. All of the patients received 100 mg of aspirin per day according to the usual protocol.	None

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;

[26] Mean (standard deviation), unless otherwise stated.

Appendix Table E55: Study design characteristics of studies assessing the predictive ability of Multiplate Analyzer in patients with ischemic heart disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Prospective observational study	NO	NR	Patients undergoing PCI for coronary artery disease	Aug 2007-Apr 2008	1 day	followup after intervention	YES Accrual=100%	Non-industry [grant from the Jubiläumsfond of the Austrian National Bank (Nr. 12565)]
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	observational study	YES	Consecutive patients	Patients undergoing percutaneous coronary intervention (PCI) for CAD	Aug-Oct 2009	30 days for all patients	followup after intervention	NO	Non-industry only - grant from Government & non-profit foundation
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Prospective cohort	YES	Consecutive	Patients undergoing PCI with stenting for ACS and CAD	February 2007 to December 2008	30 days	followup after intervention	NR	partly industry (Material for platelet function analysis on the Multiplate device were provided free of charge from Dynabyte, Munich, Germany)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Prospective observational study	YES	Consecutive	Patients undergoing PCI with stenting for ACS and CAD	February 2007 to April 2008	30 day and 6 months day followup	Followup after intervention	YES; Accrual>80%	partly industry (Material for platelet function analysis on the Multiplate device were provided free of charge from Dynabyte, Munich, Germany)
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Prospective observational study	YES	Consecutive	patients undergoing PCI	NR	1 year	Followup after intervention	NR	Partial industry [Material for platelet function analysis on the Multiplate device was provided free of charge by Dynabyte (Munich, Germany)]
Freynhofer, 2011{Freynhofer, 2011 1 /id}	Prospective, registry data	NO	Consecutive	Adults undergoing PCI and coronary	May 2009 to February 2010	Total 6 month, mean/SD 189/68 days	Inpatient, then outpatient visits after	YES [YES]	Non-industry only

21614416 Austria NR				stenting with no contraindication for dual antiplatelet therapy for up to one year			discharge, at 1 mo and 6 mo		
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	Prospective observational	NO	Consecutive	Adults with CAD undergoing PCI with stenting (most elective) with clopidogrel and aspirin therapy	NR	Total, 6 month	Inpatient with followup after discharge (contacted patients at 3 and 6 mo after)	YES (YES—80%)	Nonindustry only
Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	Prospective	NO	Consecutive	Patients with stable angina or ACS with an indication for PCI, undergoing PCI with stenting	Jan 2007-March 2008	Total 30 days after PCI	Inpatient and then 30-day followup as outpatient	NO	Non-industry only
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Prospective	NO	Consecutive	CAD patients who underwent PCI and received standard therapy including ASA and clopidogrel	June 2006 to August 2006	Median follow-up was 419 days (95% CI 414–420 days)	Inpatient and then followup 30 days after PCI	NR	NR

Appendix Table E56: Study design characteristics of studies assessing the predictive ability of Multiplate Analyzer in patients with cerebrovascular disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	prospective Cohort	No	Consecutive	Patients with extracranial or intracranial stenosis	NR	NR	Hospital inpatient	NR	NR

Appendix Table E57: Study characteristics in patients with cerebrovascular disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Prospective observational study	NO	NR	Patients undergoing PCI for coronary artery disease	Aug 2007-Apr 2008	1 day	followup after intervention	YES Accrual=100%	Non-industry [grant from the Jubiläumsfond of the Austrian National Bank (Nr. 12565)]

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-elevation; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; DES=drug eluting stent; CABG=coronary artery bypass grafting; AA= arachidonic acid; SD=standard deviation; RCT=randomized controlled trial; NR=not reported;

Appendix Table E58: Phenotypic test details in studies assessing the predictive ability of Multiplate Analyzer in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer*	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Multiplate Analyzer Impedance aggregometry Dynabyte Medical, Munich, Germany	Adenosine diphosphate (ADP), prostaglandin (PGE1)	1st blood sample: in catheterization laboratory, after PCI and after 250 mg IV aspirin 2nd blood sample: 20-24 hours after PCI 3.8% citrate, 3.2% citrate and recombinant hirudin NR Clopidogrel came first 0.04 days (1 hour)	Impedence between 16-88 units Impedence between <16 units	Based on Normal ranges as reported by manufacturer	Impedence between 16-88 units: 20 (67%) Impedence between <16 units:10 (33%)
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	Multiple Electrode Platelet Aggregometry Whole blood impedence aggregometry Multiplate analyzer Dynabyte	ADP	Before PCI; 8 and 24 hrs after PCI lepirudin (25 µg/mL) 5 days (clopidogrel came first) 0.125 days (Within 3 hrs)	Multiple electrode aggregometry with ADP was not used to classify clopidogrel response in patients	NR	NR
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	multiple electrode aggregometry Multiplate analyzer Dynabyte, Munich, Germany	6.4 µmol/l ADP	Whole blood; after diagnostic angiography, before PCI lepirudin (25 µg/ml) 0.08 days (2 hours) NR	Enhanced Responders (<188 aggregation units*min) Remaining patients - Not enhanced responders (≥188 aggregation units*min) From Sibbing 2010 PMID: 20633826	ROC curve of all participants in the study	Enhanced Responders (<188 aggregation units*min): 975 (38.5%) Remaining patients - Not enhanced responders (≥188 aggregation units*min): 1558 (61.5%) From Sibbing 2010 PMID: 20633826

				Enhanced responder (AUC≤188) Normal responder (AUC189-467) Low responder (AUC≥468) For Stent thrombosis >468 aggregation units*min ≤468 aggregation units*min		Enhanced responder (AUC≤188): 975 (38%) Normal responder (AUC189-467): 1130 (45%) Low responder (AUC≥468): 428 (17%) For Stent thrombosis >468 aggregation units*min: 428 (17%) ≤468 aggregation units*min: 1180 (83%)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	multiple electrode platelet aggregometry multiple electrode platelet aggregometry Multiplate Dynabyte, Munich, Germany	6.4 µmol/l ADP	Whole blood; after diagnostic angiography, before PCI, and at least 2 min after administration of intravenous aspirin. lepirudin (25 µg/ml) 0.08 days (2 hours) 0.02 days (30 mins)	Low Responders (Quintile 5: >416 aggregation units*min) Normal Responders (Quintile 1-4 ≤416 aggregation units*min) By other quintiles High Responders (Quintile 1 ≤124 AU*min) Normal Responders (Quintile 2 >124-≤192 AU*min) Normal Responders (Quintile 3 >192-≤261 AU*min) Normal Responders (Quintile 4 >261-≤416 AU*min) Low Responders	Based on literature	Low Responders (Quintile 5: >416 aggregation units*min): 323 (20.1%) Normal Responders (Quintile 1-4 ≤416 aggregation units*min): 1285 (79.9%) By other quintiles High Responders (Quintile 1 ≤124 AU*min): 318 (19.8%) Normal Responders (Quintile 2 >124-≤192 AU*min): 322 (20%) Normal Responders (Quintile 3 >192-≤261 AU*min): 322 (20%) Normal Responders (Quintile 4 >261-≤416 AU*min): 323 (20.1%)

				(Quintile 5: >416 AU*min)		Low Responders (Quintile 5: >416 AU*min): 323 (20.1%)
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	multiple electrode platelet aggregometry multiple electrode platelet aggregometry Multiplate Dynabyte, Munich, Germany	ADP	After diagnostic angiography lepirudin NR NR	Low response (Upper quintile of MEA measurements [>416 AU*min]) Normal response (Lower 4 quintiles of MEA measurements [≤416 AU*min])	Based on literature – a previous study	Low response (Upper quintile of MEA measurements [>416 AU*min]): 323 (20%) Normal response (Lower 4 quintiles of MEA measurements [≤416 AU*min]): 1285 (80%)
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	MEA/Impedence aggregometry Multiple Platelet Function Analyzer Dynabyte Medical, Munich, Germany	ADP 6.5 umol	Samples were incubated and stirred at 37°C for 3 min in the test cuvettes. Agonists were added and the increase in electrical impedance was recorded for 6 min Lithium-heparin + 0.9% sodium chloride 6-24 h (morning) after PCI Within 30 min to 3 hr after blood collection	MEA result <47 U (high on-treatment platelet reactivity, poor response) MEA result >47 U (low reactivity, good response)	previous published literature	MEA result <47 U (high on-treatment platelet reactivity, poor response); 57/196 (29%) MEA result >47 U (low reactivity, good response); 139/196 (71%)
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	Multiple electrode aggregometry Multiplate analyzer Dynabyte Medical, Munich, Germany	ADP (6.4 uM) + PGE_1 (9.4 nM)	Samples taken directly after PCI and at least 5 min after IV aspirin dose (250 mg). Hirudin and 0.9% NaCl Dose first (clopidogrel loading dose given at least 2 hr before PCI). NR	MEA (n=402; 14 pts not tested because of glycoprotein IIb/IIIa): No platelet hyperreactivity (<54U) Platelet hyperreactivity (≥54U)	ROC curve analysis	MEA (n=402; 14 pts not tested because of glycoprotein IIb/IIIa): 346 (86%) No platelet hyperreactivity (<54U) Platelet hyperreactivity (≥54U) 56 (14%)
Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	whole blood impedance platelet aggregometry the multiple electrode aggregometry Multiplate analyzer	ADP 6.4 umol/L	peripheral venous blood samples were drawn from an antecubital vein using a 21-gauge needle and collected in a polyethylene tube containing a stabilized direct thrombin inhibitor (melagatran 15 µg/mL). Sample was diluted with NaCl 0.9% in a 1:1 ratio	Low response to clopidogrel only= results of ADP test AUC within the upper quartile and results of aspirin test AUC below the upper quartile.	AUC plots in present study (see Fig. 4 and previous publications and findings [refs 7,14,16,17,27-30]	Low response to clopidogrel only= results of ADP test AUC within the upper quartile and results of aspirin test AUC below the upper quartile.: 33 (15%)

	Dynabyte, Munich, Germany		Melagatran 12 to 18 hr after PCI within 30 to 60 minutes after the blood sampling	Low response to ASA and clopidogrel (dual low response) =results of aspirin test AUC and ADP test AUC within the upper quartile. Controls (dual normal response)= results of aspiring test AUC and ADP test AUC below the upper quartile. [Also low response to asprin; this group ignored re data extraction since not relevant]		Low response to ASA and clopidogrel (dual low response) =results of aspirin test AUC and ADP test AUC within the upper quartile: 19 (9%) Controls (dual normal response)= results of aspiring test AUC and ADP test AUC below the upper quartile: 133 (60%) [Also low response to asprin; this group ignored re data extraction since not relevant]: 34 (16%)
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	whole-blood impedance aggregometry CA560 lumi-aggregometer ChronoLog	6.4 µmol/l ADP	NR NR NR the day after clopidogrel loading NR	Nonresponse, defined as impedance exceeded 5 ohms after 6 min of aggregation, to clopidogrel Full response (to aspirin and clopidogrel) Dual nonresponse (to aspirin and clopidogrel) Nonresponse to clopidogrel but full response to aspirin	Not explicitly reported	Nonresponse, defined as impedance exceeded 5 ohms after 6 min of aggregation, to clopidogrel: 34 (18.7%) Full response (to aspirin and clopidogrel):163 (73.6%) Dual nonresponse (to aspirin and clopidogrel): 19 (10.4%) Nonresponse to clopidogrel but full response to aspirin: 15 (8%)

*If more than one test, use separate rows
**E.g., nonresponsive vs. responsive to clopidogrel, high vs. low platelet reactivity;
ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-

treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported.

Appendix Table E59: Phenotypic test details in studies assessing the predictive ability of Multiplate Analyzer in patients with cerebrovascular disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer*	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	Impedance aggregometry Multiplate analyzer Dynabyte Medical, Munich, Germany	ADP	300 microL of saline and 300microL of patient blood are pipetted into the test cell. Pipetting is performed by an attached electronic pipette. Hirudin, 25microg/mL NR 6 minutes	Non –responder >52U Responder ≤ 52U	Not explicitly reported	Non –responder >52U: 14 (28%) Responder ≤ 52U: 36 (72%)

ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E60: Results from studies assessing the ability of Multiplate Analyzer to predict death in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Death	Death	30 days	Low Responders (>416 aggregation units*min)	Death	4 (1.2%)	OR=3.2	0.92-11.1	P=0.07 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		5 (0.4%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Mortality	Death	6 months	Low Responders (>416 aggregation units*min)	Mortality	10 (3.2%)	OR=1.6	0.8-3.3	P=0.20 (low vs normal responder) [log rank]	NO	NR	Secondary

						Normal Responders (≤416 aggregation units*min)		25 (2%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Cardiac Death	Cardiac Death	6 months	Low Responders (>416 aggregation units*min)	Cardiac Death	8 (2.5%)	OR=2.5	1.1-5.8	P=0.037 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		13 (1%)						
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Death	Death	1 year	Low responder	Death	16 (5%)	HR=1.5	0.9-2.7	0. 144 (low vs normal) cox proportional hazard model	NO	NR	Secondary outcome
						Normal responder		42 (3.3%)						
	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Cardiac Death	Cardiac Death	1 year	Low responder	Cardiac Death	9 (2.8%)	HR=1.8	0.8-4	0. 139 (low vs normal) cox proportional hazard model	NO	NR	Secondary outcome
						Normal responder		20 (1.6%)						

Freynhofer 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 or 600mg LDClopidogrel and maintain dose 75 mg+aspirin 100mg	MEA	CV death	CV death	6 months	High reactivity/poor response	CV death	4/57	OR (calculate) =23	NR	P=0.006 (High vs low reactivity) [Fisher's exact test]			Fig 1
						Low reactivity/good response		0/139						Fig 1
Eshtehardi,2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	600 mg LD Clopidogrel +500 mg aspirin	Aggregometry	Death	Death	30 days	Clopidogrel low response	Death	0	OR (calculate) =9.8	NR	P=0.023 (High vs low reactivity) [Fisher's exact test]			
						Aspirin low response		0						
						Dual low response		1 (5.3%)						
						Normal response		0						
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Clopidogrel 600mg LD+aspires 0.5g	Aggregometry	Cardiac death	Cardiac death	14 months	Responders (n=163)	Cardiac death	4 (2.4%)	OR (calculate) =0.91	NR	P=1.0 (dual nonrespondER + clopidogrel nonrespondER vs responder) [Fisher's exact test]			
						Dual nonresponders (n=19)		0 (0%)						

Appendix Table E61: Results from studies assessing the ability of Multiplate Analyzer to predict myocardial infarction in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	Multiple Electrode Platelet Aggregometry (MEA-ADP)	Periprocedural MI	Postprocedural ↑ of troponin or CK-MB >3 times the 99th percentile of the ULN in patients with normal baseline levels (or >3 times in pts with elevated baseline levels).	From PCI to 30 days	30 days	MI+	NR	NR	NR	NR	NR	NR	AUC=0.419; P=0.310 (Fig2d)	Multiple Electrode Platelet Aggregometry (MEA-ADP)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Myocardial infarction	according to TIMI criteria	30 days	Low Responders (>416 aggregation units*min)	Myocardial infarction	12 (3.7%)	OR=1.16	0.61-2.21	P=0.64 (low vs normal responder) [log rank]	NO	NR	Secondary

						Normal Responders (≤416 aggregation units*min)		41 (3.2%)						
			Myocardial infarction	according to TIMI criteria	6 months	Low Responders (>416 aggregation units*min)	Myocardial infarction	17 (5.2%)	OR=1.4	0.8-2.4	P=0.25 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		49 (3.8%)						
			MI >24 h post-PCI	according to TIMI criteria	30 days	Low Responders (>416 aggregation units*min)	MI >24 h post-PCI	5 (1.5%)	OR=4.02	1.28-12.63	P=0.02 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		5 (0.4%)						
			Q-wave MI	according to TIMI criteria	30 days	Low Responders (>416 aggregation units*min)	Q-wave MI	5 (1.5%)	OR=4.99	1.53-16.29	P=0.008 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		4 (0.3%)						
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	MI	according to Thrombolysis in Myocardial Infarction criteria	1 year	Low responder	MI	17 (5.3%)	HR=1.3	0.7-2.2	0.378 (low vs normal) Chisquare	NO	NR	Secondary outcome
						Normal responder		43 (4.1%)						

			Q-wave MI	according to Thrombolysis in Myocardial Infarction criteria	1 year	Low responder	Q-wave MI	8 (2.5%)	HR=4	1.5-10.7	0.005 (low vs normal) Chisquare	NO	NR	Secondary outcome
						Normal responder		8 (0.6%)						
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 or 600mg LDClopidogrel and maintain dose 75 mg+aspirin 100mg	MEA	STEMI			High reactivity/poor response		0						Fig 1
						Low reactivity/good response		3						Fig 1
Eshtehardi 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	600 mg LD Clopidogrel+500 mg aspirin	Aggregometry	PCI-related MI	peak CK-MB >3x ULN if baseline troponin was normal, and >20% increase of CK or CK-MB postprocedure in case of elevated baseline Troponin [ref 25]	Within 30 days after PCI	Clopidogrel low response	PCI-related MI	2 (6.1%)	NR	NR	0.039 across this and next 3 rows (Fisher's exact or chi-square)	NR	NR	NONE
						Aspirin low response		3 (8.8%)						
						Dual low response		5 (26.3%)						
						Normal response		9 (6.8%)						

			MI	new Q waves ≥0.4-sec duration in at least 2 contiguous leads on ECG with or without elevate CK or CK-MB; In the absence of pathologic Q waves, an elevation of CK levels >3x ULN with elevated CK-MB or troponin I or T level	after the periprocedural period	Clopidogrel low response		0			0.004 across this and next three rows (Fisher's exact or chi-square)			
						Aspirin low response		0						
						Dual low response		2 (10.5%)						
						Normal response		1 (0.8%)						
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Clopidogrel600mg LD+aspires 0.5g	Aggregometry	STEMI	ST-elevation myocardial infarction	30days or later after PCI	Responders (n=163)	ST-elevation myocardial infarction	1 (0.6%)	Relative risk vs. previous row, 8.58	0.56-131.65	NR	NR	NR	
						Dual nonresponders (n=19)		1 (5.3%)						

Appendix Table E62: Results from studies assessing the ability of Multiplate Analyzer to predict stent thrombosis in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	>468 aggregation units*min	definite ST	9/428 (2.1%)	OR=3.6 (calculated)	NR	P<0.001 (>468 AU*min vs ≤ 468 AU*min) [chi square]	NO	NR	Secondary
						≤468 aggregation units*min		7/1180 (0.3)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	Mutliplate analyzer	Definite or probable stent thrombosis	Definite or probable stent thrombosis	30 days (all outcomes)	Enhanced responder (AUC≤188) (N=975)	Yes thrombosis	NR	NR	NR	0.38 enhanced responder vs. the remaining			Fig. 2
						Normal responder (AUC189-467) (N=1130)	Yes thrombosis	NR						

						Low responder (AUC≥468) (N=428)	Yes thrombosis	NR (2.8%)			<0.001 low responder vs the remaining two rows			
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	Low Responders (>416 aggregation units*min) n=323	definite ST	7 (2.2%)	OR=9.4	3.1-28.4	P<0.0001 (low vs normal responder) [log rank]	NO	NR	Primary
						Normal Responders (≤416 aggregation units*min) n=1285		3 (0.2%)						
Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	6 months	Low Responders (>416 aggregation units*min) n=323	definite ST	8 (2.5%)	OR=6.5	2.4-17	P<0.0001 (low vs normal responder) [log rank]	NO	NR	Primary
						Normal Responders (≤416 aggregation units*min) n=1285		6 (0.4%)						

Sibbing, 2009{Sibbing, 2009 135 /id} 19264241	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	Low Responders (>416 aggregation units*min) n=323	definite ST	7 (2.2%)	HR=10.95	2.31-51.99	P=0.003 (low vs normal responder) [cox proportional hazards regression]	YES; Diabetes mellitus, active smoking, body mass index, ejection fraction, platelet count, time from clopidogrel loading to blood sampling, and CAD presentation (including STEMI, NSTEMI, stable angina, and unstable angina)	NR	Primary
						Normal Responders (≤416 aggregation units*min) n=1285		3 (0.2%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	6 months	Low Responders (>416 aggregation units*min)	**definite ST**	**8 (2.5%)**	HR=5.3	2.3-13.7	P=0.0006 (low vs normal responder) [cox proportional hazards regression]	YES; Diabetes mellitus, active smoking, body mass index, ejection fraction, platelet count, time from clopidogrel loading to blood sampling, and CAD presentation (including STEMI, NSTEMI, stable angina, and unstable angina)	NR	Primary
						Normal Responders (≤416 aggregation units*min)		6 (0.4%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Probable Stent thrombosis	As per Academic Research Consortium criteria	30 days	Low Responders (>416 aggregation units*min)	Probable Stent thrombosis	2 (0.6%)	OR=4	0.65-24.47	P=0.13 (low vs normal responder) [log rank]	NO	NR	Primary
						Normal Responders (≤416 aggregation units*min)		2 (0.2%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Probable Stent thrombosis	As per Academic Research Consortium criteria	6 months	Low Responders (>416 aggregation units*min)	Probable Stent thrombosis	5 (1.6%)	OR=5	1.5-16.3	P=0.008 (low vs normal responder) [log rank]	NO	NR	Primary
						Normal Responders (≤416 aggregation units*min)		4 (0.3%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Possible stent thrombosis	As per Academic Research Consortium criteria	6 months	Low Responders (>416 aggregation units*min)	Possible stent thrombosis	0/323	OR=0.4 (calculated)	NR	P=0.26 (low vs normal responder) [log rank]	NO	NR	Primary

						Normal Responders (≤416 aggregation units*min)		5/1285 (0.4%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Stent thrombosis	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	Low Responders (>416 aggregation units*min)	Stent thrombosis	9 (2.8%)	Sensitivity: 0.7 Specificity: 0.84 AUC=0.78	0.60-0.96	P<0.001	NR	NR	Primary
						Normal Responders (≤416 aggregation units*min)		5 (0.4%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Stent thrombosis	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	6 months	Low Responders (>425 aggregation units*min)	Stent thrombosis	13 (4.1%)	Sensitivity: 0.59 Specificity: 0.81 AUC=0.74	0.62-0.86	P<0.0001	NR	NR	Primary
						Normal Responders (≤425 aggregation units*min)		9 (0.7%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	High Responders (Quintile 1 ≤124 AU*min)	definite ST	1 (0.3%)	NR	NR	P=0.003 [Chi square]	NO	NR	Primary
						Normal Responders (Quintile 2 >124-≤192 AU*min)		0						
						Normal Responders (Quintile 3 >192-≤261 AU*min)		1 (0.3%)						
						Normal Responders (Quintile 4 >261-≤416 AU*min)		1 (0.3%)						
						Low Responders (Quintile 5: >416 AU*min)		7 (2.2%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Probable/ definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	High Responders (Quintile 1 ≤124 AU*min)	Probable/ definite ST	1 (0.3%)	NR	NR	P=0.001 [Chi square]	NO	NR	Primary
						Normal Responders (Quintile 2 >124-≤192 AU*min)		0						
						Normal Responders (Quintile 3 >192-≤261 AU*min)		2 (0.6%)						
						Normal Responders (Quintile 4 >261-≤416 AU*min)		2 (0.6%)						
						Low Responders (Quintile 5: >416 AU*min)		9 (2.8%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Combined probable/definite stent thrombosis	As per Academic Research Consortium criteria	30 days	Low Responders (>416 aggregation units*min)	Combined probable/definite stent thrombosis	9 (2.8%)	OR=7.26	2.86-18.46	P<0.0001 (low vs normal responder) [log rank]	NO	NR	Landmark
						Normal Responders (≤416 aggregation units*min)		5 (0.4%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Combined probable/definite stent thrombosis	As per Academic Research Consortium criteria	6 months	Low Responders (>416 aggregation units*min)	Combined probable/definite stent thrombosis	13 (4.1%)	OR=5.8	2.8-12.3	P<0.0001 (low vs normal responder) [log rank]	NO	NR	Landmark
						Normal Responders (≤416 aggregation units*min)		9 (0.7%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Combined probable/definite stent thrombosis	As per Academic Research Consortium criteria	30 days to 6 months	Low Responders (>416 aggregation units*min)	Combined probable/definite stent thrombosis	4 (1.2%)	OR=4.1	1.1-14.7	P=0.03 (low vs normal responder) [log rank]	NO	NR	Landmark

						Normal Responders (≤416 aggregation units*min)		4 (0.3%)						
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Definite stent thrombosis	Based on definition of the Academic Research Consortium (ARC)	1 year	Low responder	Definite stent thrombosis	8 (2.5%)	HR=5.4	1.9-15.6	0.02 (low vs normal) cox proportional hazard model	NO	NR	Secondary outcome
						Normal responder		6 (0.5%)						
	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Probable stent thrombosis	Based on definition of the Academic Research Consortium (ARC)	1 year	Low responder	Probable stent thrombosis	5 (1.6%)	HR=3.4	1-11	0.046 (low vs normal) cox proportional hazard model	NO	NR	Secondary outcome
						Normal responder		6 (0.5%)						
Siller-Matula 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily	MEA	Definite stent thrombosis	Defined by ARC as ACS with angiographic or pathologic confirmation of thrombosis	Within 6 mo after stenting	Platelet hyperreactivity vs. no hyperreactivity	Definite stent thrombosis	--	AUC, 0.92 (SE 0.04) ROC cutoff, 54U Sensitivity 100% and specificity 86%;	For AUC, 0.85-0.99	0.012 from ROC	NR	NR	NONE
						No platelet hyperreactivity	Definite stent thrombosis	0/341	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3

						Platelet hyperreactivity		3/61	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3
	600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily	MEA	Composite of definite or probable stent thrombosis	Probable defined any unexplained death within 30 days or target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion		Platelet hyperreactivity vs. no hyperreactivity	Composite of definite or probable stent thrombosis	--	AUC, 0 .81 (SE 0.10) ROC cutoff, 54U Sensitivity 86% and specificity 87%	For AUC, 0.61-1.02	0.004 from ROC	NR	NR	NONE
						No platelet hyperreactivity		1/341	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3
						Platelet hyperreactivity		6/61	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3
	600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily	MEA	Probable stent thrombosis	Probable stent thrombosis		No platelet hyperreactivity	Probable stent thrombosis	0/341	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3

						Platelet hyperreactivity		3/61	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3
Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	600 mg LD Clopidogrel+500 mg aspirin	Aggregometry	Stent thrombosis (early definite)	Defined according to the Academic Research Consortium Definitions [ref 26]		Clopidogrel low response		0	NR	NR	0.004 across this and next three rows (Fisher's exact or chi-square)			
						Aspirin low response		0						
						Dual low response		2 (10.5%)						
						Normal response		1 (0.8%)						

Appendix Table E63: Results from the studies assessing the ability of Multiplate Analyzer to predict major adverse cardiovascular events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	75 mg/d clopidogrel & 100 mg/d aspirin	Multiple Electrode Platelet Aggregometry (MEA-ADP)	Major adverse cardiovascular events (MACE)	Death, MI, stroke, and target vessel revascularization	From PCI to 30 days	NR	MACE +	NR	NR	NR	NR	NR	NR	AUC=0.443; P=0.415 (Fig2b)
Sibbing 2010{Sibbing, 2010 88 /id} 19943882 Sibbing 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	Mutliplate analyzer	adverse event	Definite or probable stent thrombosis or in-hospital TIMI major bleeding	30 days	AUC≤ 188 Enhanced responder (N=975)	adverse event	NR	incidence of adverse events	NR	0.008 across all 3 groups chi square test	NR	NR	Fig 1
						AUC 189-467 normal responders n=1130								
						AUC ≥468 low responders n=428								

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	Mutliplate analyzer	adverse event	Definite or probable stent thrombosis or in-hospital TIMI major bleeding	30 days	Normal responder (N=1130)	adverse event	NR	OR=0.40	0.22-0.75	0.003 between normal responder and remaining patients NR	NR	NR	
						Enhanced or low responder (N=1403)								

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing 2009{Sibbing, 2009 135 /id} 19264241 Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	MACE	Death or Stent thrombosis	30 days	Low Responders (>416 aggregation units*min)	MACE	10 (3.1%)	OR=5.1	2.2-11.6	P<0.001 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		8 (0.6%)						
Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR		MEA	MACE	Death or Stent thrombosis	6 months	Low Responders (>416 aggregation units*min)	MACE	16 (5%)	OR=5.1	2.2-11.6	P<0.001 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		30 (2.3%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			MACE	Cardiac Death + Definite ST	6 months	Low Responders (>416 aggregation units*min)	MACE	14 (4.4%)	OR=3.3	1.7-6.5	P<0.001 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		17 (1.3%)						
			MACE	Death + ST As per Academic Research Consortium criteria	30 days	Low Responders (>416 aggregation units*min)	Combined death/definite ST	10 (3.1%)	OR=5.05	2.19-11.64	P<0.001 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		8 (0.6%)						
			MACE	Death or definite Stent thrombosis	6 months	Low Responders (>416 aggregation units*min)	MACE	16 (5%)	OR=2.2	1.2-4.1	P=0.008 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		29 (2.3%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Schulz 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	MACE	Death or MI	1 year	Low responder	MACE	27 (8.4%)	HR=1.3	0.8-1.9	0. 298 (low vs normal) cox proportional harzard model	NO	NR	Secondary outcome
						Normal responder		86 (6.7%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Freynhofer 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 or 600mg LDClopidogrel and maintain dose 75 mg+aspirin 100mg	MEA	MACE	MACE included: 1) definite and probable ST according to the ARC-definition; 2) cardiovascular death, defined as death associated with ACS, significant arrhythmia, or congestive heart failure; and 3) non-fatal STEMI (STEMI: acute onset of prolonged typical ischaemic chest pains, ST-segment elevation of at least 1 mm in 2 or more contiguous electrocardiogram leads and increased biomarkers of myocardial necrosis)	6 months	High reactivity/poor response n=59	MACE	3 (5.4%)	OR=23.5 (calculate)	NR	0.670 high vs. low reactivity chi square	NR	NR	Fig 1

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Low reactivity/good response n=137		4 (2.9%)						Get n's from Fig 1 (pasted in on last page of this form)
Eshtehardi 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	600 mg LD Clopidogrel+500 mg aspirin	Aggregometry	MACE	Composite of PCI-related MI, stent thrombosis, death, or MI	30 days	Clopidogrel low response n=33	MACE	2 (6.1%)	OR=8.0 dual vs normal OR= 9.0 dual vs clopidogrel low response (calculated)	NR	<0.001 across this and next three rows; <0.001 for dual vs normal; 0.005 for dual vs clopidogrel (Fisher's exact or chi-square)	NR	NR	none
						Aspirin low response n=34		3 (8.8%)						
						Dual low response n=19		7 (36.8%)	odds 7.35	2.21-24.42	<0.001(Multivariable logistic regression analysis)			
						Normal response n=133		9 (6.8%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Ivandic 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Clopidogrel600mg LD+aspires 0.5g	Aggregometry	Combined end point:	Combined end point: first occurrence of any of the following cardiovascular events: cardiovascular death, myocardial infarction, target vessel revascularization, or stent thrombosis occurring 30 days or later after PCI.	>/= 30 days after PCI	Clopidogrel nonresponder (n=34)	Combined end point	8 (23.5%)	HR= 1.04	0.24-4.44	NS non-responder vs. full (cox proportional hazard model) Also NS vs full responders below	NR	NR	NONE
						Nonresponse to clopidogrel but response to aspirin (n=15)		2 (13.3%)						
						Full responders (n=134)		18 (13.4%)						
						Dual nonresponder (n=19)		6 (31.6%)	HR 2.57 HR in multivariate analysis, 2.9	1.18-5.61 In multivariate, 1.17-7.2	0.03 dual non-responder vs. any responders, In multivariate, 0.02 (Cox regression)			

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel600mg LD+aspires 0.5g	Aggregometry	cardiovascular events	Freedom from combined end point myocardial infarction, target vessel revascularization, late stent thrombosis, or cardiac death in KM curve	>/= 30 days after PCI	Responders (n=163)	cardiovascular events	40/163	OR=5.3 (calculated)	NR	0.03 dual nonresponder vs. responder (log rank)	NR	NR	K-M curves are in Fig. 1
						Dual nonresponders (n=19)		12/19						K-M curves are in Fig. 1
	Clopidogrel600mg LD+aspires 0.5g	Aggregometry	Any cardiovascular event	Any cardiovascular event	>/= 30 days after PCI	Responders (n=163)	Any cardiovascular event	20 (12.2%)	Relative risk 2.57 dual non-responder vs. responder	1.18-5.61	NR	NR	NR	
						Dual nonresponders (n=19)		6 (31.5%)						

Appendix Table E64: Results from studies assessing the ability of Multiplate Analyzer to predict major adverse cardiovascular events in patients with cerebrovascular disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	LD 300 mg of clopidogrel 75 mg/day continuously	Impedance aggregometry	Adverse event	Transient intrainterventional thrombosis, TIA or infarction	NR	Non-responder	Adverse event	5/14	OR=42.3 (calculated)	NR	0.001 non-responder vs. responder Fisher exact test	NR	NR	
						Responder		0/36						
	LD 300 mg of clopidogrel 75 mg/day continuously	Impedance aggregometry	Adverse event	Transient intrainterventional thrombosis, TIA or infarction	NR	1 Aggregation unit	Adverse event	NR	OR=1.15	NR	0.0321U increase of aggregation logistic regression	NR	NR	

Appendix Table E65: Results from studies assessing the ability of Multiplate Analyzer to predict stroke in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Ischemic stroke	confirmation by CT/MRI imaging of the head.	30 days	Low Responders (>416 aggregation units*min)	Ischemic stroke	3 (0.9%)	OR=6.01	1.25-28.88	P=0.03 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		2 (0.2%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Ischemic stroke	confirmation by CT/MRI imaging of the head.	6 months	Low Responders (>416 aggregation units*min)	Ischemic stroke	3 (0.9%)	OR=4	0.9-17.6	P=0.07 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		3 (0.2%)						

Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Stroke	By CT/MRI	1 year	Low responder	Stroke	4 (1.3%)	HR=2.3	0.7-7.8	0.185 (low vs normal) Chisquare	NO	NR	Secondary outcome
						Normal responder		7 (0.6%)						
	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Hemorrhagic Stroke	By CT/MRI	1 year	Low responder	Hemorrhagic Stroke	0/323	OR=0.4 (calculated)	NR	0. 853 (low vs normal) Chi square	NO	NR	Secondary outcome
						Normal responder		4/1285(0.3%)						
	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Ischemic Stroke	By CT/MRI	1 year	Low responder	Ischemic Stroke	4 (1.3%)	HR=5.4	1.2-24	0. 028 (low vs normal) Chisquare	NO	NR	Secondary outcome
						Normal responder		3 (0.2%)						

Appendix Table E66: Results from studies assessing the ability of Multiplate Analyzer to predict bleeding events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing 2010{Sibbing, 2010 88 /id} 19943882 Sibbing 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	in-hospital major bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI major bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital major bleed	21/975 (2.2%)	Sensitivity: 0.62 Specificity: 0.62 AUC=0.61	0.51-0.7	P=0.017 for ROC	NR	NR	Primary
						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		13/1558 (0.8%)						
			in-hospital major bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI major bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital major bleed	21/975 (2.2%)	OR=2.6	1.3-5.2	P=0.005 (enhanced vs remaining responder) [llogistic regression]	NO	NR	Primary

						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		13/1558 (0.8%)						

			in-hospital major bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI major bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital major bleed	21/975 (2.2%)	OR=3.5	1.6-7.3	P=0.001 (enhanced vs remaining responder) [multiple logistic regression]	YES; age, body mass index, diabetes, renal failure, presence of an MI at admission, treatment at admission with aspirin, a thienopyridine, a statin or a coumarin derivate, use of abciximab, use of intra-aortic balloon pumping, number of lesions treated and complex lesions (defined as type B2/C lesions according to AHA/ACC lesions morphology).	NR	Primary

						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		13/1558 (0.8%)						
			in-hospital major bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI major bleeding	30 days	Enhanced responder (AUC≤188) (N=975)	Yes bleeding	NR /975(2.2%)	NR	NR	0.018 across this and next two rows of enhanced, normal and low responders			Data for this outcome are %s in Fig. 1—can be obtained by digitizing
						Normal responder (AUC189-467) (N=1130)	Yes bleeding	NR/1130			0.72 between noral and low responder			
						Low responder (AUC≥468) (N=428)	Yes bleeding	NR/428						
			in-hospital minor bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI minor bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital minor bleed	55/975 (5.6%)	OR=1.1	0.8-1.5	P=0.68 (enhanced vs remaining responder) [logistic regression	NO	NR	Primary
						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		82/1558 (5.3%)						

			Bleeding Composite	TIMI major and minor bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital major and minor bleed	76/975 (7.8%)	OR=1.3	0.95-1.8	P=0.1 (lenhanced vs remaining responder) [logistic regression]	NO	NR	Primary
						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		95/1558 (6.1%)						
Sibbing 2009{Sibbing, 2009 135 /id} 19264241 Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Thrombolysis In Myocardial Infarction (TIMI) major bleeding	TIMI criteria	30 days	High Responders (Quintile 1 ≤124 AU*min)	Thrombolysis In Myocardial Infarction (TIMI) major bleeding	4/318 (1.3%)	OR=1.8 (calculated)	NR	P=0.32 between quintile 1 and 2-5 [Chi square]	NO	NR	Safety
						Normal Responders and low responders (Quintile 2 - 5)		9/1290 (0.7%)						
			Thrombolysis In Myocardial Infarction (TIMI) minor bleeding	TIMI criteria	30 days	High Responders (Quintile 1 ≤124 AU*min)	Thrombolysis In Myocardial Infarction (TIMI) minor bleeding	10/318 (3.1%)	OR=1.3 (calculated)	NR	P=0.45 between high responder and remaining [Chi square]	NO	NR	Safety

						Normal Responders and low responders (Quintile 2 - 5)		31/1290 (2.4%)						
Schulz 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	In-hospital TIMI major bleeding	defined according to Thrombolysis in Myocardial Infarction criteria	1 year	Low responder	In-hospital TIMI major bleeding	1 (0.3%)	HR=0.3	0.01-2.4	0. 460 (low vs normal) Cox proportional hazards model	NO	NR	Secondary outcome
						Normal responder		12 (0.9%)						

Appendix Table E67: Results from studies assessing the ability of Multiplate Analyzer to predict other clinical events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Target lesion reintervention	NR	30 days	Low Responders (>416 aggregation units*min)	Target lesion reintervention	7 (2.2%)	OR=4.02	1.53-10.58	P=0.005 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		7 (0.5%)						
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	clinical restenosis defined as target lesion revascularization (TLR)	repeat PCI of the target lesion or bypass surgery of the target vessel	1 year	Low responder	Clinical restenosis	34 (10.9%)	HR=1.2	0.8-1.7	0.441 (low vs normal) cox proportional hazard model	NO	NR	Primary outcome
						Normal responder		119 (9.5)						

	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	clinical restenosis defined as target lesion revascularization (TLR)	repeat PCI of the target lesion or bypass surgery of the target vessel	1 year	Low responder	Clinical restenosis	34 (10.9%)	HR=1	0.9-1.1	0. 717 (low vs normal) Cox regression	YES; chronic occlusions, complex lesions, lesion length, and diameter stenosis before PCI	NR	Secondary outcome
						Normal responder		119 (9.5)						
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Clopidogrel600 mg LD+aspires 0.5g	Aggregometry	Target vessel revascularization	Target vessel revascularization	30days or later after PCI	Responders (n=163)	Target vessel revascularization	7 (4.3%)	Relative risk 3.68	1.03-13.04	NR	NR	NR	
						Dual nonresponders (n=19)		3 (15.8%)						

Appendix Table E68: Results from studies assessing the ability of Multiplate Analyzer to predict platelet reactivity during followup (when used as a discrete outcome) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Clopidogrel 75 mg MD	Impedence aggregometry	Impedence aggregometry	Aggregation measured with PGE1 and ADP	24 hrs after PCI	Impedence between 16-88 units	Impedence between 16-88 units	In Fig 1D; difficult to interpret	NR	NR	NR	NR	NR	NR	Fig 1D shows shaded area greater than normal range reported in the text
						Impedence between 16-88 units	Impedence between <16 units	In Fig 1D; difficult to interpret	NR	NR	NR	NR	NR	NR	
						Impedence between <16 units	Impedence between 16-88 units	In Fig 1D; difficult to interpret	NR	NR	NR	NR	NR	NR	
						Impedence between <16 units	Impedence between <16 units	In Fig 1D; difficult to interpret	NR	NR	NR	NR	NR	NR	

Appendix Table E69: Quality Assessment of studies assessing the predictive ability of Multiplate Analyzer in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	NR	yes	yes	low	low	NR	yes	unclear	high	No	NR	high	high	no	yes	yes	yes	low
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	YES	YES	YES	LOW	LOW	YES	NO	HIGH	LOW	YES	NR	UNCLEAR	LOW	NO [30 days]	YES	YES	YES	LOW
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany	YES	YES	YES	LOW	LOW	YES	NO;(Sibbing 19943882 was used as reference for Sibbing 20638826))	UNCLEAR	HIGH	YES	YES; (NR in Sibbing 20638826)	LOW; (Unclear in Sibbing 20638826)	LOW	NO	YES	YES	YES	LOW

NR																		
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	YES	YES	YES	LOW	LOW	YES	NO	UNCLEAR	HIGH	YES	YES	LOW	LOW	NO	YES	YES	YES	LOW
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	YES	YES	YES	LOW	LOW	NR	YES	UNCLEAR	HIGH	YES	YES	LOW	LOW	YES [1 year]	YES	YES	YES	LOW
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	yes	yes	yes	low	low	NR	yes	unclear	low	yes	yes	low	low	no	yes	yes	yes	low
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	yes	yes	yes	low	low	NR	yes	unclear	Low	yes	NR	unclear	low	no (6 months)	yes	yes	yes	low

Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	YES	YES	YES	low	low	YES (“The operators	YES	low	low	YES	YES (“All events were independently adjudicated by a	low	low	NO (30 days)	YES	YES	YES	LOW
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	YES	YES	YES	LOW	LOW	NR	NO	HIGH	UNCLEAR	YES	NR	UNCLEAR	LOW	NO (30 days)	YES	YES	YES	LOW

Appendix Table E70: Quality Assessment of studies assessing the predictive ability of Multiplate Analyzer in patients with cerebrovascular disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	Yes	No	Yes	Low	Low	NR	NO	HIGH	LOW	YES	NR	UNCLEAR	LOW	NO (30 days)	YES	YES	YES	LOW

Appendix Table E71: Baseline characteristics of patients with ischemic heart disease in studies assessing the predictive ability of Multiplate Analyzer

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[27]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	30 NR 84 63±10	100 NR CVD 7 PCI 43 NR NR 10 37 NR	hyper 77 57 HTN 77 33	NR 100 100 NR	NR NR NR	not used	Patients had been on chronic aspirin (100 mg/day) and clopidogrel (75 mg/day) treatment for three months on average.	All patients received unfractionated heparin and 250 mg of injectable acetyl-salicylic acid during PCI
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	222 ?Asian 152 (69) 63.3 ± 10	100 NR CVA: 14.9 PCI: 37 (16.7); CABG: 1 (0.5) NR NR	Hypercholesterolemia: 46.8 Current: 12.2 HTN: 72.1 32	NR 72.1 89.6 NR	100 Drug eluting Multi-vessel; Stents/pt: 1.8±1	Patients undergoing percutaneous coronary intervention (PCI) for CAD	All patients were pretreated with aspirin (100 mg/d) and clopidogrel (75 mg/d) at least 5 days before PCI or received oral loading doses of 250	NR

[27] Mean (standard deviation), unless otherwise stated.

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[27]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR 5.9 NSTEMI: 10.1					mg aspirin and 300 mg clopidogrel 12 to 24 hours before PCI. Maintenance doses of 100 mg aspirin and 75 mg clopidogrel after PCI After PCI, dual antiplatelet therapy with 100 mg/d aspirin and 75 mg/d clopidogrel was continued for at least 6 months	
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	2533 NR 2034 (80.3%) mean: 67.8	NR NR NR CABG: 14.3% NR NR	Hypercholesterolemia: 68.4% Active: 13.2% Arterial HTN:90.6% 28.6%	10.9% Thienopyridine: 41.3% 74.3 NR	Stents per lesion: 1.3; Lesions per patient: 1.9 NR Multivessel disease: 85.5%	Patients undergoing PCI with stenting for ACS and CAD	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD Aspirin: 500 mg IV LD + 100 mg	PCI: Intravenous anticoagulant: unfractionated heparin or bivalirudin (140 U/kg body weight for unfractionated heparin and for bivalirudin with a dosing regimen of 0.75 mg/kg body

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[27]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR 31.4 NSTEMI/STEMI: 14.5%					aspirin (twice per day) MD	weight for bivalirudin before PCI, followed by an infusion of 1.75 mg/kg/h bivalirudin for the procedure); Some pts received glycoprotein IIb/IIIa inhibitor abciximab (0.25 mg/kg of body weight bolus, followed by a 0.125 µg/kg/min infusion for 12 h) with reduced heparin dose
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	1608 NR 1234 (77%) 67.5±40.5	NR NR NR CABG: 14% NR NR NR 32	Hypercholesterolemia: 70% Active: 13% HTN: 91.6% 29	NR NR 99.1 NR	NR NR NR	Patients undergoing PCI with stenting for ACS and CAD	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	PCI: Intravenous anticoagulant: unfractionated heparin or bivalirudin (140 U/kg body weight for unfractionated heparin and for bivalirudin with a dosing regimen of 0.75 mg/kg body weight for bivalirudin before PCI, followed by an infusion of 1.75 mg/kg/h bivalirudin for the

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[27]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR						procedure); Some pts received glycoprotein IIb/IIIa inhibitor abciximab (0.25 mg/kg of body weight bolus, followed by a 0.125 µg/kg/min infusion for 12 h) with reduced heparin dose
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	1608 NR 1234 (76.7%) 67.4	NR NR NR CABG: 14.4% 66.9 22.2 NR 31.5 STEMI: 2.5%; NSTEMI: 8.4%	Hypercholesterolemia: 69.8% Active: 13.4% HTN: 91% 28.7	NR NR NR NR	94.8% BMS: 2.2%; DES: 92.6% Multivessel: 85.1%	patients undergoing PCI	600 mg clopidogrel before PCI and 500 mg aspirin LD directly before the intervention; Postinterventional therapy: clopidogrel 75 mg twice daily for 3 days, then 75 mg per day for 6 months with aspirin 100 mg twice daily	Periprocedural therapy: unfractionated heparin (as a bolus of 140 U/kg bodyweight) or bivalirudin (0.75 mg per kg bodyweight bolus, followed by an infusion of 1.75 mg per kg bodyweight per hour for the duration of the procedure) or abciximab (0.25-mg/kg bodyweight bolus, followed by an infusion of 0.125 µg/kg bodyweight per min for 12 hours)

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[27]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
								along with 70 U/kg bodyweight unfractionated heparin
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 NR 205 62±16	43.3 NR NR PCI 24.3 NR see UA/NSTEMI 10 22.7 29.7/34.3	hyper 69.3 27.3 HTN 74.7 27.3	NR 100 100 81.3	100 DES 65.3 multi-vessel 58.7	PCI and coronary stenting	Clopidogrel-naïve patients received a 300 or 600 mg loading dose (LD). Patients on chronic clopidogrel therapy with 75 mg clopidogrel of at least seven consecutive days did not receive an additional LD.	According to actual evidence, all patients received in parallel ASA (100 mg daily dose). The use of GP-IIb/IIIa-blockers during PCI as well as the choice of the anticoagulant depended on the individual situation and the thrombus load at angiography, and was left to the discretion of the operator
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	416 NR 76 64±12	100 NR NR 47	hyper 76 55 85 32	NR 100 100 77	99 NR NR	PCI with stenting	Clopidogrel loading dose at least 2 hr before PCI (600 mg); thereafter, a daily dose of	Also all patients received unfractionated heparin (100 IU per kg) during PCI and 250 mg aspirin

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[27]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
		NR NR 13 33 NR					75 mg, with planned treatment with clopidogrel and aspirin for at least 6 months.	intravenously immediately after stent placement (and daily dose of 100 mg thereafter).
Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	219 NR 168 (77%) Mean/SD 66+/-9 yr	NR ACS 82 (37%) [not sure ACS=heart failure] NR PCI 70 (32%); CABG 26 (12%) 137 (63%) NR NR 60 (27%) NR	155 (71%) Current 57 (26%) Atrial HTN 163 (74%) 43 (20%)	NR 100%; (pretreatment in study) 100% (pretreatment in study) NR	NR 1 DES 164 (75%); BMS 55 (25%) Multi 77 (34%)	Patients with stable angina or ACS with an indication for PCI, undergoing PCI with stenting	500 mg ASA intravenously (unless if already on 100 mg daily); then 600 mg clopidogrel loading dose (unless already on 75 mg daily)	unfractionated heparin (70-100 U/kg body weight) before or at time of PCI
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	182 (163 full responders, 19 dual nonresponders) NR 130 (71%) Median age (95% CI); Nonresponders 68 (59–72); Responders 65	NR NR NR NR 78 (43%) 14 (8%) NR NR 40 (22%)/52 (29%)	Hypercholesterolemia 113 (82%) 61 (34%) HTN (arterial) 146 (80%) 57 (31%)	NR 100% 100% NR	100% DES only 77 (42%); BMS only 75 (41%); Both 23 (13%) 3-vessel 90 (49%)	CAD patients who underwent PCI	Emergency patients with ACS received 0.5 g ASA intravenously and an oral loading dose of 600 mg clopidogrel before PCI. Electively hospitalized	A single bolus of unfractionated heparin (10 000 U) was given immediately before PCI. The type of stent used for PCI was left at the discretion of the operator.

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[27]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
	(67–72)						patients with suspected CAD or suspected progression of CAD received 0.5 g ASA intravenously before and loading dose of 600 mg clopidogrel immediately after PCI and stenting. After PCI, all patients received maintenance doses of 100 mg ASA and 75 mg clopidogrel once daily.	

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DES=Drug eluting stent; HTN = hypertension, MI = myocardial infarction; NSTEMI = non-ST-elevation MI; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack;

Appendix Table E72: Baseline characteristics of patients with cerebrovascular disease in studies assessing the predictive ability of Multiplate Analyzer

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled Race (% by group) Male (%) Age[28]**	**Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)**	**Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)**	**Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)**	**Stent implantation(%) Type of stent(%) Multi-or single vessel(%)**			
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	50 NR 36(72) 65±8	NR NR Stroke 31 (63); TIA 19 (38) NR NR NR NR NR NR	NR NR NR NR	NR 100% NR NR	NR NR NR	Patients with extracranial or intracranial stenosis	All 50 of the patients received a loading dose of 300 mg of clopidogrel at least 12 hours before the intervention and after loading were treated with 75 mg/day continuously. All of the patients received 100 mg of aspirin per day according to the usual protocol.	None

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;

[28] Mean (standard deviation), unless otherwise stated.

Appendix Table E73: Study design characteristics of studies assessing the predictive ability of Multiplate Analyzer in patients with ischemic heart disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Prospective observational study	NO	NR	Patients undergoing PCI for coronary artery disease	Aug 2007-Apr 2008	1 day	followup after intervention	YES Accrual=100%	Non-industry [grant from the Jubiläumsfond of the Austrian National Bank (Nr. 12565)]
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	observational study	YES	Consecutive patients	Patients undergoing percutaneous coronary intervention (PCI) for CAD	Aug-Oct 2009	30 days for all patients	followup after intervention	NO	Non-industry only - grant from Government & non-profit foundation
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Prospective cohort	YES	Consecutive	Patients undergoing PCI with stenting for ACS and CAD	February 2007 to December 2008	30 days	followup after intervention	NR	partly industry (Material for platelet function analysis on the Multiplate device were provided free of charge from Dynabyte, Munich, Germany)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Prospective observational study	YES	Consecutive	Patients undergoing PCI with stenting for ACS and CAD	February 2007 to April 2008	30 day and 6 months day followup	Followup after intervention	YES; Accrual>80%	partly industry (Material for platelet function analysis on the Multiplate device were provided free of charge from Dynabyte, Munich, Germany)
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Prospective observational study	YES	Consecutive	patients undergoing PCI	NR	1 year	Followup after intervention	NR	Partial industry [Material for platelet function analysis on the Multiplate device was provided free of charge by Dynabyte (Munich, Germany)]
Freynhofer, 2011{Freynhofer, 2011 1 /id}	Prospective, registry data	NO	Consecutive	Adults undergoing PCI and coronary	May 2009 to February 2010	Total 6 month, mean/SD 189/68 days	Inpatient, then outpatient visits after	YES [YES]	Non-industry only

21614416 Austria NR				stenting with no contraindication for dual antiplatelet therapy for up to one year			discharge, at 1 mo and 6 mo		
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	Prospective observational	NO	Consecutive	Adults with CAD undergoing PCI with stenting (most elective) with clopidogrel and aspirin therapy	NR	Total, 6 month	Inpatient with followup after discharge (contacted patients at 3 and 6 mo after)	YES (YES—80%)	Nonindustry only
Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	Prospective	NO	Consecutive	Patients with stable angina or ACS with an indication for PCI, undergoing PCI with stenting	Jan 2007-March 2008	Total 30 days after PCI	Inpatient and then 30-day followup as outpatient	NO	Non-industry only
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Prospective	NO	Consecutive	CAD patients who underwent PCI and received standard therapy including ASA and clopidogrel	June 2006 to August 2006	Median follow-up was 419 days (95% CI 414–420 days)	Inpatient and then followup 30 days after PCI	NR	NR

Appendix Table E74: Study design characteristics of studies assessing the predictive ability of Multiplate Analyzer in patients with cerebrovascular disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	prospective Cohort	No	Consecutive	Patients with extracranial or intracranial stenosis	NR	NR	Hospital inpatient	NR	NR

Table 2. Study characteristics in patients with cerebrovascular disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Prospective observational study	NO	NR	Patients undergoing PCI for coronary artery disease	Aug 2007-Apr 2008	1 day	followup after intervention	YES Accrual=100%	Non-industry [grant from the Jubiläumsfond of the Austrian National Bank (Nr. 12565)]

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-elevation; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; DES=drug eluting stent; CABG=coronary artery bypass grafting; AA= arachidonic acid; SD=standard deviation; RCT=randomized controlled trial; NR=not reported;

Appendix Table E75: Phenotypic test details in studies assessing the predictive ability of Multiplate Analyzer in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer*	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Multiplate Analyzer Impedance aggregometry Dynabyte Medical, Munich, Germany	Adenosine diphosphate (ADP), prostaglandin (PGE1)	1st blood sample: in catheterization laboratory, after PCI and after 250 mg IV aspirin 2nd blood sample: 20-24 hours after PCI 3.8% citrate, 3.2% citrate and recombinant hirudin NR Clopidogrel came first 0.04 days (1 hour)	Impedence between 16-88 units Impedence between <16 units	Based on Normal ranges as reported by manufacturer	Impedence between 16-88 units: 20 (67%) Impedence between <16 units:10 (33%)
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	Multiple Electrode Platelet Aggregometry Whole blood impedence aggregometry Multiplate analyzer Dynabyte	ADP	Before PCI; 8 and 24 hrs after PCI lepirudin (25 µg/mL) 5 days (clopidogrel came first) 0.125 days (Within 3 hrs)	Multiple electrode aggregometry with ADP was not used to classify clopidogrel response in patients	NR	NR
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	multiple electrode aggregometry Multiplate analyzer Dynabyte, Munich, Germany	6.4 µmol/l ADP	Whole blood; after diagnostic angiography, before PCI lepirudin (25 µg/ml) 0.08 days (2 hours) NR	Enhanced Responders (<188 aggregation units*min) Remaining patients - Not enhanced responders (≥188 aggregation units*min) From Sibbing 2010 PMID: 20633826	ROC curve of all participants in the study	Enhanced Responders (<188 aggregation units*min): 975 (38.5%) Remaining patients - Not enhanced responders (≥188 aggregation units*min): 1558 (61.5%) From Sibbing 2010 PMID: 20633826

				Enhanced responder (AUC≤188) Normal responder (AUC189-467) Low responder (AUC≥468) For Stent thrombosis >468 aggregation units*min ≤468 aggregation units*min		Enhanced responder (AUC≤188): 975 (38%) Normal responder (AUC189-467): 1130 (45%) Low responder (AUC≥468): 428 (17%) For Stent thrombosis >468 aggregation units*min: 428 (17%) ≤468 aggregation units*min: 1180 (83%)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	multiple electrode platelet aggregometry multiple electrode platelet aggregometry Multiplate Dynabyte, Munich, Germany	6.4 µmol/l ADP	Whole blood; after diagnostic angiography, before PCI, and at least 2 min after administration of intravenous aspirin. lepirudin (25 µg/ml) 0.08 days (2 hours) 0.02 days (30 mins)	Low Responders (Quintile 5: >416 aggregation units*min) Normal Responders (Quintile 1-4 ≤416 aggregation units*min) By other quintiles High Responders (Quintile 1 ≤124 AU*min) Normal Responders (Quintile 2 >124-≤192 AU*min) Normal Responders (Quintile 3 >192-≤261 AU*min) Normal Responders (Quintile 4 >261-≤416 AU*min) Low Responders (Quintile 5: >416 AU*min)	Based on literature	Low Responders (Quintile 5: >416 aggregation units*min): 323 (20.1%) Normal Responders (Quintile 1-4 ≤416 aggregation units*min): 1285 (79.9%) By other quintiles High Responders (Quintile 1 ≤124 AU*min): 318 (19.8%) Normal Responders (Quintile 2 >124-≤192 AU*min): 322 (20%) Normal Responders (Quintile 3 >192-≤261 AU*min): 322 (20%) Normal Responders (Quintile 4 >261-≤416 AU*min): 323 (20.1%) Low Responders (Quintile 5: >416

						AU*min): 323 (20.1%)
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	multiple electrode platelet aggregometry multiple electrode platelet aggregometry Multiplate Dynabyte, Munich, Germany	ADP	After diagnostic angiography lepirudin NR NR	Low response (Upper quintile of MEA measurements [>416 AU*min]) Normal response (Lower 4 quintiles of MEA measurements [≤416 AU*min])	Based on literature – a previous study	Low response (Upper quintile of MEA measurements [>416 AU*min]): 323 (20%) Normal response (Lower 4 quintiles of MEA measurements [≤416 AU*min]): 1285 (80%)
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	MEA/Impedence aggregometry Multiple Platelet Function Analyzer Dynabyte Medical, Munich, Germany	ADP 6.5 umol	Samples were incubated and stirred at 37°C for 3 min in the test cuvettes. Agonists were added and the increase in electrical impedance was recorded for 6 min Lithium-heparin + 0.9% sodium chloride 6-24 h (morning) after PCI Within 30 min to 3 hr after blood collection	MEA result <47 U (high on-treatment platelet reactivity, poor response) MEA result >47 U (low reactivity, good response)	previous published literature	MEA result <47 U (high on-treatment platelet reactivity, poor response); 57/196 (29%) MEA result >47 U (low reactivity, good response); 139/196 (71%)
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	Multiple electrode aggregometry Multiplate analyzer Dynabyte Medical, Munich, Germany	ADP (6.4 uM) + PGE_1 (9.4 nM)	Samples taken directly after PCI and at least 5 min after IV aspirin dose (250 mg). Hirudin and 0.9% NaCl Dose first (clopidogrel loading dose given at least 2 hr before PCI). NR	MEA (n=402; 14 pts not tested because of glycoprotein IIb/IIIa): No platelet hyperreactivity (<54U) Platelet hyperreactivity (≥54U)	ROC curve analysis	MEA (n=402; 14 pts not tested because of glycoprotein IIb/IIIa): 346 (86%) No platelet hyperreactivity (<54U) Platelet hyperreactivity (≥54U) 56 (14%)
Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	whole blood impedance platelet aggregometry the multiple electrode aggregometry Multiplate analyzer Dynabyte, Munich, Germany	ADP 6.4 umol/L	peripheral venous blood samples were drawn from an antecubital vein using a 21-gauge needle and collected in a polyethylene tube containing a stabilized direct thrombin inhibitor (melagatran 15 µg/mL). Sample was diluted with NaCl 0.9% in a 1:1 ratio Melagatran 12 to 18 hr after PCI	Low response to clopidogrel only= results of ADP test AUC within the upper quartile and results of aspirin test AUC below the upper quartile. Low response to ASA and clopidogrel (dual low response) =results of aspirin test AUC and ADP test AUC within the	AUC plots in present study (see Fig. 4 and previous publications and findings [refs 7,14,16,17,27-30]	Low response to clopidogrel only= results of ADP test AUC within the upper quartile and results of aspirin test AUC below the upper quartile.: 33 (15%) Low response to ASA and clopidogrel (dual low response) =results of aspirin test AUC and

			within 30 to 60 minutes after the blood sampling	upper quartile. Controls (dual normal response)= results of aspiring test AUC and ADP test AUC below the upper quartile. [Also low response to asprin; this group ignored re data extraction since not relevant]		ADP test AUC within the upper quartile: 19 (9%) Controls (dual normal response)= results of aspiring test AUC and ADP test AUC below the upper quartile: 133 (60%) [Also low response to asprin; this group ignored re data extraction since not relevant]: 34 (16%)
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	whole-blood impedance aggregometry CA560 lumi-aggregometer ChronoLog	6.4 µmol/l ADP	NR NR NR the day after clopidogrel loading NR	Nonresponse, defined as impedance exceeded 5 ohms after 6 min of aggregation, to clopidogrel Full response (to aspirin and clopidogrel) Dual nonresponse (to aspirin and clopidogrel) Nonresponse to clopidogrel but full response to aspirin	Not explicitly reported	Nonresponse, defined as impedance exceeded 5 ohms after 6 min of aggregation, to clopidogrel: 34 (18.7%) Full response (to aspirin and clopidogrel):163 (73.6%) Dual nonresponse (to aspirin and clopidogrel): 19 (10.4%) Nonresponse to clopidogrel but full response to aspirin: 15 (8%)

*If more than one test, use separate rows
**E.g., nonresponsive vs. responsive to clopidogrel, high vs. low platelet reactivity;
ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E76: Phenotypic test details in studies assessing the predictive ability of Multiplate Analyzer in patients with cerebrovascular disease

Author, year [ref] UID Country Study Name	**Test/Device name Device category Device name & manufacturer***	**Agonist used**	**Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):**	**Grouping of Phenotypes** [Definition]**	**Rational for the grouping of phenotypes reported (Yes/No) [short description]**	**Frequency of phenotypes**
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	Impedance aggregometry Multiplate analyzer Dynabyte Medical, Munich, Germany	ADP	300 microL of saline and 300microL of patient blood are pipetted into the test cell. Pipetting is performed by an attached electronic pipette. Hirudin, 25microg/mL NR 6 minutes	Non –responder >52U Responder ≤ 52U	Not explicitly reported	Non –responder >52U: 14 (28%) Responder ≤ 52U: 36 (72%)

ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E77: Results from studies assessing the ability of Multiplate Analyzer to predict death in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)

Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Death	Death	30 days	Low Responders (>416 aggregation units*min)	Death	4 (1.2%)	OR=3.2	0.92-11.1	P=0.07 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		5 (0.4%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Mortality	Death	6 months	Low Responders (>416 aggregation units*min)	Mortality	10 (3.2%)	OR=1.6	0.8-3.3	P=0.20 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		25 (2%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Cardiac Death	Cardiac Death	6 months	Low Responders (>416 aggregation units*min)	Cardiac Death	8 (2.5%)	OR=2.5	1.1-5.8	P=0.037 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		13 (1%)						
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Death	Death	1 year	Low responder	Death	16 (5%)	HR=1.5	0.9-2.7	0. 144 (low vs normal) cox proportional hazard model	NO	NR	Secondary outcome
						Normal responder		42 (3.3%)						
	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Cardiac Death	Cardiac Death	1 year	Low responder	Cardiac Death	9 (2.8%)	HR=1.8	0.8-4	0. 139 (low vs normal) cox proportional hazard model	NO	NR	Secondary outcome
						Normal responder		20 (1.6%)						

Freynhofer 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 or 600mg LDClopidogrel and maintain dose 75 mg+aspirin 100mg	MEA	CV death	CV death	6 months	High reactivity/poor response	CV death	4/57	OR (calculate) =23	NR	P=0.006 (High vs low reactivity) [Fisher's exact test]			Fig 1
						Low reactivity/good response		0/139						Fig 1
Eshtehardi,2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	600 mg LD Clopidogrel +500 mg aspirin	Aggregometry	Death	Death	30 days	Clopidogrel low response	Death	0	OR (calculate) =9.8	NR	P=0.023 (High vs low reactivity) [Fisher's exact test]			
						Aspirin low response		0						
						Dual low response		1 (5.3%)						
						Normal response		0						
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Clopidogrel 600mg LD+aspires 0.5g	Aggregometry	Cardiac death	Cardiac death	14 months	Responders (n=163)	Cardiac death	4 (2.4%)	OR (calculate) =0.91	NR	P=1.0 (dual nonrespondER + clopidogrel nonrespondER vs responder) [Fisher's exact test]			
						Dual nonresponders (n=19)		0 (0%)						

Appendix Table E78: Results from studies assessing the ability of Multiplate Analyzer to predict myocardial infarction in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	Multiple Electrode Platelet Aggregometry (MEA-ADP)	Periprocedural MI	Postprocedural ↑ of troponin or CK-MB >3 times the 99th percentile of the ULN in patients with normal baseline levels (or >3 times in pts with elevated baseline levels).	From PCI to 30 days	30 days	MI+	NR	NR	NR	NR	NR	NR	AUC=0.419; P=0.310 (Fig2d)	Multiple Electrode Platelet Aggregometry (MEA-ADP)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Myocardial infarction	according to TIMI criteria	30 days	Low Responders (>416 aggregation units*min)	Myocardial infarction	12 (3.7%)	OR=1.16	0.61-2.21	P=0.64 (low vs normal responder) [log rank]	NO	NR	Secondary

						Normal Responders (≤416 aggregation units*min)		41 (3.2%)						
			Myocardial infarction	according to TIMI criteria	6 months	Low Responders (>416 aggregation units*min)	Myocardial infarction	17 (5.2%)	OR=1.4	0.8-2.4	P=0.25 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		49 (3.8%)						
			MI >24 h post-PCI	according to TIMI criteria	30 days	Low Responders (>416 aggregation units*min)	MI >24 h post-PCI	5 (1.5%)	OR=4.02	1.28-12.63	P=0.02 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		5 (0.4%)						
			Q-wave MI	according to TIMI criteria	30 days	Low Responders (>416 aggregation units*min)	Q-wave MI	5 (1.5%)	OR=4.99	1.53-16.29	P=0.008 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		4 (0.3%)						
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	MI	according to Thrombolysis in Myocardial Infarction criteria	1 year	Low responder	MI	17 (5.3%)	HR=1.3	0.7-2.2	0.378 (low vs normal) Chisquare	NO	NR	Secondary outcome
						Normal responder		43 (4.1%)						

			Q-wave MI	according to Thrombolysis in Myocardial Infarction criteria	1 year	Low responder	Q-wave MI	8 (2.5%)	HR=4	1.5-10.7	0.005 (low vs normal) Chisquare	NO	NR	Secondary outcome
						Normal responder		8 (0.6%)						
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 or 600mg LDClopidogrel and maintain dose 75 mg+aspirin 100mg	MEA	STEMI			High reactivity/poor response		0						Fig 1
						Low reactivity/good response		3						Fig 1
Eshtehardi 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	600 mg LD Clopidogrel+500 mg aspirin	Aggregometry	PCI-related MI	peak CK-MB >3x ULN if baseline troponin was normal, and >20% increase of CK or CK-MB postprocedure in case of elevated baseline Troponin [ref 25]	Within 30 days after PCI	Clopidogrel low response	PCI-related MI	2 (6.1%)	NR	NR	0.039 across this and next 3 rows (Fisher's exact or chi-square)	NR	NR	NONE
						Aspirin low response		3 (8.8%)						
						Dual low response		5 (26.3%)						
						Normal response		9 (6.8%)						

			MI	new Q waves ≥0.4-sec duration in at least 2 contiguous leads on ECG with or without elevate CK or CK-MB; In the absence of pathologic Q waves, an elevation of CK levels >3x ULN with elevated CK-MB or troponin I or T level	after the periprocedural period	Clopidogrel low response		0			0.004 across this and next three rows (Fisher's exact or chi-square)			
						Aspirin low response		0						
						Dual low response		2 (10.5%)						
						Normal response		1 (0.8%)						
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Clopidogrel600mg LD+aspires 0.5g	Aggregometry	STEMI	ST-elevation myocardial infarction	30days or later after PCI	Responders (n=163)	ST-elevation myocardial infarction	1 (0.6%)	Relative risk vs. previous row, 8.58	0.56-131.65	NR	NR	NR	
						Dual nonresponders (n=19)		1 (5.3%)						

Appendix Table E79: Results from studies assessing the ability of Multiplate Analyzer to predict stent thrombosis in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	>468 aggregation units*min	definite ST	9/428 (2.1%)	OR=3.6 (calculated)	NR	P<0.001 (>468 AU*min vs ≤ 468 AU*min) [chi square]	NO	NR	Secondary
						≤468 aggregation units*min		7/1180 (0.3)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	Mutliplate analyzer	Definite or probable stent thrombosis	Definite or probable stent thrombosis	30 days (all outcomes)	Enhanced responder (AUC≤188) (N=975)	Yes thrombosis	NR	NR	NR	0.38 enhanced responder vs. the remaining			Fig. 2

						Normal responder (AUC189-467) (N=1130)	Yes thrombosis	NR						
						Low responder (AUC≥468) (N=428)	Yes thrombosis	NR (2.8%)			<0.001 low responder vs the remaining two rows			
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	Low Responders (>416 aggregation units*min) n=323	definite ST	7 (2.2%)	OR=9.4	3.1-28.4	P<0.0001 (low vs normal responder) [log rank]	NO	NR	Primary
						Normal Responders (≤416 aggregation units*min) n=1285		3 (0.2%)						
Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	6 months	Low Responders (>416 aggregation units*min) n=323	definite ST	8 (2.5%)	OR=6.5	2.4-17	P<0.0001 (low vs normal responder) [log rank]	NO	NR	Primary

						Normal Responders (≤416 aggregation units*min) n=1285		6 (0.4%)						
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	Low Responders (>416 aggregation units*min) n=323	definite ST	7 (2.2%)	HR=10.95	2.31-51.99	P=0.003 (low vs normal responder) [cox proportional hazards regression]	YES; Diabetes mellitus, active smoking, body mass index, ejection fraction, platelet count, time from clopidogrel loading to blood sampling, and CAD presentation (including STEMI, NSTEMI, stable angina, and unstable angina)	NR	Primary
						Normal Responders (≤416 aggregation units*min) n=1285		3 (0.2%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	6 months	Low Responders (>416 aggregation units*min)	**definite ST**	**8 (2.5%)**	HR=5.3	2.3-13.7	P=0.0006 (low vs normal responder) [cox proportional hazards regression]	YES; Diabetes mellitus, active smoking, body mass index, ejection fraction, platelet count, time from clopidogrel loading to blood sampling, and CAD presentation (including STEMI, NSTEMI, stable angina, and unstable angina)	NR	Primary
						Normal Responders (≤416 aggregation units*min)		6 (0.4%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Probable Stent thrombosis	As per Academic Research Consortium criteria	30 days	Low Responders (>416 aggregation units*min)	Probable Stent thrombosis	2 (0.6%)	OR=4	0.65-24.47	P=0.13 (low vs normal responder) [log rank]	NO	NR	Primary
						Normal Responders (≤416 aggregation units*min)		2 (0.2%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Probable Stent thrombosis	As per Academic Research Consortium criteria	6 months	Low Responders (>416 aggregation units*min)	Probable Stent thrombosis	5 (1.6%)	OR=5	1.5-16.3	P=0.008 (low vs normal responder) [log rank]	NO	NR	Primary
						Normal Responders (≤416 aggregation units*min)		4 (0.3%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Possible stent thrombosis	As per Academic Research Consortium criteria	6 months	Low Responders (>416 aggregation units*min)	Possible stent thrombosis	0/323	OR=0.4 (calculated)	NR	P=0.26 (low vs normal responder) [log rank]	NO	NR	Primary

						Normal Responders (≤416 aggregation units*min)		5/1285 (0.4%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Stent thrombosis	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	Low Responders (>416 aggregation units*min)	Stent thrombosis	9 (2.8%)	Sensitivity: 0.7 Specificity: 0.84 AUC=0.78	0.60-0.96	P<0.001	NR	NR	Primary
						Normal Responders (≤416 aggregation units*min)		5 (0.4%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Stent thrombosis	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	6 months	Low Responders (>425 aggregation units*min)	Stent thrombosis	13 (4.1%)	Sensitivity: 0.59 Specificity: 0.81 AUC=0.74	0.62-0.86	P<0.0001	NR	NR	Primary
						Normal Responders (≤425 aggregation units*min)		9 (0.7%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	High Responders (Quintile 1 ≤124 AU*min)	definite ST	1 (0.3%)	NR	NR	P=0.003 [Chi square]	NO	NR	Primary
						Normal Responders (Quintile 2 >124-≤192 AU*min)		0						
						Normal Responders (Quintile 3 >192-≤261 AU*min)		1 (0.3%)						
						Normal Responders (Quintile 4 >261-≤416 AU*min)		1 (0.3%)						
						Low Responders (Quintile 5: >416 AU*min)		7 (2.2%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Probable/ definite ST	Occurrence of an acute coronary syndrome with either angiographic or pathological confirmation of thrombosis.	30 days	High Responders (Quintile 1 ≤124 AU*min)	Probable/ definite ST	1 (0.3%)	NR	NR	P=0.001 [Chi square]	NO	NR	Primary
						Normal Responders (Quintile 2 >124-≤192 AU*min)		0						
						Normal Responders (Quintile 3 >192-≤261 AU*min)		2 (0.6%)						
						Normal Responders (Quintile 4 >261-≤416 AU*min)		2 (0.6%)						
						Low Responders (Quintile 5: >416 AU*min)		9 (2.8%)						

	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Combined probable/definite stent thrombosis	As per Academic Research Consortium criteria	30 days	Low Responders (>416 aggregation units*min)	Combined probable/definite stent thrombosis	9 (2.8%)	OR=7.26	2.86-18.46	P<0.0001 (low vs normal responder) [log rank]	NO	NR	Landmark
						Normal Responders (≤416 aggregation units*min)		5 (0.4%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Combined probable/definite stent thrombosis	As per Academic Research Consortium criteria	6 months	Low Responders (>416 aggregation units*min)	Combined probable/definite stent thrombosis	13 (4.1%)	OR=5.8	2.8-12.3	P<0.0001 (low vs normal responder) [log rank]	NO	NR	Landmark
						Normal Responders (≤416 aggregation units*min)		9 (0.7%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Combined probable/definite stent thrombosis	As per Academic Research Consortium criteria	30 days to 6 months	Low Responders (>416 aggregation units*min)	Combined probable/definite stent thrombosis	4 (1.2%)	OR=4.1	1.1-14.7	P=0.03 (low vs normal responder) [log rank]	NO	NR	Landmark

						Normal Responders (≤416 aggregation units*min)		4 (0.3%)						
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Definite stent thrombosis	Based on definition of the Academic Research Consortium (ARC)	1 year	Low responder	Definite stent thrombosis	8 (2.5%)	HR=5.4	1.9-15.6	0.02 (low vs normal) cox proportional hazard model	NO	NR	Secondary outcome
						Normal responder		6 (0.5%)						
	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Probable stent thrombosis	Based on definition of the Academic Research Consortium (ARC)	1 year	Low responder	Probable stent thrombosis	5 (1.6%)	HR=3.4	1-11	0.046 (low vs normal) cox proportional hazard model	NO	NR	Secondary outcome
						Normal responder		6 (0.5%)						
Siller-Matula 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily	MEA	Definite stent thrombosis	Defined by ARC as ACS with angiographic or pathologic confirmation of thrombosis	Within 6 mo after stenting	Platelet hyperreactivity vs. no hyperreactivity	Definite stent thrombosis	--	AUC, 0.92 (SE 0.04) ROC cutoff, 54U Sensitivity 100% and specificity 86%;	For AUC, 0.85-0.99	0.012 from ROC	NR	NR	NONE
						No platelet hyperreactivity	Definite stent thrombosis	0/341	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3

						Platelet hyperreactivity		3/61	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3
	600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily	MEA	Composite of definite or probable stent thrombosis	Probable defined any unexplained death within 30 days or target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion		Platelet hyperreactivity vs. no hyperreactivity	Composite of definite or probable stent thrombosis	--	AUC, 0 .81 (SE 0.10) ROC cutoff, 54U Sensitivity 86% and specificity 87%	For AUC, 0.61-1.02	0.004 from ROC	NR	NR	NONE
						No platelet hyperreactivity		1/341	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3
						Platelet hyperreactivity		6/61	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3
	600 mg LD Clopidogrel followed by MD 75 mg daily+250 mg LD aspirin followed by 100 mg daily	MEA	Probable stent thrombosis	Probable stent thrombosis		No platelet hyperreactivity	Probable stent thrombosis	0/341	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3

						Platelet hyperreactivity		3/61	NR	NR	NR	NR	NR	Data also given for MEA +VASP in Fig 3
Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	600 mg LD Clopidogrel+500 mg aspirin	Aggregometry	Stent thrombosis (early definite)	Defined according to the Academic Research Consortium Definitions [ref 26]		Clopidogrel low response		0	NR	NR	0.004 across this and next three rows (Fisher's exact or chi-square)			
						Aspirin low response		0						
						Dual low response		2 (10.5%)						
						Normal response		1 (0.8%)						

Appendix Table E80: Results from the studies assessing the ability of Multiplate Analyzer to predict major adverse cardiovascular events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	75 mg/d clopidogrel & 100 mg/d aspirin	Multiple Electrode Platelet Aggregometry (MEA-ADP)	Major adverse cardiovascular events (MACE)	Death, MI, stroke, and target vessel revascularization	From PCI to 30 days	NR	MACE +	NR	NR	NR	NR	NR	NR	AUC=0.443; P=0.415 (Fig2b)
Sibbing 2010{Sibbing, 2010 88 /id} 19943882 Sibbing 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	Mutliplate analyzer	adverse event	Definite or probable stent thrombosis or in-hospital TIMI major bleeding	30 days	AUC≤ 188 Enhanced responder (N=975)	adverse event	NR	incidence of adverse events	NR	0.008 across all 3 groups chi square test	NR	NR	Fig 1
						AUC 189-467 normal responders n=1130								
						AUC ≥468 low responders n=428								

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	Mutliplate analyzer	adverse event	Definite or probable stent thrombosis or in-hospital TIMI major bleeding	30 days	Normal responder (N=1130)	adverse event	NR	OR=0.40	0.22-0.75	0.003 between normal responder and remaining patients NR	NR	NR	
						Enhanced or low responder (N=1403)								

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing 2009{Sibbing, 2009 135 /id} 19264241 Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	MACE	Death or Stent thrombosis	30 days	Low Responders (>416 aggregation units*min)	MACE	10 (3.1%)	OR=5.1	2.2-11.6	P<0.001 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		8 (0.6%)						
Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR		MEA	MACE	Death or Stent thrombosis	6 months	Low Responders (>416 aggregation units*min)	MACE	16 (5%)	OR=5.1	2.2-11.6	P<0.001 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		30 (2.3%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
			MACE	Cardiac Death + Definite ST	6 months	Low Responders (>416 aggregation units*min)	MACE	14 (4.4%)	OR=3.3	1.7-6.5	P<0.001 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		17 (1.3%)						
			MACE	Death + ST As per Academic Research Consortium criteria	30 days	Low Responders (>416 aggregation units*min)	Combined death/definite ST	10 (3.1%)	OR=5.05	2.19-11.64	P<0.001 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		8 (0.6%)						
			MACE	Death or definite Stent thrombosis	6 months	Low Responders (>416 aggregation units*min)	MACE	16 (5%)	OR=2.2	1.2-4.1	P=0.008 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		29 (2.3%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Schulz 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	MACE	Death or MI	1 year	Low responder	MACE	27 (8.4%)	HR=1.3	0.8-1.9	0. 298 (low vs normal) cox proportional harzard model	NO	NR	Secondary outcome
						Normal responder		86 (6.7%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Freynhofer 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	300 or 600mg LDClopidogrel and maintain dose 75 mg+aspirin 100mg	MEA	MACE	MACE included: 1) definite and probable ST according to the ARC-definition; 2) cardiovascular death, defined as death associated with ACS, significant arrhythmia, or congestive heart failure; and 3) non-fatal STEMI (STEMI: acute onset of prolonged typical ischaemic chest pains, ST-segment elevation of at least 1 mm in 2 or more contiguous electrocardiogram leads and increased biomarkers of myocardial necrosis)	6 months	High reactivity/poor response n=59	MACE	3 (5.4%)	OR=23.5 (calculate)	NR	0.670 high vs. low reactivity chi square	NR	NR	Fig 1

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Low reactivity/good response n=137		4 (2.9%)						Get n's from Fig 1 (pasted in on last page of this form)
Eshtehardi 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	600 mg LD Clopidogrel+500 mg aspirin	Aggregometry	MACE	Composite of PCI-related MI, stent thrombosis, death, or MI	30 days	Clopidogrel low response n=33	MACE	2 (6.1%)	OR=8.0 dual vs normal OR= 9.0 dual vs clopidogrel low response (calculated)	NR	<0.001 across this and next three rows; <0.001 for dual vs normal; 0.005 for dual vs clopidogrel (Fisher's exact or chi-square)	NR	NR	none
						Aspirin low response n=34		3 (8.8%)						
						Dual low response n=19		7 (36.8%)	odds 7.35	2.21-24.42	<0.001(Multivariable logistic regression analysis)			
						Normal response n=133		9 (6.8%)						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Ivandic 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Clopidogrel600mg LD+aspires 0.5g	Aggregometry	Combined end point:	Combined end point: first occurrence of any of the following cardiovascular events: cardiovascular death, myocardial infarction, target vessel revascularization, or stent thrombosis occurring 30 days or later after PCI.	>/= 30 days after PCI	Clopidogrel nonresponder (n=34)	Combined end point	8 (23.5%)	HR= 1.04	0.24-4.44	NS non-responder vs. full (cox proportional hazard model) Also NS vs full responders below	NR	NR	NONE
						Nonresponse to clopidogrel but response to aspirin (n=15)		2 (13.3%)						
						Full responders (n=134)		18 (13.4%)						
						Dual nonresponder (n=19)		6 (31.6%)	HR 2.57 HR in multivariate analysis, 2.9	1.18-5.61 In multivariate, 1.17-7.2	0.03 dual non-responder vs. any responders, In multivariate, 0.02 (Cox regression)			

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	Clopidogrel600mg LD+aspires 0.5g	Aggregometry	cardiovascular events	Freedom from combined end point myocardial infarction, target vessel revascularization, late stent thrombosis, or cardiac death in KM curve	>/= 30 days after PCI	Responders (n=163)	cardiovascular events	40/163	OR=5.3 (calculated)	NR	0.03 dual nonresponder vs. responder (log rank)	NR	NR	K-M curves are in Fig. 1
						Dual nonresponders (n=19)		12/19						K-M curves are in Fig. 1
	Clopidogrel600mg LD+aspires 0.5g	Aggregometry	Any cardiovascular event	Any cardiovascular event	>/= 30 days after PCI	Responders (n=163)	Any cardiovascular event	20 (12.2%)	Relative risk 2.57 dual non-responder vs. responder	1.18-5.61	NR	NR	NR	
						Dual nonresponders (n=19)		6 (31.5%)						

Appendix Table E81: Results from studies assessing the ability of Multiplate Analyzer to predict major adverse cardiovascular events in patients with cerebrovascular disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	LD 300 mg of clopidogrel 75 mg/day continuously	Impedance aggregometry	Adverse event	Transient intrainterventional thrombosis, TIA or infarction	NR	Non-responder	Adverse event	5/14	OR=42.3 (calculated)	NR	0.001 non-responder vs. responder Fisher exact test	NR	NR	
						Responder		0/36						
	LD 300 mg of clopidogrel 75 mg/day continuously	Impedance aggregometry	Adverse event	Transient intrainterventional thrombosis, TIA or infarction	NR	1 Aggregation unit	Adverse event	NR	OR=1.15	NR	0.0321U increase of aggregation logistic regression	NR	NR	

Appendix Table E82: Results from studies assessing the ability of Multiplate Analyzer to predict stroke in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Ischemic stroke	confirmation by CT/MRI imaging of the head.	30 days	Low Responders (>416 aggregation units*min)	Ischemic stroke	3 (0.9%)	OR=6.01	1.25-28.88	P=0.03 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		2 (0.2%)						
	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Ischemic stroke	confirmation by CT/MRI imaging of the head.	6 months	Low Responders (>416 aggregation units*min)	Ischemic stroke	3 (0.9%)	OR=4	0.9-17.6	P=0.07 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		3 (0.2%)						

Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Stroke	By CT/MRI	1 year	Low responder	Stroke	4 (1.3%)	HR=2.3	0.7-7.8	0.185 (low vs normal) Chisquare	NO	NR	Secondary outcome
						Normal responder		7 (0.6%)						
	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Hemorrhagic Stroke	By CT/MRI	1 year	Low responder	Hemorrhagic Stroke	0/323	OR=0.4 (calculated)	NR	0. 853 (low vs normal) Chi square	NO	NR	Secondary outcome
						Normal responder		4/1285(0.3%)						
	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	Ischemic Stroke	By CT/MRI	1 year	Low responder	Ischemic Stroke	4 (1.3%)	HR=5.4	1.2-24	0. 028 (low vs normal) Chisquare	NO	NR	Secondary outcome
						Normal responder		3 (0.2%)						

Appendix Table E83: Results from studies assessing the ability of Multiplate Analyzer to predict bleeding events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing 2010{Sibbing, 2010 88 /id} 19943882 Sibbing 2010{Sibbing, 2010 73 /id} 20633826 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	in-hospital major bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI major bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital major bleed	21/975 (2.2%)	Sensitivity: 0.62 Specificity: 0.62 AUC=0.61	0.51-0.7	P=0.017 for ROC	NR	NR	Primary
						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		13/1558 (0.8%)						
			in-hospital major bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI major bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital major bleed	21/975 (2.2%)	OR=2.6	1.3-5.2	P=0.005 (enhanced vs remaining responder) [llogistic regression]	NO	NR	Primary

						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		13/1558 (0.8%)						

			in-hospital major bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI major bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital major bleed	21/975 (2.2%)	OR=3.5	1.6-7.3	P=0.001 (enhanced vs remaining responder) [multiple logistic regression]	YES; age, body mass index, diabetes, renal failure, presence of an MI at admission, treatment at admission with aspirin, a thienopyridine, a statin or a coumarin derivate, use of abciximab, use of intra-aortic balloon pumping, number of lesions treated and complex lesions (defined as type B2/C lesions according to AHA/ACC lesions morphology).	NR	Primary

						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		13/1558 (0.8%)						
			in-hospital major bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI major bleeding	30 days	Enhanced responder (AUC≤188) (N=975)	Yes bleeding	NR /975(2.2%)	NR	NR	0.018 across this and next two rows of enhanced, normal and low responders			Data for this outcome are %s in Fig. 1—can be obtained by digitizing
						Normal responder (AUC189-467) (N=1130)	Yes bleeding	NR/1130			0.72 between noral and low responder			
						Low responder (AUC≥468) (N=428)	Yes bleeding	NR/428						
			in-hospital minor bleed	As per Thrombolysis in Myocardial Infarction (TIMI) criteria - TIMI minor bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital minor bleed	55/975 (5.6%)	OR=1.1	0.8-1.5	P=0.68 (enhanced vs remaining responder) [logistic regression	NO	NR	Primary
						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		82/1558 (5.3%)						

			Bleeding Composite	TIMI major and minor bleeding	30 days	Enhanced Responders (<188 aggregation units*min)	in-hospital major and minor bleed	76/975 (7.8%)	OR=1.3	0.95-1.8	P=0.1 (lenhanced vs remaining responder) [logistic regression]	NO	NR	Primary
						Remaining patients - Not enhanced responders (≥188 aggregation units*min)		95/1558 (6.1%)						
Sibbing 2009{Sibbing, 2009 135 /id} 19264241 Sibbing 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Thrombolysis In Myocardial Infarction (TIMI) major bleeding	TIMI criteria	30 days	High Responders (Quintile 1 ≤124 AU*min)	Thrombolysis In Myocardial Infarction (TIMI) major bleeding	4/318 (1.3%)	OR=1.8 (calculated)	NR	P=0.32 between quintile 1 and 2-5 [Chi square]	NO	NR	Safety
						Normal Responders and low responders (Quintile 2 - 5)		9/1290 (0.7%)						
			Thrombolysis In Myocardial Infarction (TIMI) minor bleeding	TIMI criteria	30 days	High Responders (Quintile 1 ≤124 AU*min)	Thrombolysis In Myocardial Infarction (TIMI) minor bleeding	10/318 (3.1%)	OR=1.3 (calculated)	NR	P=0.45 between high responder and remaining [Chi square]	NO	NR	Safety

						Normal Responders and low responders (Quintile 2 - 5)		31/1290 (2.4%)						
Schulz 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	In-hospital TIMI major bleeding	defined according to Thrombolysis in Myocardial Infarction criteria	1 year	Low responder	In-hospital TIMI major bleeding	1 (0.3%)	HR=0.3	0.01-2.4	0. 460 (low vs normal) Cox proportional hazards model	NO	NR	Secondary outcome
						Normal responder		12 (0.9%)						

Appendix Table E84: Results from studies assessing the ability of Multiplate Analyzer to predict other clinical events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	Clopidogrel: 600 mg LD + 150 mg/day clopidogrel for 3 days + 75 mg/day clopidogrel MD & Aspirin: 500 mg IV LD + 100 mg aspirin (twice per day) MD	MEA	Target lesion reintervention	NR	30 days	Low Responders (>416 aggregation units*min)	Target lesion reintervention	7 (2.2%)	OR=4.02	1.53-10.58	P=0.005 (low vs normal responder) [log rank]	NO	NR	Secondary
						Normal Responders (≤416 aggregation units*min)		7 (0.5%)						
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	clinical restenosis defined as target lesion revascularization (TLR)	repeat PCI of the target lesion or bypass surgery of the target vessel	1 year	Low responder	Clinical restenosis	34 (10.9%)	HR=1.2	0.8-1.7	0.441 (low vs normal) cox proportional hazard model	NO	NR	Primary outcome
						Normal responder		119 (9.5)						

	Clopidogrel 75 mg/d + Aspirin 100 mg/d	MEA by Multiplate analyzer	clinical restenosis defined as target lesion revascularization (TLR)	repeat PCI of the target lesion or bypass surgery of the target vessel	1 year	Low responder	Clinical restenosis	34 (10.9%)	HR=1	0.9-1.1	0. 717 (low vs normal) Cox regression	YES; chronic occlusions, complex lesions, lesion length, and diameter stenosis before PCI	NR	Secondary outcome
						Normal responder		119 (9.5)						
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	Clopidogrel600 mg LD+aspires 0.5g	Aggregometry	Target vessel revascularization	Target vessel revascularization	30days or later after PCI	Responders (n=163)	Target vessel revascularization	7 (4.3%)	Relative risk 3.68	1.03-13.04	NR	NR	NR	
						Dual nonresponders (n=19)		3 (15.8%)						

Appendix Table E85: Results from studies assessing the ability of Multiplate Analyzer to predict platelet reactivity during followup (when used as a discrete outcome) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Clopidogrel 75 mg MD	Impedence aggregometry	Impedence aggregometry	Aggregation measured with PGE1 and ADP	24 hrs after PCI	Impedence between 16-88 units	Impedence between 16-88 units	In Fig 1D; difficult to interpret	NR	NR	NR	NR	NR	NR	Fig 1D shows shaded area greater than normal range reported in the text
						Impedence between 16-88 units	Impedence between <16 units	In Fig 1D; difficult to interpret	NR	NR	NR	NR	NR	NR	
						Impedence between <16 units	Impedence between 16-88 units	In Fig 1D; difficult to interpret	NR	NR	NR	NR	NR	NR	
						Impedence between <16 units	Impedence between <16 units	In Fig 1D; difficult to interpret	NR	NR	NR	NR	NR	NR	

Appendix Table E86: Quality Assessment of studies assessing the predictive ability of Multiplate Analyzer in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	NR	yes	yes	low	low	NR	yes	unclear	high	No	NR	high	high	no	yes	yes	yes	low
Ko, 2011{Ko, 2011 26 /id} 21315223 Korea NR	YES	YES	YES	LOW	LOW	YES	NO	HIGH	LOW	YES	NR	UNCLEAR	LOW	NO [30 days]	YES	YES	YES	LOW
Sibbing, 2010{Sibbing, 2010 88 /id} 19943882 Sibbing, 2010{Sibbing, 2010 73 /id} 20633826 Germany	YES	YES	YES	LOW	LOW	YES	NO;(Sibbing 19943882 was used as reference for Sibbing 20638826))	UNCLEAR	HIGH	YES	YES; (NR in Sibbing 20638826)	LOW; (Unclear in Sibbing 20638826)	LOW	NO	YES	YES	YES	LOW

NR																		
Sibbing, 2009{Sibbing, 2009 135 /id} 19264241 Sibbing, 2010{Sibbing, 2010 100 /id} 20062919 Germany NR	YES	YES	YES	LOW	LOW	YES	NO	UNCLEAR	HIGH	YES	YES	LOW	LOW	NO	YES	YES	YES	LOW
Schulz, 2010{Schulz, 2010 67 /id} 20691843 Germany NR	YES	YES	YES	LOW	LOW	NR	YES	UNCLEAR	HIGH	YES	YES	LOW	LOW	YES [1 year]	YES	YES	YES	LOW
Freynhofer, 2011{Freynhofer, 2011 1 /id} 21614416 Austria NR	yes	yes	yes	low	low	NR	yes	unclear	low	yes	yes	low	low	no	yes	yes	yes	low
Siller-Matula, 2010{Siller-Matula, 2010 89 /id} 19943879 Austria NR	yes	yes	yes	low	low	NR	yes	unclear	Low	yes	NR	unclear	low	no (6 months)	yes	yes	yes	low

Eshtehardi, 2010{Eshtehardi, 2010 78 /id} 20435201 Switzerland NR	YES	YES	YES	low	low	YES (“The operators	YES	low	low	YES	YES (“All events were independently adjudicated by a	low	low	NO (30 days)	YES	YES	YES	LOW
Ivandic, 2009{Ivandic, 2009 125 /id} 19359538 Germany NR	YES	YES	YES	LOW	LOW	NR	NO	HIGH	UNCLEAR	YES	NR	UNCLEAR	LOW	NO (30 days)	YES	YES	YES	LOW

Appendix Table E87: Quality Assessment of studies assessing the predictive ability of Multiplate Analyzer in patients with cerebrovascular disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Muller-Schunk, 2008{Muller-Schunk, 2008 175 /id} 18223094 Germany NR	Yes	No	Yes	Low	Low	NR	NO	HIGH	LOW	YES	NR	UNCLEAR	LOW	NO (30 days)	YES	YES	YES	LOW

Appendix Table E88: Baseline characteristics of patients with ischemic heart disease in studies assessing the predictive ability of TEG

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	Total N Enrolled Race (% by group) Male (%) Age[29]	Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)	Stent implantation(%) Type of stent(%) Multi-or single vessel(%)			
Bliden, 2006{Bliden, 2007 202 /id} 17291930 USA NR	100 Caucasian male 60 African-American male 12 66±11	NR NR NR CABG 31 NR 13 NR 40 NR	83 56 HTN 74; systolic 145±22; diastolic 76±16 44	NR 100 100 NR	100 DES 75 BMS 24 NR	Non-emergent coronary stenting	Clopidogrel therapy (75 mg qd) for ≥1 month before undergoing non-emergent coronary stenting were enrolled after giving informed consent. A clopidogrel loading dose was not administered. All patients had received at least 81 mg aspirin for 7 days before the procedure.	Eptifibatide was administered at the discretion of the treating physician with the ESPRIT study protocol as a double bolus (180 ug/kg) followed by an infusion (2 ug/kg/min) for 18 to 24 h after procedure. Unfractionated heparin was administered according to the ESPRIT dosing regimen (60 U/kg) as a bolus to all patients in the catheterization laboratory immediately before stenting.
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK	49 NR 67	NR NR 0	hyper 59 Ex-smoker 29 current 31 HTN 61	NR 100 94	NR NR one vessel 45 two vessel 10	ACS	at least 300 mg clopidogrel loading dose if >12 prior to angiography	NR

[29] Mean (standard deviation), unless otherwise stated.

NR	63±11	CABG 6 NR NR NR 29 NR	24	39	three vessel 0		followed by 75 mg daily as maintenance , or 600 mg loading if <12 h prior to angiography with 75 mg daily maintenance	
Kwak, 2010{Kwak, 2010 41 /id} 211266640 Korea OPCABG	99 NR 72 65±7	NR NR 3 NR NR NR NR 6 NR	NR NR 65 41	NR NR NR NR	NR NR NR	patients scheduled for CABG	Dual antiplatelet therapy consisting of aspirin 100 mg and clopidogrel 75 mg was started 24 h after the surgery as adequate.	NR
Gurbel, 2010{Gurbel, 2010 68 /id} 20691842 USA PREPARE POST-STENTING	225 White male: 54 African American male: 13 66±12	NR NR CVA 12 PTCA 35;CABG 24 NR NR 8 33 NR	hyper 80 55 Systolic BP, mm Hg: 144 ± 25 Diastolic BP, mm Hg 75 ± 17;HTN: 74 41	NR NR NR 34	NR NR NR	Patients undergoing percutaneous coronary intervention (PCI) fro ACS	Clopidogrel: 300 (n=73) to 600 mg (n=75) LD + 75 mg/d MD; no LD for pts on clopidogrel (n=77) Aspirin: 325 mg LD + 81-325 mg MD	Eptifibatide (n=123) Unfractionated heparin to achieve a clotting time of 200 to 250 seconds (for those given GPIIb/IIIa inhibitor) and >300 seconds (all other patients)
Gurbel, 2005{Gurbel, 2005	182 White: 115	NR NR	Hyperlipidemia: 66.7%	NR 100	96% DES: 69.8%/BMS:	PCI for ACS	Clopidogrel (loading dose of 300	

215 /id} 16286165 USA PREPARE POST-STENTING	(59%) 108 (56) 65±12	 NR PTCA:39.6/CABG:24.5% NR NR NR 36.9% NR	43.8% HTN: 66.2% 42.2%	 NR NR	28.1% NR		or 600 mg or continuation of pre-enrollment maintenance dose; maintenance dose 75 mg daily) + aspirin (81- to 325-mg daily dose for seven days before the procedure, and 325 mg on day of procedure and daily thereafter)	

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;
Add headings for additional subgroups. Data are means unless otherwise indicated; estimated is noted if reported as an estimate.

Appendix Table E89: Study design characteristics of studies assessing the predictive ability of TEG in patients with ischemic heart disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Bliden, 2006{Bliden, 2007 202 /id} 17291930 USA NR	prospective Cohort	no	Consecutive	Patients receiving clopidogrel	NR	12 months	Hospital inpatient	With the sample size calculation from SigmaStat software, it is estimated that the sample size required for 95% power with the alpha of 0.05 is approximately 100 patients.	Partly industry (NIH and Bayer)
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	prospective Cohort	No	Patients with ACS history	Patients with ACS history	Jan-June , 2008	6 months	Hospital inpatient	NR	NR
Preisman, 2010{Preisman, 2010 77 /id} 20181490 Israel None	Prospective observational	NO	NR	Patients undergoing first CABG and receiving either or both aspirin and clopidogrel	13 May 2008 to 24 November 2008	NR	Inpatient	YES [YES}	Nonindustry (except PlateletMapping kits donated by manufacturer)
Kwak, 2010{Kwak, 2010 41 /id} 211266640 Korea OPCABG	prospective cohort	no	patients scheduled for CABG	patients scheduled for CABG	Dec 2007-March 2009	5 days	hospital inpatient	yes. 80%	non-industry

Gurbel, 2010{Gurbel, 2010 68 /id} 20691842 USA PREPARE POST-STENTING	Prospective observational study	NO	Consecutive	Patients undergoing percutaneous coronary intervention (PCI) for ACS	2004 and 2005	Max of 36 months	Follwoup after intervention	YES; Accrual>80%	Non-industry (Sinai Hospital, Baltimore & NIH grant R44-HL059753)
Gurbel, 2005{Gurbel, 2005 215 /id} 16286165 USA PREPARE POST-STENTING	Prospective, observational	NO	Consecutive patients	Patients undergoing percutaneous coronary intervention (PCI) for ACS	NR	NR	Hospital, then outpatient	NO	NR

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-elevation; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; DES=drug eluting stent; CABG=coronary artery bypass grafting; AA= arachidonic acid; SD=standard deviation; RCT=randomized controlled trial; NR=not reported;

Appendix Table E90: Phenotypic test details in studies assessing the predictive ability of TEG in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer *	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Bliden, 2006{Bliden, 2007 202 /id} 17291930 USA NR	Thrombelastograph Hemostasis Analyzer With Platelet-Mapping. Thrombelastograph Hemostasis Analyzer With Platelet-Mapping assay (Haemoscope Corp., Niles, Illinois)	ADP and AA	Baseline samples were obtained before coronary intervention and at 3 h and 18 to 24 h after stenting. Heparin at 3 h and 18 to 24 h within 2h	High on-treatment platelet reactivity (HPR): ≥70% ADP-induced aggregation with 2-µmol ADP at baseline as measured by TEG Normal on-treatment platelet reactivity (NPR): <70% ADP-induced aggregation with 2-µmol ADP at baseline as measured by TEG	based on previous literature	HPR: 22/100 (22%) NPR: 78/100 (22%)
Kwak, 2010{Kwak, 2010 41 /id} 211266640 Korea OPCABG	TEG/ thromboelastography platelet mapping assay NR Haemoscope Corp., Niles, Illinois	ADP	Blood sampling and TEG platelet mapping assay were performed immediately before the induction of anesthesia Heparin NR NR	platelet inhibitory response 70%	ROC curve	platelet inhibitory response 70% n=33
Gurbel, 2010{Gurbel, 2010 68 /id} 20691842 USA PREPARE POST-STENTING	Thromboelastography TEG Hemostasis System Haemoscope	Thrombin & ADP	Blood; 18 to 24 hours post-PCI or 5 days post-PCI (if eptifibatide used) 40 USP lithium heparin Clopidogrel came first	Quartile of TEG Maximum amplitude with Thrombin Quartile 1 <65 mm Quartile 2 65-69 mm Quartile 3 >69-72 mm Quartile 4 >72 mm Quartile of TEG Maximum	ROC curve analysis	Quartile of TEG Maximum amplitude with Thrombin Quartile 1 <65 mm 56 (25%) Quartile 2 65-69 mm56 (25%) Quartile 3 >69-72 mm56 (25%) Quartile 4 >72 mm57 (25%) Quartile of TEG Maximum

	Corporation, Niles, IL		NR	amplitude with ADP Quartile 1 <29 mm Quartile 2 29-39 mm Quartile 3 >39-72 mm Quartile 4 >72 mm		amplitude with ADP Quartile 1 <29 mm 56 (25%) Quartile 2 29-39 mm 56 (25%) Quartile 3 >39-72 mm 56 (25%) Quartile 4 >72 mm 57 (25%)
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	Clot strength and speed of clot formation TEG R _ platelet mapping kit Haemoscope Corp	ADP	Study sample drawn into a 6 mL Lithium Heparin Vacutainer Lithium Heparin NR NR	sTEG <800 mm/min sTEG >800 mm/min	Based on literature	sTEG <800 mm/min: NR sTEG >800 mm/min: NR
Gurbel, 2005{Gurbel, 2005 215 /id} 16286165 USA PREPARE POST-STENTING	Thromboelastography TEG Hemostasis System NR	20um ADP	At discharge 40 USP lithium heparin 2 hrs NR	TEG: Low reaction time R (time to initial thrombin-generated fibrin formation) <3.9 minutes TEG: Normal reaction time R(time to initial thrombin-generated fibrin formation) ≥3.9 minutes TEG: High maximum amplitude of thrombin-generated clot (MA) >72 mm TEG: Not High maximum amplitude of thrombin-generated clot (MA) ≤72 mm	Defined by ROC curve in the same study	TEG: Low reaction time R: NR TEG: Normal reaction time R: NR TEG: High maximum amplitude : NR TEG: Not High maximum amplitude : NR

*If more than one test, use separate rows
**E.g., nonresponsive vs. responsive to clopidogrel, high vs. low platelet reactivity,
ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E91: Results from studies assessing the ability of TEG to predict death in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Bliden, 2006{Bliden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	death	death	Day 0-30	Total n=100	death	0/100	NR	NR	NR	NR	NR	Figure 2 with dotted box plot for association of ADP inducing light transmittance aggregometry
					Day 31-365	Total n=100	death	0/100						
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	death)	death	Day 0-30	HPR n=22	death	0/22	OR=3.5 (calculated)	NR	p=0.54 HPR vs NPR Fisher's exact test	NR	NR	
					Day 0-30	NPR N=78	death	0/78						
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	death	death	Day 31-365	HPR n=22	death	0/22	OR=3.5 (calculated)	NR	p=0.54 HPR vs NPR Fisher's exact test	NR	NR	
					Day 31-365	NPR N=78	death	0/78						

Appendix Table E92: Results from studies assessing the ability of TEG to predict myocardial infarction in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Bliden, 2006{Bliden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Myocardial infarction	Myocardial infarction	Day 0-30	HPR n=22	Myocardial infarction	3/22	OR=12.2 (calculated)	NR	p=0.03 HPR vs NPR Fisher's exact test	NR	NR	
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Myocardial infarction	Myocardial infarction	Day 0-30	NPR N=78	Myocardial infarction	1/78						
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Myocardial infarction	Myocardial infarction	Day 31-365	HPR n=22	Myocardial infarction	1/22	OR=10.95 (calculate)	NR	P=0.15 HPR vs NPR Fisher's exact test	NR	NR	
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Myocardial infarction	Myocardial infarction	Day 31-365	NPR N=78	Myocardial infarction	0/78						

Appendix Table E93: Results from studies assessing the ability of TEG to predict major adverse cardiovascular events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Gurbel, 2010{Gurbel, 2010 68 /id} 20691842 USA PREPARE POST-STENTING	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	TEG-ADP	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	TEG MA-ADP >47mm	MACE	NR	Sensitivity: 0.76 Specificity: 0.85 AUC: 0.84	0.78-0.89	P<0.001 from ROC	NO	NR	Primary endpoint; 14/59 (24%) of first events occurred after clopidogrel stopped (mean duration of Tx=of 6.4 ± 3 months)
						TEG MA-ADP ≤47mm		NR						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	TEG-Thrombin	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	TEG MA-Thrombin >69mm	MACE	NR	Sensitivity: 0.76 Specificity: 0.60 AUC: 0.70	0.64-0.76	P<0.001 from ROC	NO	NR	Primary endpoint; 14/59 (24%) of first events occurred after clopidogrel stopped (mean duration of Tx=of 6.4 ± 3 months)

						TEG MA-Thrombin≤47mm		NR						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	TEG-ADP	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	TEG MA-ADP >47mm	MACE	NR	HR=10.3	5.4-20	P<0.001 cox proportional hazard model	NO	NR	Primary endpoint
						TEG MA-ADP ≤47mm		NR						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	TEG-Thrombin	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	TEG MA-Thrombin >69mm	MACE	NR	HR=3.8	2.1-7.0	P<0.001 cox proportional hazard model	NO	NR	Primary endpoint
						TEG MA-Thrombin≤47mm		NR						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	TEG-ADP	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	TEG MA-ADP >47mm	MACE	NR	HR=10.9	5.6-21.3	P<0.001 cox proportional hazard model	YES; MA-THROMBIN >69 mm and calcium-channel blockers	NR	Primary endpoint
						TEG MA-ADP ≤47mm		NR						

	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	TEG-Thrombin	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization1	First event over f/u of 36 months	TEG MA-Thrombin >69mm	MACE	NR	HR=3.5	1.9-6.4	P<0.001 cox proportional hazard model	YES; MA-ADP>47 mm and calcium-channel blockers	NR	Primary endpoint
						TEG MA-Thrombin≤47mm		NR						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	TEG-ADP	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	Quartile 1 <29 mm	MACE	3 (6%)	NR	NR	NR	NR	NR	Primary endpoint
						Quartile 2 29-39 mm		4 (8%)						
						Quartile 3 >39-72 mm		16 (29%)						
						Quartile 4 >72 mm		36 (65%)						
	Clopidogrel 300-600 mg LD + 75 mg MD & Aspirin 325 mg LD + 81-325 mg MD	TEG-THROMBIN	MACE	Cardiac death, stent thrombosis, myocardial infarction, ischemic stroke, and unplanned revascularization	First event over f/u of 36 months	Quartile 1 <65 mm	MACE	5 (10%)	NR	NR	NR	NR	NR	Primary endpoint
						Quartile 2 65-69 mm		8 (15%)						
						Quartile 3 >69-72 mm		21 (38%)						

						Quartile 4 >72 mm		25 (43%)						
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	300 mg or 600 mg LD Clopidogrel and maintaining 75 mg+ Aspirin	sTEG AUC 15	Adverse event	MI+revascularization+cardiovascular admissions	1 year	sTEG <800 mm/min	Adverse event	0/NR	NR	NR	<0.02 sTEG <800 vs >800mm/min	NR	NR	
						sTEG AUC>800mm/min		5/NR						
Gurbel, 2005{Gurbel, 2005 215 /id} 16286165 USA PREPARE POST-STENTING	Clopidogrel (300- 600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/d x 7 days LD + 325 md/f MD)	TEG-MA	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	High TEG-MA- Quartile 4 (>72mm%)	Ischemic events	NR	OR=22.6	6.202-82.604	P<0.0001 (Mulitple logistic regression)	YES; Low TEG-R (reaction time<3.9 mins), High LTA(Max agg>67 %) and combination of High TEG-MA and low R	NR	Tab 4; it's not clear if all predictor were in the same model
	Clopidogrel (300- 600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/d x 7 days LD + 325 md/f MD)	TEG-R	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	Low-R Quartile 1 (<3.9 mins)	Ischemic events	NR	OR=4.4	1.002-19.051	P=0.0498 (Mulitple logistic regression)	YES; High TEG-MA (ma amplitude >72mm), High LTA(Max agg>67 %) and combination of High TEG-MA and low R	NR	Tab 4; it's not clear if all predictor were in the same model

	Clopidogrel (300- 600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/d x 7 days LD + 325 md/f MD)	TEG-MA	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	High TEG-MA- Quartile 4 (>72mm%)	Ischemic events	NR	Sens=0.74 Spec=0.89	NR	NR	NO	No	Tab 4; it's not clear if all predictor were in the same model
	Clopidogrel (300- 600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/d x 7 days LD + 325 md/f MD)	TEG-R	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	Low-R Quartile 1 (>3.9 mins)	Ischemic events	NR	Sens=0.42 Spec=0.79	NR	NR	NO	No	Tab 4; it's not clear if all predictor were in the same model
	Clopidogrel (300- 600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/d x 7 days LD + 325 md/f MD)	TEG-MA	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	Quartile 1 (<65 mm)	Ischemic events	2%	NR	NR	P<0.001 (Q1 vs Q4) P<0.001 (Q2 vs Q4) P<0.001 (Q3 vs Q4) Logistic regression with appropriate contrasts	NO	NR	Fig 7
						Quartile 2 (65-68 mm)		8%						
						Quartile 3 (69-72 mm)		9%						
						High TEG-MA - Quartile 4 (>72 mm)		58%						

	Clopidogrel (300- 600 mg LD+75 mg daily MD) + aspirin (81- to 325-mg/d x 7 days LD + 325 md/f MD)	TEG-R	Ischemic events	Cardiovascular death, MI, unstable angina and stroke requiring rehospitalization	6 months	Quartile 1 (<3.9 mins)	Ischemic events	33%	NR	NR	P=0.41 (Q1 vs Q2) P=0.006 (Q1 vs Q3) P=0.004 (Q1 vs Q4) Logistic regression with appropriate contrasts	NO	NR	Fig 8
						Quartile 2 (3.9-5.1 min)		26%						
						Quartile 3 (5.2-6.1 min)		9%						
						Quartile 4 (6.1-14 min)		7%						
Bliden, 2006{Bliden, 2007 202 /id} 172919 30 USA NR	clopidogrel 75 mg qd	TEG	Ischemic events	Ischemic events	1 year	HPR	Ischemic event	NR	OR=26.8	6.7-107.5	<0.001 cox regression	Yes, age, presentation, diabetes, hypertension, current smoking, BMS(bare-metal stents)	NR	

Appendix Table E94: Results from studies assessing the ability of TEG to predict bleeding events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Blinden, 2006{Blinden, 2007 202 /id} 17291930 USA NR	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Major bleeding	Major bleeding	Day 0-30	HPR n=22	Major bleeding	1/22	OR=10.95 (calculated)	NR	p=0.15 HPR vs NPR Fisher's exact test	NR	NR	
						NPR N=78	Major bleeding	0/78						
					Day 31-365	HPR n=22	Major bleeding	0/22	OR=3.5 (calculated)	NR	p=0.53 HPR vs NPR Fisher's exact test	NR	NR	
						NPR N=78	Major bleeding	0/78						
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	Minor bleeding	Minor bleeding	Day 0-30	HPR n=22	Minor bleeding	1/22	OR=3.7 (calculated)	NR	P=0.37 HPR vs NPR Fisher's exact test	NR	NR	
						NPR N=78	Minor bleeding	1/100						
					Day 31-365	HPR n=22	Minor bleeding	0/22	OR=3.5	NR	p=0.54 HPR vs NPR Fisher's exact test	NR	NR	

						NPR N=78	Minor bleeding	0/100						
	clopidogrel 75 mg qd	ADP-induced platelet reactivity	bleeding events	bleeding events	Day 0-30	HPR n=22	bleeding events	2/22	OR=7.7 (calculated)	NR	p=0.10 HPR vs NPR Fisher's exact test	NR	NR	
						NPR N=78	bleeding events	1/78						
					Day 31-365	HPR n=22	Bleeding events	0/22	OR=3.5 (calculated)	NR	p=0.54 HPR vs NPR Fisher's exact test	NR	NR	
						NPR N=78	Bleeding events	0/78						
Kwak, 2010{Kwak, 2010 41 /id} 211266640 Korea OPCABG	aspirin 100 mg and clopidogrel 75 mg	TEG platelet inhibitory response to clopidogrel	post-operative transfusion requirement	post-operative transfusion requirement	5 days	Third tertile of platelet inhibitory response (>76.5%)	post-operative transfusion requirement	2/33	OR=10.63	2.7-41.78	0.001 comparing first and second tertile logistic regression model	No	NR	
						First & Second tertile of platelet inhibitory response (<76.5%)		4/66						

	aspirin 100 mg and clopidogrel 75 mg	TEG platelet inhibitory response to clopidogrel	post-operative transfusion requirement	post-operative transfusion requirement	5 days	Third tertile of platelet inhibitory response (>76.5%)	post-operative transfusion requirement	2/33	OR=11.44	2.77-47.3	0.001 comparing first and second tertile logistic regression model	yes (variable with p<0.2 the discontinuation date of clopidogrel, tertile distribution of the percentage of the platelet inhibitory response, the number of grafts performed)	NR	
						First & Second tertile of platelet inhibitory response (<76.5%)		4/66						
	aspirin 100 mg and clopidogrel 75 mg	TEG platelet inhibitory response to clopidogrel	post-operative transfusion requirement	post-operative transfusion requirement	5 days	platelet inhibitory response ≥70%	post-operative transfusion requirement	NR	AUC= 0.771 Sensitivity = 0.778 Specificity = 0.75	0.674-0.868	<0.001 from ROC	No	NR	
						platelet inhibitory response <70%		NR						

Appendix Table E95: Quality Assessment of studies assessing the predictive ability of TEG in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	**2**	**3**	**ROB (selection)**	**Applicability (selection)**	**4**	**5**	**ROB (index)**	**Applicability (index)**	**6**	**7**	**ROB (reference)**	**Applicability (reference)**	**8**	**9**	**10**	**11**	**ROB (flow & timing)**
Bliden, 2006{Bliden, 2007 202 /id} 17291930 USA NR	yes	yes	yes	low	low	NR	yes	unclear	high	yes	NR	unclean	low	yes	yes	yes	yes	low
Cotton, 2010{Cotton, 2010 75 /id} 20406238 UK NR	no	yes	yes	low	low	NR	No	high	low	yes	NR	yes	low	yes	yes	yes	yes	low
Gurbel, 2010{Gurbel, 2010 68 /id} 20691842 USA PREPARE POST-STENTING	yes	yes	yes	low	low	NR	NO	high	high	yes	yes	low	low	yes	yes	yes	yes	low
Kwak, 2010{Kwak, 2010 41 /id} 211266640 Korea OPCABG	no	yes	yes	low	low	NR	no	high	low	yes	yes	low	low	no	yes	yes	yes	low
Gurbel, 2005{Gurbel, 2005 215 /id} 16286165	Yes	No	No	High	Low	NR	NR	Unclear	HIgh	Yes	Yes	Low	Low	No [6 months]	yes	yes	yes	low

USA PREPARE POST-STENTING																		

Appendix Table E96: Baseline characteristics of patients with ischemic heart disease in studies assessing the predictive ability of the PFA-100 system

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	**Total N Enrolled** **Race (% by group)** **Male (%)** **Age**[30]	**Previous CAD (%)** **Previous heart failure(%)** **Previous TIA/stroke(%)** **History of PCI or CABG(%):** **Stable angina(%)** **Unstable angina(%)** **Previous PAD(%)** **History of MI(%)** **STEMI/non-STEMI(%)**	**Dyslipidemia (%)** **Smokers (%)** **BP(mmHg diastolic/systolic** **HTN (%)** **Diabetes (%)**	**Vitamin K antagonist(%)** **Clopidogrel(%)** **Aspirin(%)** **PPI(%)**	**Stent implantation(%)** **Type of stent(%)** **Multi-or single vessel(%)**			
Malek, 2007{Malek, 1946201 /id} 17295159 Poland NR	91 NR 68 median age Group1 66 (38, 85) Group 2 59 (51, 82) Group 3 54.5 (48, 71) Controls 58 (35, 86)	NR NR NR NR NR NR 17.6 NR	34.1 48.4 HTN 50.5 15.4	NR 98.9 100 NR	NR NR NR	underwent PCI with stent implantation	All patients received a loading dose of 300 mg of aspirin followed by daily regimen of 75 mg and a loading dose of either 300 or 600 mg of clopidogrel followed by 75 mg daily.	NR
Breet, 2011{Breet, 2010 86 /id} 20179285 Netherlands NR	1069 NR 75 64±10.6	NR NR NR NR NR NR	80.3 11.1 HTN 76.9 18.6	NR 100 89.4 27.8	100 DES 63.5 NR	coronary artery disease scheduled for elective PCI with stent	clopidogrel treatment (a maintenance of 75 mg/d therapy for>5 days or a loading dose of 300 mg ≥24 hours before PCI or 600 mg ≥4 hours	unless they were receiving long-term anticoagulation with warfarins

[30] Mean (standard deviation), unless otherwise stated.

		NR 54.5 NR					before PCI) and aspirin (80-100 mg/d ≥10 days).	
Foussas, 2007{Foussas, 2007 195 /id} 17892990 Greece None	612 NR 81.7 62±10.8	NR NR NR CABG 4.7 23.5 NR NR 17.7 STEMI 36.3	Hyper 67.3 51 HTN 48.6 28.7	NR 100 100 NR	100 BMS 79.8 Sirolimus eluting 20.2 55.5	PCI with stenting	aspirin (100-325 mg/d) and clopidogrel (300 or 600 mg as loading dose and then 75 mg/d).	Unfractioned heparin (70 IU/kg) was given at the start of the procedure.
Smit, 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	648 NR 75.8 62.3	NR NR CVA 1.7 PCI 7.4; CABG 2.5 15.2 NR NR 7.8 STEMI 100	18.8 44.9 HTN 29.6; systolic 132.8 mmHg; diastolic 79.8 mmHg 9.9	NR NR NR NR	NR NR NR	Patients with ACS (STEMI)	Clopidogrel: (600 mg LD + 75 mg MD daily for 1 year);	acetylsalicylic acid 500 mg IV; unfractionated heparin 5000 IU IV ± tirobiban (25 mg/kg bolus + MD infusion of 0.15 mg/kg/min of tirofiban or placebo)
Huczek, 2008{Huczek, 2008 235 /id} 18301358 Poland NR	125 NR 66 Mean 62 (range 60-63)	22 NR CV event 3 NR NR	37 48 HTN 52 24	NR NR NR NR	NR NR NR	Patients undergoing percutaneous coronary intervention (PCI) for ACS	Clopidogrel: 600-mg LD + 75 mg daily MD for of 30 days Aspirin: 300 mg before angiography + 75 mg daily MD	Abciximab - at the discretion of the operator as a 0.25 mg/kg bolus or a 0.125 µg/kg/min 12-hour infusion.

		NR NR 15 NR						
Moerenhout, 2010{Moerenhout, 2010 85 /id} 20211306 Belgium NR	250 NR NR 66.1	post ACS 30.1 NR NR NR 72 NR NR NR NR	cholesterol 190.2 (mean) 27.7 HTN 59.9 22.6	NR NR NR NR	NR NR 56.2	Patients undergoing percutaneous coronary intervention (PCI)	aspirin 160 mg LD + 450 mg LD of clopidogrel (300-mg clopidogrel 12 hours before PCI and 150 mg the day of PCI) Clopidogrel 75 mg MD x 6 weeks (bare metal stents) to 6 months (drug-eluting stent)	Unfractionated heparin was administered at the beginning of the procedure and titrated to obtain activated clotted time (ACT) levels between 300 and 350 seconds.
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	30 NR 63±10	100 NR CVD 7 PCI 43 NR NR 10 37 NR	hyper 77 57 HTN 77 33	NR 100 100 NR	NR NR NR	Patients undergoing PCI for coronary artery disease	Patients had been on chronic aspirin (100 mg/day) and clopidogrel (75 mg/day) treatment for three months on average.	All patients received unfractionated heparin and 250 mg of injectable acetyl-salicylic acid during PCI
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOS	746 NR 75 68±12	NR NR NR PCI 23; coronary artery surgery 6	hyper 49 23 HTN 61 20	NR NR NR NR	100 DES 93 multi 57	RECLOSE patients who underwent DES implantation for whom complete AA- and collagen-	All patients received aspirin (325 mg) and a loading dose of 600 mg of clopidogrel followed by a	Patients on a maintenance dose of ticlopidine or clopidogrel at the time of admission received a

E		33 40 NR 25 26				induced platelet aggregation values were available.	maintenance dose of 75 mg daily.	loading dose of clopidogrel (600 mg).

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent; HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;
Add headings for additional subgroups. Data are means unless otherwise indicated; estimated is noted if reported as an estimate.

Appendix Table E97: Study design characteristics of studies assessing the predictive ability of PFA-100 system in patients with ischemic heart disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Malek, 2007{Malek, 1946 201 /id} 17295159 Poland NR	prospective Cohort	No	Consecutive patients	Patients who underwent PCI with stent implantation in the course of ACS	NR	In hospital stay Median 6 days (min 3, max 12)	Hospital inpatient	NR	NR
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	prospective Cohort	No	Patients scheduled for PCI with stent implantation	Patients with PCI and stent implantation	Dec 2005-Dec 2007	1-year	Hospital inpatient	Yes. 80%	NR
Foussas, 2007{Foussas, 2007 195 /id} 17892990 Greece None	Prospective	NO	Consecutive	Patients undergoing coronary artery stenting	April 2003-Jan. 2005	Total 1 yr	Inpatient and then outpatient followup for 1 yr	NR	NR
Smit, 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	Substudy of the Ongoing Tirofiban in Myocardial Infarction Evaluation 2 (On-TIME-2) trial	yes	Selected sample (For whom Platelet aggregation inhibition data was available)	Patients with ACS (STEMI)	June 2004 until November 2007	Max 30 days	follow up after intervention	NR	NR
Huczek, 2008{Huczek, 2008 235 /id} 18301358 Poland NR	Prospective observational	NO	Consecutive	Patients undergoing percutaneous coronary intervention (PCI) for ACS	NR	6 months	Followup after intervention	NO	NR
Moerenhout, 2010{Moerenhout, 2010 85 /id} 20211306 Belgium NR	Prospective observational	NO	NR	Patients undergoing percutaneous coronary intervention (PCI)	Jan 2006-June 2007	6 months followup	followup after intervention	YES; Accrual >80%	non-industry
Siller-Matula, 2009{Siller-Matula, 2009 234 /id}	Prospective observational study	NO	NR	Patients undergoing PCI for coronary artery	Aug 2007-Apr 2008	1 day	followup after intervention	YES Accrual=100%	Non-industry [grant from the Jubiläums fond of the

19135705 Austria NR				disease					Austrian National Bank (Nr. 12565)]
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	Prospective	NR but probably NO	Consecutive	RECLOSE patients who underwent DES implantation for whom complete AA- and collagen-induced platelet aggregation values were available.	July 2005 to February 2006	Total 6 mo	Outpatient followup of cohort at 1, 3, and 6 mo	YES [YES]	Nonindustry

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-elevation; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; DES=drug eluting stent; CABG=coronary artery bypass grafting; AA= arachidonic acid; SD=standard deviation; RCT=randomized controlled trial; NR=not reported;

Appendix Table E98: Phenotypic test details in studies assessing the predictive ability of PFA-100 in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer*	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Malek, 2007{Malek, 1946 201 /id} 17295159 Poland NR	Platelet function analysis PFA-100 point-of-care device – PFA-100; Dade Behring, Germany	ADP	sample collected after the acute phase of ACS (2-9 days after admission) 3.2% sodium citrate NR NR	Group 1 with CADP-CT<104 s group 2 with CEPI-CT <190 s group 3 with CADP CT <104 s and CEPI-CT <190 s both CT values above the cut-off limits	not explicitly reported.	Group 1 (n=10, 11%), group 2 (n=10, 11%), group 3 (n=9, 9.9%) a control group (n=62, 68.1%).
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	PFA 100 the Dade PFA collagen/ADP test cartridge(PFA-100system) Siemens Healthcare Diagnostics Products GmbH,Marburg, Germany	ADP	NR 3.8% buffered citrated blood NR 2 hours	PFA ≤147 seconds	Based on ROC curve	NR
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	INNOVANCE® PFA P2Y* NR NR	ADP, PGE1, calcium	NR 3.8% buffered citrated blood NR 2 hours	PFA ≤59 seconds	Based on ROC curve	NR
Foussas, 2007{Foussas, 2007 195 /id} 17892990 Greece	PFA-100 Closure time Dade-Behring, Collagen+ADP or	Collagen+ADP or epiephrine	Blood samples obtained after femoral or brachial arterial sheath insertion in the catheterization laboratory. After rejection of the first few milliliters, blood for PFA-100 analysis was collected into tubes.	CEPI-CT >193 sec (responders) CEPI-CT ≤193 sec (nonresponders)	Based on literature	CEPI-CT >193 sec 489 (79.9%) (responders) CEPI-CT ≤193 sec (nonresponders) 123 (20.1%)

None	epiephrine Marburg, Germany		The time required to occlude the aperture is automatically reported as the closure time (CT). Measurements are terminated after ≤300 seconds. citrate Aspirin+clopidogrel loading done >12 hr before stenting; mean/SD 37.4/23.5 hr within 1 hour			
Smit, 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	PFA Platelet function analyser PFA-100/ Dade Behring, Marburg, Germany	2 mg type I collagen with either 50 mg epinephrine bi-tartrate (col-EPI) or 50 mg ADP (col-ADP)	Whole blood; collected before PCI NR NR Clopidogrel came first NR	quartiles 1-4	Not explicitly reported	quartiles 1 162 (25%) quartiles 2 162 (25%) quartiles 3 162 (25%) quartiles 4 162 (25%)
Huczek, 2008{Huczek, 2008 235 /id} 18301358 Poland NR	PFA-100 PFA-100 Dade Behring, Newark, Delaware	epinephrine and collagen (for Thromboxane A2 pathway) and ADP and collagen (for ADP-dependent pathway)	Venous blood; day 3 & 30 after stenting 3.8% buffered sodium citrate 0.08 days (2 hours) Clopidogrel came first 0.02-0.04 days (0.5-1 hr)	group I (CEPI-CT ≥193 seconds and CADP-CT ≥130 seconds, i.e. complete platelet function inhibition) Group II (either CEPI-CT<193 seconds or CADP-CT<130 seconds, i.e. partial platelet function inhibition) Group III (CEPI-CT<193 seconds and CADP-CT<130 seconds, i.e. no platelet function inhibition).	Previously published information	group I 67 (53.6%) Group II 21(16.8%) Group III 37 (29.6%)
Moerenhout, 2010{Moerenhout, 2010 85 /id} 20211306 Belgium NR	PFA-100 platelet function analyzer (PFA-100 C/ADP) NR	Collagen and ADP	blood before PCI NR 0.5 days (12 hrs) Clopidogrel came first NR	nonresponder (PFA value <71 seconds) responder (PFA value >71 seconds)	Based on literature	nonresponder (PFA value <71 seconds) 17 (7%) responder (PFA value >71 seconds) 225 (93%)
Siller-Matula, 2009{Siller-	PFA-100	collagen and adenosine	1st blood sample: in catheterization laboratory, after PCI and after 250	Collagen ADP closure time between 65-120 s	Normal ranges as reported by	Collagen ADP closure time between 65-120 s by PFA-

Matula, 2009 234 /id} 19135705 Austria NR	PFA-100 Dade Behring, Marburg, Germany	diphosphate (ADP)	mg IV aspirin 2nd blood sample: 20-24 hours after PCI 3.8% citrate NR Clopidogrel came first 0.04 days (1 hour)	by PFA-100 Collagen ADP closure time between <65 s & >120 s by PFA-100	manufacturer	100 ; 20 (67%) Collagen ADP closure time between <65 s & >120 s by PFA-100; 10 (33%)
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	PFA-100 system NR Dade-Behring, Marburg, Germany	Collagen/epinephrine or collage/ADP	Platelet reactivity measured 12 to 18 hr after clopidogrel loading citrate For patients receiving in the catheterization laboratory both the loading dose of clopidogrel and a IIb/IIIa inhibitor, blood samples were obtained after six days while the patient was on the 75-mg maintenance dose of clopidogrel. NR	RPR by CEPI PFA-100 (<203 sec) No RPR Patients at high risk for adverse events: RPR by CEPI PFA-100 (<238 sec) RPR by CADP PFA-100.(<105 sec)	previous literature	RPR by CEPI PFA-100 (<203 sec);133/746 (18%) No RPR; 613/746 (82%) RPR by CEPI PFA-100 (<238 sec) :238/746 (32%) RPR by CADP PFA-100.(<105 sec) :196/398 (49%)

*If more than one test, use separate rows
**E.g., nonresponsive vs. responsive to clopidogrel, high vs. low platelet reactivity,
ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E99: Results from studies assessing the ability of PFA-100 to predict death in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	PFA 100 collagen/ ADP	Death	death,	1-year	High OTPR	Death	10/506 (2)	OR=1.21	0.41-3.58	0.73	No	NR	
						Normal OTPR		5/306 (1.6)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	Innovance PFA P2Y	Death	death,	1-year	High OTPR	Death	6/147 (4.1)	OR=4.65	1.29-16.7	0.01	No	NR	
						Normal OTPR		4/441 (0.9)						
Foussas, 2007{Foussas, 2007 195 /id} 17892990 Greece None	300 or 600 mg LD and 75mg MD Clopidogrel+100-325 mg/day aspirin	PFA-100	Cardiac death	Cardiac death	1 yr	Nonresponder	Cardiac death	6.5%	HR 2.5	1.1-6.1	0.04 (non-responder vs. responder, Cox regression)			
						Responder		2.7%						

	300 or 600 mg LD and 75mg MD Clopidogrel+100-325 mg/day aspirin	PFA-100	In-hospital death	In-hospital death		Responder	In-hospital death	0.8%			0.13 non-responder vs. responder			
						Nonresponder		2.4%	HR 3.1	0.7-8.3				
	300 or 600 mg LD and 75mg MD Clopidogrel+100-325 mg/day aspirin	PFA-100	Cardiac death	Cardiac death	1 yr	Q1 of CEPI-CT (shortest time, least responsive)	Cardiac death	6.5%	HR 4.1	1.2-13.9	0.02 for HR Q1 vs. Q4, 0.03 across Q1-Q4			
						Q2		5.6%						
						Q3		1.6%						
						Q4 (most responsive)		1.7%						
Huczek, 2008{Huczek, 2008 235 /id} 18301358 Poland NR	Clopidogrel 75 mg	Combination of CT-EPI and CT-ADP by PFA-100	Cardiac death	cardiac death	6 months	Group I (complete platelet function inhibition)	cardiac death	1	NR	NR	P=0.038 P for trend [ANOVA]	NO	NR	
						Group II (partial platelet function inhibition)		1						
						Group III (no platelet function inhibition).		5						

Appendix Table E100: Results from studies assessing the ability of PFA-100 to predict myocardial infarction in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2011{Breet, 2010 86 /id} 20179285 Netherlands NR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	PFA 100 collagen/ ADP	MI	MI	1-year	High OTPR	MI	4/506 (6.7)	OR=1.31	0.71-2.41	0.39 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		16/306 (5.2)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	Innovance PFA P2Y	MI	MI	1-year	High OTPR	MI	11/147 (7.5)	OR=1.7	0.8-3.64	0.17 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		20/441 (4.5)						
Foussas, 2007{Foussas, 2007 195 /id} 17892990 Greece None	300 or 600 mg LD and 75mg MD Clopidogrel+100-325 mg/day aspirin	PFA-100	Rehospitalization for MI	Rehospitalization for MI		Nonresponder	Rehospitalization for MI	12.2%	HR 2.7	1.4-5.2	0.002 non-responder vs. responder (Cox regression)			
						Responder		4.9%						

	300 or 600 mg LD and 75mg MD Clopidogrel+100-325 mg/day aspirin	PFA-100	MI	MI	1 yr	Q1 of CEPI-CT (shortest time, least responsive)	MI	12.2%	HR, 3.2	1.4-7.3	0.006 Q1 vs Q4 for HR 0.02 across Q1-Q4			
						Q2		7.1%						
						Q3		4%						
						Q4 (most responsive)		4.2%						
Huczek, 2008{Huczek, 2008 235 /id} 18301358 Poland NR	Clopidogrel 75 mg	Combination of CT-EPI and CT-ADP by PFA-100	nonfatal reinfarction	nonfatal reinfarction	6 months	Group I (complete platelet function inhibition)	nonfatal reinfarction	0	NR	NR	P=0.026 P for trend [ANOVA]	NO	NR	
						Group II (partial platelet function inhibition)		1						
						Group III (no platelet function inhibition).		4						
Moerenhout, 2010{Moerenhout, 2010 85 /id} 20211306 Belgium NR	aspirin 160 mg LD + 450 mg LD of clopidogrel +Clopidogrel 75 mg MD x 6 weeks to 6 months	PFA-100	Myocardial infarction post PCI	CK-MB increase of >3× ULN post-PCI	6 months	nonresponder (PFA value <71 seconds)	MI post PCI	2/17 (12%)	OR=3.2 (calculate)	NR	P=0.2 (between nonresponder and responder) Chi Square test	NO	NR	Secondary endpoint
						responder (PFA value >71 seconds)		9/225 (4%)						

Malek, 2007{Malek, 1946 201 /id} 17295159 Poland NR	Clopidogrel LD 300 or 600mg and maintaining 75mg daily	PFA-100	Re-infarction	Re-infarction	In-hospital 6 days	Groups 1-3	Re-infarction	2/29 (6.9)	OR=4.5 (calculate)	NR	p=0.23	NR	NR	Bar graph showed cardiovascular events by group. Figure 1
						Control		1/62 (1.6)						
	Clopidogrel LD 300 or 600mg and maintaining 75mg daily	PFA-100	Cardiac arrest	Cardiac arrest	In-hospital 6 days	Groups 1-3	Cardiac arrest	2/29 (6.9)	OR=1.5 (calculate)	NR	p=0.69 groups 1-3 vs control Fisher's exact test	NR	NR	
						Control		3/62 (4.8)						

Appendix Table E101: Results from studies assessing the ability of PFA-100 to predict stent thrombosis in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2011{Breet, 2010 86 /id} 20179285 Netherlands NR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	PFA 100 collagen/ ADP	Stent thrombosis	Stent thrombosis	1-year	High OTPR	Stent thrombosis	5/506 (1)	OR=0.75	0.20-2.83	0.67high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		4/306 (1.3)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	Innovance PFA P2Y	Stent thrombosis	Stent thrombosis	1-year	High OTPR	Stent thrombosis	1/147 (0.7)	OR=0.75	0.08-6.75	0.8 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		4/441 (0.9)						

Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CADP PFA-100 among patients at high risk for AEs	Stent thrombosis	definite or probable: ACS + either angiographic confirmation of thrombosis or pathological confirmation of thrombosis; or unexplained death or MI in the territory supplied by a stented vessel without angiographic confirmation	6 mo	residual platelet reactivity RPR (n=196)	Stent thrombosis	NA	• 100% sensitivity • 52% (47-57%) specificity		For sensitivity and specificity, <0.001 vs CEPI–PFA-100	NR	NR	
	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100	Stent thrombosis	see above	6 -month	residual platelet reactivity RPR	Stent thrombosis		OR 3.97	1.61-9.79	0.003 logistic regression Univariate analysis	NR	NR	
	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100	Stent thrombosis	see above	6-month	residual platelet reactivity RPR	Stent thrombosis	NR	OR 3.25	1.26-8.39	0.025 logistic regresssion Multivariate analysis		NR	

	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100	Stent thrombosis	see above	6-month	residual platelet reactivity RPR (n=133)	Stent thrombosis	9	OR=3.97 (calculated)	NR	p=0.002RPR vs. no RPR Fisher's exact test	NR	NR	
						No RPR (n=613)		11				NR	NR	
	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100	Stent thrombosis	see above	6 -month	residual platelet reactivity RPR (n=133)	Stent thrombosis	NA	• Cutoff from AUC 238 sec • 45% (23-69%) sensitivity • 83% (80-86%) specificity		For specificity, <0.01 vs. LTA-ADP and <0.0001 vs. LTA-collagen	NR	NR	
	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100 among patients at high risk for AEs	Stent thrombosis	see above	6-month	residual platelet reactivity RPR (n=238)	Stent thrombosis	NA	• 40% (19-61%) sensitivity • 81% (78-89%) specificity		For specificity, <0.0001 vs. LTA-ADP	NR	NR	

Appendix Table E102: Results from studies assessing the ability of PFA-100 to predict major adverse cardiovascular events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Foussas, 2007{Foussas, 2007 195 /id} 17892990 Greece None	300 or 600 mg LD and 75mg MD Clopidogrel+100-325 mg/day aspirin	PFA-100	Composite of cardiac death and rehospitalization for nonfatal MI	Composite of cardiac death and rehospitalization for nonfatal MI	1 yr	Nonresponder	Composite of cardiac death and rehospitalization for nonfatal MI	18.7%	HR= 2.7	1.6-4.5	<0.001 non-responder vs. responder (Cox regression)	No	NR	NONE
						Responder		7.6%						
	300 or 600 mg LD and 75mg MD Clopidogrel+100-325 mg/day aspirin	PFA-100	Composite of cardiac death and rehospitalization for nonfatal MI	Composite of cardiac death and rehospitalization for nonfatal MI	1 yr	Q1 of CEPI-CT (shortest time, least responsive)	Composite of cardiac death and rehospitalization for nonfatal MI	18.7%	HR= 3.7	1.8-7.5	<0.001 Q1 vs. Q4,for HR and for trend across this and next 3 rows			
						Q2		12.7%						
						Q3		5.6%						
						Q4 (most responsive)		5.9%						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	300 or 600 mg LD and 75mg MD Clopidogrel+100-325 mg/day aspirin	PFA-100	Composite endpoint	Composite endpoint		Nonresponders	Composite endpoint		HR =2.9	1.7-3.9	<0.001 among pts with CK-MB data, (multivariate regression)	YES; Table 4		
									HR= 2.5	1.6-3.8	<0.001 among all pts, (multivariate 2.5regression)	YES; Table 5		
Smit, 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	Clopidogrel 300 mg LD + 75 mg MD	PFA-ADP	MACE	mortality, urgent target vessel revascularisation or recurrent myocardial infarction	30 days	Quartile 1	MACE	NR	NR	NR	0.035; between all quartiles [Chi-square]	NO	NR	Data in figures only shows percentages; needs to be digitized to obtain accurate values
						Quartile 2		NR						
						Quartile 3		NR						
						Quartile 4		NR						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Malek, 2007{Malek, 1946201 /id} 17295159 Poland NR	Clopidogrel LD 300 or 600mg and maintaining 75mg daily	PFA-100	Early cardiovascular events	in-hospital re-infarction, cardiac arrest, recurrent angina with changes in electrocardiogram characteristic for acute ischaemia, stroke, ventricular and supraventricular arrythmias requiring electrical cardioversion or intravenous infusion of antiarrythmic drugs, pulmonary oedema, cardiogenic shock or major bleeding	Early cardiovascular events	Group 3 vs control	Early cardiovascular events	RR=9.0	2.4-33.9	NR	<0.005 comparing group 3 vs control	NR	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Huczek, 2008{Huczek, 2008 235 /id} 18301358 Poland NR	Clopidogrel 75 mg	Combination of CT-EPI and CT-ADP by PFA-100	MACE	cardiovascular death, nonfatal reinfarction, stroke, and rehospitalization for congestive heart failure	6 months	Group I (complete platelet function inhibition)	MACE	2	HR=3.8 HR=1.6	2.2-6.8 0.9-4.1	P<0.0001 Groups II & III vs I [Cox regression] P=0.082 (group III vs II) [Cox regression]	YES; age, sex, treatment delay, diabetes, previous MI, chronic aspirin therapy, acute heart failure (Killip >I), anterior STEMI, culprit lesion located in the left anterior descending (LAD) artery, threevessel disease in angiography, abciximab administration, and baseline ejection fraction	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Group II (partial platelet function inhibition)		5						
						Group III (no platelet function inhibition).		20						
Moerenhout, 2010{Moerenhout, 2010 85 /id} 20211306 Belgium NR	aspirin 160 mg LD + 450 mg LD of clopidogrel +Clopidogrel 75 mg MD x 6 weeks to 6 months	PFA-100	major thrombotic adverse cardiac events (MACE)	death, nonfatal myocardial infarction (MI), and stent thrombosis[31]	6 months	nonresponder (PFA value <71 seconds)	MACE	2/17 (12%)	OR=2.6 (calculate)	NR	P=0.2 (between nonresponder and responder) Chi Square test	NO	NR	
						responder (PFA value >71 seconds)		11/225 (5%)						

[31] Myocardial infarction was defined as any typical rise and fall of cardiac markers in the setting of clinical signs or symptoms consistent with the new definitions of MI as described by the European Society of Cardiology. The academic research consortium definitions were used for stent thrombosis (definite, probable, and possible).

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	aspirin 160 mg LD + 450 mg LD of clopidogrel +Clopidogrel 75 mg MD x 6 weeks to 6 months	PFA-100	major thrombotic adverse cardiac events (MACE)	death, nonfatal myocardial infarction (MI), and stent thrombosis[31]	6 months	nonresponder (PFA value <71 seconds)	MACE	2/17 (12%)	OR=13	0.9-183	P=0.057 (between nonresponder and responder) [Logistic regression]	YES; sex, age, height, weight, cholesterol level, arterial hypertension, diabetes status, use of statins, use of angiotensinconverting enzyme inhibitors, multivessel disease, lesion length, total stent length, number of stents, balloon to reference ratio, post-PCI diameter stenosis, contrast dose, maximum balloon inflation pressure, balloon inflation duration, platelet count	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						responder (PFA value >71 seconds)		11/225 (5%)						
Breet , 2010{Breet, 2010 86 /id} 20179285Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	PFA-100	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR ≤147 s	Death combined	33/262 (12.6)	AUC: 0.5 Sens: 0.7 Spec: 0.384	0.46-0.55 0.585-0.795 0.35-0.42	NR	No	NR	
			Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR ≤147s	Death combined	49/506 (9.7)	OR=1.46	0.85-2.48	0.17 high OTPR vs. normal logistic regression	No	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Normal OTPR >147		21/306 (6.9)						
		Innovance PFA P2Y	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR ≤159 secs	Death combined	33/262 (12.6)	AUC: 0.56 Sens: 0.391 Spec: 0.762	0.5-0.62 0.264-0.535 0.724-0.796	NR	No	NR	
			Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR ≤159 secs	Death combined	18/147 (12.2)	OR=2.06	1.1-3.84	0.02 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR >159 secs		28/441 (6.3)						
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100	Stent thrombosis or cardiac death (composite)			residual platelet reactivity RPR (n=133)		10	NR	NR	NS RPR vs. no RPR	NR	NR	
						No RPR (n=613)		15	NR	NR		NR	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100	Stent thrombosis or cardiac death (composite)			residual platelet reactivity RPR (n=133)			• 40% (21-61%) sensitivity • 83% (80-86%) specificity		For specificity, <0.01 vs. LTA-ADP and <0.0001 vs. LTA-collagen			
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100 among patients at high risk for AEs	Stent thrombosis or cardiac death (composite)			residual platelet reactivity RPR (n=238)		NA	• 36% (17-55%) sensitivity • 83% (80-86%) specificity		For sensitivity, p<0.01 vs. LTA-ADP For specificity, p<0.0001 vs. LTA-ADP and p<0.0001 vs. LTA-collagen	NR	NR	
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CADP PFA-100 among patients at high risk for AEs	Stent thrombosis or cardiac death (composite)			residual platelet reactivity RPR (n=196)		NA	• 80% (55-100%) sensitivity • 52% (46[a] - 57%) specificity		For specificity, p<0.001 vs CEPI–PFA-100	NR	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100	Stent thrombosis or cardiac death (composite)			residual platelet reactivity RPR			OR 3.24	1.42-7.38	0.003 logistic regression Univariate analysis	NR	NR	
Gori, 2008{Gori, 2008 151 /id} 19132241 Italy RECLOSE	600mg LD and 75mg/day MD Clopidogrel+325 mg aspirin	CEPI PFA-100	Stent thrombosis or cardiac death (composite)			residual platelet reactivity RPR		NR	OR 2.60	1.08-6.21	0.031 logistic regression Multivariate analysis		NR	

a: reported as 467, we used 46 (because 467 was not possible).

Appendix Table E103: Results from studies assessing the ability of PFA-100 to predict stroke in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands NR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	PFA 100 collagen/ ADP	stroke	Stroke	1-year	High OTPR	Stroke	7/506 (1.4)	OR=4.28	0.52-34.9	0.14 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		1/306 (0.3)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	Innovance PFA P2Y	stroke	Stroke	1-year	High OTPR	Stroke	1/147 (0.7)	OR=0.60	0.07-5.15	0.65 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		5/441 (1.1)						
Huczek, 2008{Huczek, 2008 235 /id} 18301358 Poland NR	Clopidogrel 75 mg	Combination of CT-EPI and CT-ADP by PFA-100	stroke	stroke	6 months	Group I (complete platelet function inhibition)	stroke	0	NR	NR	NR	NO	NR	
						Group II (partial platelet function inhibition)		0						

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Group III (no platelet function inhibition).		1						

Appendix Table E104: Results from studies assessing the ability of PFA-100 to predict bleeding events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Malek, 2007{Malek, 1946201 /id}172951 59Poland NR	Clopidogrel LD 300 or 600mg and maintaining 75mg daily	PFA-100	Major bleeding	Major bleeding	Early cardiovascular events	Groups 1-3	Major bleeding	0/29 (0)	OR=2.1 (calculated)	NR	p=0.71 groups 1-3 vs. control Fisher's exact test	NR	NR	
						Control		0/62 (0)						

Appendix Table E105: Results from studies assessing the ability of PFA-100 to predict other clinical events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Malek, 2007{Malek, 1946201 /id} 17295159 Poland NR	Clopidogrel LD 300 or 600mg and maintaining 75mg daily	PFA-100	Recurrent angina	Recurrent angina	In-hospital 6 days	Groups 1-3	Recurrent angina	2/29 (6.9)	OR=4.5 (calculated)	NR	p=0.23 groups 1-3 vs control Fisher's exact test	NR	NR	
						Control		1/62 (1.6)						
	Clopidogrel LD 300 or 600mg and maintaining 75mg daily	PFA-100	Arrhythmia	Arrhythmia	In-hospital 6 days	Groups 1-3	Arrhythmia	3/29 (10.3)	OR=3.5 (calculated)	NR	p=0.19 groups 1-3 vs control Fisher's exact test	NR	NR	
						Control		2/62 (3.2)						
	Clopidogrel LD 300 or 600mg and maintaining 75mg daily	PFA-100	Pulmonary oedema	Pulmonary oedema	In-hospital 6 days	Groups 1-3	Pulmonary oedema	1/29 (3.4)	OR=2.2 (calculated0	NR	p=0.59 groups 1-3 vs control Fisher's exact test	NR	NR	
						Control		1/62 (1.6)						

	Clopidogrel LD 300 or 600mg and maintaining 75mg daily	PFA-100	Cardiogenic shock	Cardiogenic shock	In-hospital 6 days	Groups 1-3	Cardiogenic shock	3/29 (10.3)	OR=16.5(calculated)	NR	p=0.07 groups 1-3 vs control Fisher's exact test	NR	NR	
						Control		0/62 (0)						
Huczek, 2008{Huczek, 2008235 /id} 18301358 Poland NR	Clopidogrel 75 mg	Combination of CT-EPI and CT-ADP by PFA-100	rehospitalization for CHF	rehospitalization for CHF	6 months	Group I (complete platelet function inhibition)	rehospitalization for CHF	2	NR	NR	P<0.001 P for trend [ANOVA]	NO	NR	
						Group II (partial platelet function inhibition)		3						
						Group III (no platelet function inhibition).		12						

Appendix Table E106: Results from studies assessing the ability of PFA-100 to predict platelet reactivity during followup (when used as a discrete outcome) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Siller-Matula, 2009{Siller-Matula, 2009 234 /id} 19135705 Austria NR	Clopidogrel 75 mg MD	PFA-100	PFA-100	Closure time with collage and ADP using PFA-100	24 hrs after PCI	Collagen ADP closure time between 65-120 s by PFA-100	Collagen ADP closure time between 65-120 s by PFA-100	18	NR	NR	NR	0.141 (fisher's exact calculated from data)	NR	NR	Fig 2B
						Collagen ADP closure time between 65-120 s by PFA-100	Collagen ADP closure time between <65 s & >120 s by PFA-100	2	NR	NR	NR	NR	NR	NR	
						Collagen ADP closure time between <65 s & >120 s by PFA-100	Collagen ADP closure time between 65-120 s by PFA-100	6	NR	NR	NR	NR	NR	NR	
						Collagen ADP closure time between <65 s & >120 s by PFA-100	Collagen ADP closure time between <65 s & >120 s by PFA-100	4	NR	NR	NR	NR	NR	NR	

Appendix Table E107: Quality Assessment of studies assessing the predictive ability of PFA-100 in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	**Patients selection**					**Index test**				**Reference standard**				**Flow and timing**				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Malek, 2007{Malek, 1946201 /id} 17295159 Poland NR	yes	yes	yes	low	low	NR	no	high	low	yes	NR	unclear	low	no	yes	yes	yes	low
Breet, 2011{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	yes	yes	yes	low	low	NR	NO	high	low	yes	yes	low	low	yes	yes	yes	yes	low
Foussas, 2007{Foussas, 2007 195 /id} 17892990 Greece None	yes	yes	yes	low	low	yes	yes	low	low	yes	yes	low	low	yes	yes	yes	yes	low

Smit, 2010{ Smit, 2010 53 /id} 20889 993 Netherlands ON-TIME-2	yes	yes	yes	low	low	NR	NO	high	low	yes	NR	unclear	low	no	yes	yes	yes	low
Huczek, 2008{ Huczek, 2008 235 /id} 18301 358 Poland NR	yes	yes	yes	low	low	NR	yes	unclear	low	yes	NR	unclear	low	no	yes	yes	yes	low
Moerenhout, 2010{ Moerenhout, 2010 85 /id} 20211 306 Belgium NR	NR	yes	yes	low	low	NR	yes	unclear	high	yes	NR	unclear	low	no	yes	yes	yes	low
Siller-Matula, 2009{ Siller-Matula, 2009 234 /id} 19135 705 Austria NR	NR	yes	yes	low	low	NR	yes	unclear	high	No	NR	high	high	no	yes	yes	yes	low

Gori, 2008{ Gori, 2008 151 /id} 19132 241 Italy RECL OSE	yes	yes	yes	low	low	NR	yes	uncle ar	low	yes	NR	uncle ar	low	no	yes	yes	yes	low

Appendix Table E108: Baseline characteristics of patients with ischemic heart disease in studies assessing the predictive ability of miscellaneous platelet function tests

	Demographics	Vascular disease history	Vascular risk factors	Prior medications (pre-study)	Procedural data	Current indication for clopidogrel treatment	Current antiplatelet regimen	Co-medication
Author, year [ref] UID Country Study Name	Total N Enrolled Race (% by group) Male (%) Age[32]	Previous CAD (%) Previous heart failure(%) Previous TIA/stroke(%) History of PCI or CABG(%): Stable angina(%) Unstable angina(%) Previous PAD(%) History of MI(%) STEMI/non-STEMI(%)	Dyslipidemia (%) Smokers (%) BP(mmHg diastolic/systolic HTN (%) Diabetes (%)	Vitamin K antagonist(%) Clopidogrel(%) Aspirin(%) PPI(%)	Stent implantation(%) Type of stent(%) Multi-or single vessel(%)			
Smit, 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	648 NR 75.8 62.3	NR NR CVA 1.7 PCI 7.4; CABG 2.5 15.2 NR NR 7.8 STEMI 100	18.8 44.9 HTN 29.6; systolic 132.8 mmHg; diastolic 79.8 mmHg 9.9	NR NR NR NR	NR NR NR	Patients with ACS (STEMI)	Clopidogrel: (600 mg LD + 75 mg MD daily for 1 year);	acetylsalicylic acid 500 mg IV; unfractionated heparin 5000 IU IV ± tirobiban (25 mg/kg bolus + MD infusion of 0.15 mg/kg/min of tirofiban or placebo)
Dziewierze, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	31 NR 77.4 54.3±9.9	NR NR NR PCI 19.4; CABG 0; 100 NR NR 61.3	74.2 25.8 58.1 12.9	NR NR 100	NR NR multi 70.9	Patients with stable angina selected for PCI	Loading dose 300 mg with 75 mg per day until PCI was performed or 28 days until stent had been implanted.	The use of GP IIb/IIIa inhibitors and heparin titration during PCI were left to the discretion of the operator.

[32] Mean (standard deviation), unless otherwise stated.

		NR						
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	1069 NR 75 64±10.6	NR NR NR NR NR NR 54.5 NR	80.3 11.1 HTN 76.9 18.6	NR 100 89.4 27.8	100 DES 63.5 NR	coronary artery disease scheduled for elective PCI with stent	clopidogrel treatment (a maintenance of 75 mg/d therapy for>5 days or a loading dose of 300 mg ≥24 hours before PCI or 600 mg ≥4 hours before PCI) and aspirin (80-100 mg/d ≥10 days).	unless they were receiving long-term anticoagulation with warfarins
Mobley, 2004{Mobley, 2004 221 /id} 14969622 USA NONE	50 NR NR NR	NR NR NR NR NR NR NR NR	NR NR NR NR	NR NR NR(most to be) NR	NR NR NR	Candidates for cardiac catheterization with clinical suspicion of PCI who were on aspirin and clopidogrel	75 mg clopidogrel per day after 300-mg loading dose (if physician judges the loading dose to be necessary); most patients already on aspirin	NR
Lindvall, 2009{Lindvall, 2009 119 /id} 19477870 Sweden None	15 NR 80 61.8±11.6	NR NR NR NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR	Patients with ACS undergoing CABG	loading dose of 300 – 600 mg of clopidogel orally, followed by 75 mg daily; oral aspirin, 75 mg per day,	subcutaneous low molecular weight heparin. At the time of the study, aprotinin was routinely administered according to the Hammersmith regime: consisting of 2 million KIU before start of surgery, 2 million KIU in the CPB prime, and

		NR NR						500,00- KIU per hr during surgery . Aspirin and low molecular weight heparin treatment was continued until the day of surgery, but not given on the day of surgery. ACE inhibitors were omitted on the day of surgery.
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA No	63 NR 60 67±11	NR NR NR CABG 18 NR NR NR 24 NR	hyper 60 NR HTN 72 39	NR 100 100 NR	100 NR NR	Patients undergoing PCI with stenting	all received ± 81 mg of aspirin for 7 days before the procedure. All patients received the same clopidogrel regimen (300 mg in the catheterization laboratory after stent implantation, then 75 mg/day for 30 days) with 325 mg/day aspirin.	Heparin (activated clotting time >300 seconds) was administered to all patients immediately before stent implantation, and per protocol, GP IIb/IIIa inhibitors were not given.
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	1058 NR 70.1 62.2±11.2	62.2±11.2 NR 3.6% PCI 30.4% NR NR NR 20.9% NR	19% 39.8% 52% 29%	NR 25.3% NR NR	NR NR 27.6%	Patients treated with coronary stenting for symptomatic coronary artery disease, including acute myocardial infarction (AMI) and on chronic clopidogrel therapy	scheduled coronary stenting procedures, 300-mg loading-dose (LD) of clopidogrel at least 12 h before procedure. In AMI patients, all received a 600-mg LD of clopidogrel immediately after emergency room arrival, followed by a maintenance dose of 75 mg daily.	If use of glycoprotein IIb/IIIa inhibitor (GPI) was deemed necessary, only tirofiban, which has a short half-life, was administered.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMS=Bare metal stents; BP = blood pressure; CABG = coronary artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty; CVA=cerebrovascular accident; CVD=cerebrovascular disease; CAD = coronary artery disease; DES=Drug eluting stent; BMS=bare metal stent;

HTN = hypertension, IHD: Ischemic heart disease; MI = myocardial infarction; NSTEMI = non-ST-elevation MI; LVEF=left ventricle ejection fraction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; TIA = transient ischemic attack; PPI=proton pump inhibitor; UFH= Unfractionated Heparin; BP=blood pressure; hyper=hypercholesterolemia; LD=loading dose; MD= maintain dose; ASA=aspirin; GP IIb/IIIa inhibitors =Glycoprotein IIb/IIIa inhibitors;
Add headings for additional subgroups. Data are means unless otherwise indicated; estimated is noted if reported as an estimate.

Appendix Table E109: Study design characteristics of studies assessing the predictive ability of miscellaneous platelet function tests in patients with ischemic heart disease

Author Year PMID Country Study Name	Study design	Multicenter (yes/no)	Recruitment method	Sampling population	Enrolment period	Mean or median (state which follow up duration)	Setting	A Priori power analysis performed? (if yes, was accrual 80% of target or higher)	Funding
Smit, 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	Substudy of the Ongoing Tirofiban in Myocardial Infarction Evaluation 2 (On-TIME-2) trial	yes	Selected sample (For whom Platelet aggregation inhibition data was available)	Patients with ACS (STEMI)	June 2004 until November 2007	Max 30 days	follow up after intervention	NR	NR
Dziewierze, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	prospective Cohort	No	Consecutive	Patients with stable angina selected for PCI	NR	24 hours-28 days	Hospital inpatient	NR	NR
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	prospective Cohort	No	Patients scheduled for PCI with stent implantation	Patients with PCI and stent implantation	Dec 2005-Dec 2007	1-year	Hospital inpatient	Yes. 80%	NR
Mobley, 2004{Mobley, 2004 221 /id} 14969622 USA NONE	Prospective	NR	NR	Candidates for cardiac catheterization with clinical suspicion of PCI who were on aspirin and clopidogrel	NR	NR	Hospital and then outpatient	NO	Partly industry
Lindvall, 2009{Lindvall, 2009 119 /id} 19477870 Sweden None	Prospective observational	NR	Consecutive	Patients with ACS undergoing CABG	NR	NR	Inpatient	NO	Partly industry
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA No	Prospective	NO	NR	Patients undergoing PCI with stenting	NR	NR	Inpatient and then outpatient visit at 30 days	NR	All Industry
Kim, 2010{Kim, 2010 241	prospective cohort	no	consecutively enrolled	unselected patients	December 2007	6 months	Department of Cardiolog	NR	NR

/id} 20449634 Korea NR				treated with coronary stenting for symptomatic coronary artery disease, including acute myocardial infarction (AMI) and chronic clopidogrel therapy	to June 2009		y of the Gyeongsang National University hospital inpatient		

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-elevation; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-elevation MI; DES=drug eluting stent; CABG=coronary artery bypass grafting; AA= arachidonic acid; SD=standard deviation; RCT=randomized controlled trial; NR=not reported;

Appendix Table E110: Phenotypic test details in studies assessing the predictive ability of miscellaneous platelet function tests in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Test/Device name Device category Device name & manufacturer*	Agonist used	Sample Collection and Procurement Anticoagulant used Interval between clopidogrel doses and blood sampling (in days) Interval between sampling and testing (in days):	Grouping of Phenotypes** [Definition]	Rational for the grouping of phenotypes reported (Yes/No) [short description]	Frequency of phenotypes
Smit, 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	Fe induced platelet aggregation (FIPA) Sysmex K4500 Sysmex, Kobe, Japan	AISI 434 low carbon stainless steel	whole blood; collected before PCI Citrate (0.109 M) NR Clopidogrel came first NR	quartiles 1-4	Not explicitly reported	quartiles 1 162 (25%) quartiles 2 162 (25%) quartiles 3 162 (25%) quartiles 4 162 (25%)
Dziewierze, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	Platelet aggregation inhibition Plateletworks with Sysmex K800 Helena Laboratory	ADP	blood samples were collected at baseline and 3, 6, 12 , 24 hours from the initial loading dose of clopidogrel 3.2% natrium citrate baseline and 3, 6, 12 , 24 hours 15 minutes	DPAI≤10% non-responder DPAI>10% responder	not explicitly reported.	DPAI≤10% non-responder; N=7 DPAI>10% responder; N=24
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	Plateletworks NR (Helena Laboratories, Beaumont, Texas).	ADP	NR K3-EDTA and tubes containing diphenylalanyl-Lprolyl-L-arginine chloromethyl ketone (PPACK[50 µmol/L] NR 2 hours	plateletworks <80.5 plateletworks >=80.5	Based on ROC curves	plateletworks <80.5; n=344 plateletworks >=80.5; n=262
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands	IMPACT-R IMPACT-R Matis Medical Inc,	ADP	Before heparinization 3.2% citrate NR	High OTPR ≤2 Normal OTPR >2	Based on ROC curves	High OTPR ≤2 (n = 296) Normal OTPR >2 (n = 609)

POPULAR	Beersel, Belgium		2 hours			
Mobley, 2004{Mobley, 2004 221 /id} 14969622 USA NONE	NR/Optical platelet aggregation Dual Channel Aggregometer Chrono-Log Corp., Havertown, Pennsylvania & Thromboelastograph Hemoscope Corporation, Niles, Illinois & Optical platelet aggregation Ichor Plateletworks Helena Laboratories, Beaumont, Texas	ADP	NR Heparin for Chronolog; Reptilase and factor XIIIa for TEG; Citrate for Ichor Sampling done before and after clopidogrel (but interval NR) NR	Nonresponders (failure of clopidogrel inhibition) defined as <10% reduction from baseline averaging results from all 3 analyzers Responders ≥10% reduction from baseline averaging results from all 3 analyzers	Not explicitly stated	Nonresponders 15/50 (30%) Responders 35/50 (70%)
Mobley, 2004{Mobley, 2004 221 /id} 14969622 USA NONE	Optical platelet aggregation Ichor Plateletworks Helena Laboratories, Beaumont, Texas	ADP	NR citrate Sampling done before and after clopidogrel (but interval NR) NR	Nonresponders Responders	Not explicitly stated	Nonresponders 15/50 (30%) Responders 35/50 (70%)
Lindvall, 2009{Lindvall, 2009 119 /id} 19477870 Sweden None	Aggregometry NR Plateletworks Helena Lab, Beaumont, TX, USA	20 uM ADP	Blood samples were drawn from the radial arterial cannula before and after administration of a bolus of two million kallikrein inhibiting units (KIU) [of aprotinin]; measurements done just before and just after aprotinin given, with both measurements taken long after clopidogrel given	Clopidogrel nonresponse (>90% aggregation) Clopidogrel response (≤90% aggregation)	literature published	Clopidogrel nonresponse (>90% aggregation); 4 (27%) Clopidogrel response (≤90% aggregation); 11 (73%)

			EDTA Mean (SD) interval between last clopidogrel dose and surgery (with blood sampling occurring just before start of surgery) 63.7± 28 hours; median, 72 hours; IQR, 29.5-78 hours Testing done immediately after sampling			
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA No	P-selectin expression Flow cytometry Parmingen, San Diego, California	ADP 200 umol/liter	Blood was collected immediately before clopidogrel administration (baseline), and at 1, 5, and 30 days after stenting. 3.8% trisodium citrate at 0, 1, 5, 30 days NR	Nonresponder (change from baseline of <10%) Responder (change from baseline of <10%)	Not explicitly reported	Nonresponder (change from baseline of <10%): P-selectin expression: 9/38 (24%) P-selectin expression: 29 of 38 (76%)
Kim, 2010{Kim, 2010 241 /id} 20449634 Korea NR	turbidimetry-based optical detection device VerifyNowP2Y12 assay NR & LTA ADP AggRam aggregometer Helena Laboratories Corp., Beaumont, TX	20 µmol/L ADP for VerifyNow & 5 and 20 µmol/L ADP	Blood was drawn into a Greiner Bio-One 3.2% citrate Vacuette tube sodium citrate 3.2% clopidogrel- naı¨ve patients received a 300-mg loading-dose (LD) of clopidogrel at least 12 h before procedure, and blood sampling was performed after insertion of the arterial sheath. In the case of patients who were already on chronic clopidogrel therapy, blood sampling was performed at the catheterization lab without clopidogrel LD 60 minutes	VerifyNow PRU<240 PRU≥240 LTA: Aggregation <50% Aggregation ≥50%	Based on literature	VerifyNow PRU<240 n=512 PRU≥240 n=546 Aggregation <50%: NR Aggregation ≥50%: NR

*If more than one test, use separate rows
**E.g., nonresponsive vs. responsive to clopidogrel, high vs. low platelet reactivity;
ADP= adenosine 5'-diphosphate; Ag= aggregation; PGE1=prostaglandin; ROC=receiver operating characteristic; AUC=area under the curve; IPA= inhibition of platelet aggregation; LTA= light transmission aggregometry; MEA= multiple electrode platelet aggregometry; PFA= platelet function analysis; TEG=thromboelastography; sTEG=short thromboelastography; VASP = vasodilator-stimulated phosphoprotein; VASP-FCT=vasodilator-stimulated phosphoprotein flow cytometry; CEPI=collagen-epinephrine ; CADP=collagen-ADP; CT=closure times; HCPR=high on-clopidogrel platelet reactivity; PCI = percutaneous coronary intervention; RPA= residual platelet aggregation; GP= glycoprotein; HRP=high platelet reactivity; NPR=normal on-treatment platelet reactivity; HPPR= high post-treatment platelet reactivity; MPA= maximum platelet aggregation; RPR= residual platelet reactivity; OTPR=on-treatment platelet reactivity; DPAI= degree of platelet aggregation inhibition; PRU=P2Y12 reaction units; CRP=C-reaction protein; PRI=platelet reactivity index; LR=low responder; IQR=interquartile range; AA= arachidonic acid; LD=loading dose; MD=maintain dose; SD=standard deviation; NR=not reported;

Appendix Table E111: Results from studies assessing the ability of miscellaneous platelet function tests to predict death in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Dziewierze, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	Clopidogrel LD 300 mg, 75mg maintain dose	Platelet aggregation inhibition	Death	Death	In hospital stay	Non-responder	Death	0/7	OR=3.3 (calculated)	NR	p=0.56 nonresponder vs. responder Fisher's exact test	NR	NR	
						Responder		0/24						
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	Platelet works ADP	Death	death,	1-year	High OTPR	Death	4/262 (1.5)	OR=0.58	0.18-1.89	0.36 high OTPR vs normal logistic regression model	No	NR	
						Normal OTPR		9/344 (2.6)						
		IMPACT-R ADP	Death	death,	1-year	High OTPR	Death	6/296 (2)	OR=1.38	0.49-3.91	0.54 high OTPR vs normal logistic regression model	No	NR	
						Normal OTPR		9/609 (1.5)						

Appendix Table E112: Results from studies assessing the ability of miscellaneous platelet function tests to predict myocardial infarction in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Dziewierze, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	Clopidogrel LD 300 mg, 75mg maintain dose	Platelet aggregation inhibition	MI	Myocardial infarction	In hospital stay	Non-responder	MI	0/7	OR=3.2 (calculated)	NR	p=0.56 nonresponder vs. responder Fisher's exact test	NR	NR	
						Responder		0/24						
Breet, 2011{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	Platelet works ADP	MI	MI	1-year	High OTPR	MI	25/262 (9.5)	OR=3.52	1.66-7.47	<0.001high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		10/344 (2.9)						
	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	IMPACT-R ADP	MI	MI	1-year	High OTPR	MI	22/296 (7.4)	OR=1.61	(0.91 - 2.85)	0.10 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		29/609 (4.8)						

Appendix Table E113: Results from studies assessing the ability of miscellaneous platelet function tests to predict stent thrombosis in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	Platelet works ADP	Stent thrombosis	Stent thrombosis	1-year	High OTPR	Stent thrombosis	6/262 (2.3)	OR=2.66	0.66-10.75	<0.09 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		3/344 (0.9)						
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands NR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	IMPACT-R ADP	Stent thrombosis	Stent thrombosis	1-year	High OTPR	Stent thrombosis	3/296 (1.0)	OR=0.88	0.23-3.43	0.85 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		7/609 (1.1)						

Appendix Table E114: Results from studies assessing the ability of miscellaneous platelet function tests to predict major adverse cardiovascular events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Smit, 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	Clopidogrel 300 mg LD + 75 mg MD	FIPA	MACE	mortality, urgent target vessel revascularisation or recurrent myocardial infarction	30 days	Quartile 1	MACE	NR	NR	NR	0.281; between all quartiles [Chi-square]	NO	NR	Data in figures only shows percentages; needs to be digitized to obtain accurate values
						Quartile 2		NR						
						Quartile 3		NR						
						Quartile 4		NR						
	Clopidogrel 300 mg LD + 75 mg MD	Platelet works	MACE	mortality, urgent target vessel revascularisation or recurrent myocardial infarction	30 days	Quartile 1	MACE	NR	NR	NR	0.358; between all quartiles [Chi-square]	NO	NR	Data in figures only shows percentages; needs to be digitized to obtain accurate values

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
						Quartile 2		NR						
						Quartile 3		NR						
						Quartile 4		NR						
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	IMPACT-R ADP	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR	Death combined	32/296 (10.8)	OR=1.6	0.99-2.58	0.05 high OTPR vs normal	No	NR	
						Normal OTPR		43/609 (7.1)						
		IMPACT-R ADP	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1 year	High OTPR ≥93% surface coverage	Death combined	33/262 (12.6)	AUC: 0.53 Sens: 0.44 Spec: 0.669	0.47-0.59 0.333-0.553 0.636-0.7		No	NR	

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
		Platelet works ADP	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR ≥80.5%	Death combined	33/262 (12.6)	AUC: 0.61 Sens: 0.63 Spec: 0.585	0.53-0.69 0.496-0.746 0.544-0.626	0.001 regression model	No	NR	
		Platelet works ADP	Death combined	All-cause death, nonfatal MI, stent thrombosis and stroke	1-year	High OTPR	Death combined	33/262 (12.6)	OR=2.22	1.25-3.93	0.005 high OTPR vs normal logistic regression analysis	No	NR	
						Normal OTPR		21/344 (6.1)						
Kim, 2010{Kim, 2010241 /id} 20449634 Korea NR	300-600mg LD and 75 mg maintain dose clopidogrel	5umol ADP-induced PRmax ≥50%	ischemic events	ischemic events	6 months	5umol ADP-induced PRmax≥50%	PRmax≥50%	2.2%	OR=1.33	0.16-11.33	0.299 PR≥50 vs <50%	NR	NR	NR
		5umol ADP-induced LTA and VerifyNowP2Y12				5umol ADP-induced LTA and VerifyNowP2Y12	PRmax<50% and PRmax<240	1.6%						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
	300-600mg LD and 75 mg maintain dose clopidogrel	5umol ADP-induced PRmax ≥50%	ischemic events	ischemic events	6 months	5umol ADP-induced PRmax≥50 %	PRmax≥50 %	2.2%	OR=1.33	0.16-11.33	0.299 HPPR vs no-HPPR	NR	NR	NR
		5umol ADP-induced LTA and VerifyNowP2Y12				5umol ADP-induced LTA and VerifyNowP2Y12	no-HPPR (PRmax<50 % and PRU<240)	1.6%						
	300-600mg LD and 75 mg maintain dose clopidogrel	5umol ADP-induced LTA and VerifyNowP2Y12	ischemic events	ischemic events	6 months	5umol ADP-induced PRmax≥50 % and PRU≥240	5umol ADP-induced PRmax≥50 % and PRU≥240	6.0%	OR=3.86	1.55-9.63	0.002 HPPR vs no-HPPR	NR	NR	NR
		5umol ADP-induced LTA and VerifyNowP2Y12				5umol ADP-induced LTA and VerifyNowP2Y12	no-HPPR (PRmax<50 % and PRU<240)	1.6%						

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Mobley, 2004{Mobley, 2004 221 /id} 14969622 USA NONE	300mg LD Clopidogrel and 75mg MD	Combination of LTA, TEG & Ichor Platelet Works	Major adverse coronary events	death due to cardiovascular or unknown causes, rehospitalization for angina pectoris, rehospitalization for myocardial infarction, or need for target vessel revascularization	1 month	Nonresponder	Yes	0/15	OR=0.74 (calculated)	NR	p=0.85 nonresponder vs. responder Fisher's exact test	NR	NR	
						Responder	Yes	1/35						
			Major adverse coronary events	death due to cardiovascular or unknown causes, rehospitalization for angina pectoris, rehospitalization for myocardial infarction, or need for target vessel revascularization	6 months	Nonresponder	Yes	1/15	OR=0.76 (calculate)	NR	p=0.82 nonresponder vs. responder Fisher's exact test	NR	NR	
						Responder	Yes	3/35						

Appendix Table E115: Results from studies assessing the ability of miscellaneous platelet function tests to predict stroke in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	Platelet works ADP	stroke	Stroke	1-year	High OTPR	Stroke	4/262 (1.5)	OR=1.76	0.39-7.94	<0.45 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		3/344 (0.9)						
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	maintaining Clopidogrel 75 mg daily +aspirin 80-100mg daily	IMPACT-R ADP	stroke	Stroke	1-year	High OTPR	Stroke	4/296 (1.4)	OR=1.18	0.34-4.06	0.79 high OTPR vs. normal logistic regression	No	NR	
						Normal OTPR		7/609 (1.1)						

Appendix Table E116: Results from studies assessing the ability of miscellaneous platelet function tests to predict bleeding events in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Dziewierze, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	Clopidogrel LD 300 mg, 75mg maintain dose	Platelet aggregation inhibition	Haematoma	Haematoma	In hospital stay	Non-responder	Haematoma	1/7 (14.3)	OR=3.8 (calculate)	NR	NS (>0.05) non-responder vs. responder	NR	NR	
						Responder		1/24 (4.2)						
Mobley, 2004{Mobley, 2004 221 /id} 14969622 USA NONE	300mg LD Clopidogrel and 75mg MD	Combination of LTA, TEG & Ichor Platelet Works	Moderate bleeding perioperatively after CABG	5.7 g/dl decrease in hemoglobin plus 600 ml of total chest tube drainage in one patient, and the other had a 3.8 g/dl decrease in hemoglobin plus 840 ml of total chest tube drainage	During procedure	Nonresponder	Yes	2/2	NR	NR	NR	NR	NR	
						Responder	Yes	NA						

			Life-threatening bleeding complications	Fatal hemorrhage, reduction in hemoglobin of 5 g/dl, hypotension requiring inotropic support, symptomatic intracranial hemorrhage, or transfusion of >4 U of packed red blood cells occurred	During procedure	Nonresponder	Yes	0/15	OR=2.3 (calculated)	NR	p=0.68 nonresponder vs. responder Fisher's exact test	NR	NR	
						Responder	Yes	0/35						
			Major bleeding	intraocular hemorrhage causing visual impairment, a decrease in hemoglobin concentration of 2 to 5 g/dl, hemorrhage requiring transfusion of 2 to 4 U of packed red blood cells, and bleeding requiring surgical intervention, including elective pseudoaneurysm repair	During procedure	Nonresponder	Yes	0/15	OR=0.4 (calculate)	NR	p=0.59 nonresponder vs. responder Fisher's exact test	NR	NR	
						Responder	Yes	2/35						

			Minor bleeding	bleeding, not otherwise classified, that necessitated discontinuation of the study drug, a decrease in hemoglobin of <2 g/dl, hemorrhage requiring transfusion of <2 U of packed red blood cells, or development of a groin hematoma requiring prolonged hospitalization, surgical drainage, or a blood transfusion	During procedure	Nonresponder	Yes	1/15	OR=2.4 (calculate)	NR	p=0.54 nonresponder vs. responder Fisher's exact test	NR	NR	
						Responder	Yes	1/35						

Appendix Table E117: Results from studies assessing the ability of miscellaneous platelet function tests to predict other clinical events in patients with ischemic heart disease

Author,year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Clinical Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., bleeding or no bleeding)	No. with outcome status within phenotype group	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [Y/N/NR]	Comments (e.g., additional data in figures)
Dziewierze, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	Clopidogrel LD 300 mg, 75mg maintain dose	Platelet aggregation inhibition	Angina recurrence	Angina recurrence	In hospital stay	Non-responder	Angina recurrence	0/7	OR=3.3(calculated)	NR	p=0.56 nonresponder vs. responder Fisher's exact test	NR	NR	
						Responder		0/24						
Mobley, 2004{Mobley, 2004 221 /id} 14969622 USA NONE	300mg LD Clopidogrel and 75mg MD	Combination of LTA, TEG & Ichor PlateletWorks	PCI	NA	NA	Nonresponder	PCI	4/15	OR=0.5 (calculated)	NR	p=0.28 nonresponder vs. responder Fisher's exact test	NR	NR	NR
						Responder	PCI	15/35						
	300mg LD Clopidogrel and 75mg MD	Combination of LTA, TEG & Ichor PlateletWorks	Unsuccessful PCI	Unsuccessful PCI	NA	Nonresponder	unsuccessful PCI	0/4	OR=1.1 (calculated)	NR	p=0.97 nonresponder vs. responder Fisher's exact test	NR	NR	NR
						Responder	unsuccessful PCI	1/15						
	300mg LD Clopidogrel and 75mg MD	Combination of LTA, TEG & Ichor PlateletWorks	CABG	CABG	NA	Nonresponder	CABG	2/15	OR=13.1	NR	p=0.1 nonresponder vs. responder Fisher's exact test	NR	NR	NR
						Responder	CABG	0/35						

Appendix Table E118: Results from studies assessing the ability of miscellaneous platelet function tests to predict platelet reactivity during followup (when used as a discrete outcome) in patients with ischemic heart disease

Author, year UID Country Study name	Treatment	Phenotypic Test Used [index test]	Reactivity Outcome	Outcome Definition	Timing of measurement	Index test result: category (e.g., HPR+) – ONE ROW PER PHENOTYPE GROUP	Outcome status (e.g., HPR+ or HPR-)	No. with outcome status within phenotype group	Cut-off	Comparative metric (OR, RR, HR)	95% CI	P (between which groups?) [statistical test]	Adjusted? [YES/NO/NR] If YES, for what factors?	Procedures for multiple comparisons [YES, NO, NR]	Comments (e.g., additional data in figures)
Dziewierz, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	Clopidogrel LD 300 mg, 75mg maintain dose	Platelet aggregation	DPAI	The degree of platelet aggregation	3h	Non-responder	Non-responder	15/31 (48.4)	10%	NR	NR	NR	NR	NR	
						responder	responder	16/31 (51.6)							
	Clopidogrel LD 300 mg, 75mg maintain dose	Platelet aggregation	DPAI	The degree of platelet aggregation	6h	Non-responder	Non-responder	8/31 (25.8)	10%	NR	NR	NR	NR	NR	
						responder	responder	23/31 (74.2)							
	Clopidogrel LD 300 mg, 75mg maintain dose	Platelet aggregation	DPAI	The degree of platelet aggregation	12h	Non-responder	Non-responder	8/31 (25.8)	10%	NR	NR	NR	NR	NR	
						responder	responder	23/31 (74.2)							
	Clopidogrel LD 300 mg, 75mg maintain dose	Platelet aggregation	DPAI	The degree of platelet aggregation	24h	Non-responder	Non-responder	7/31 (22.6)	10%	NR	NR	1.0 (fishers exact between categories)	NR	NR	

						responder	responder	24/31 (77.4)							
Lindvall, 2009{Lindvall, 2009 119 /id}} 19477870 Sweden None	300-600mg LD Clopidogrel and MD 75 mg/day+75mg daily aspirin	ADP-induced aggregation	Clopidogrel response vs nonresponse	Response defined as >90% aggregation	Repeat measurement immediately after aprotinin	Baseline HPR+ N = 4	HPR-	1	>90%	NR	NR	0.07(fishers exact between categories)	NR	NR	
						Baseline HPR- N = 11	HPR+	2							
Gurbel , 2003{Gurbel, 2003 224 /id} 12714161 USA No	300mg LD clopidogrel and 75mg daily MD with 325 mg/day aspirin	Flow cytometry for P-selectin expression	Continued nonresponse since baseline	NR	5 days	Nonresponders at baseline (n=9)	Nonresponders at 5 days	5/9 (56%)	<10% change from baseline	NR	NR	0.144 (fishers exact between categories)	NR	NR	NONE
					5 days	Responders at baseline (n=29)	Responders at 5 days	29/29 (100%)							
					30 days	Nonresponders at baseline (n=9)	Nonresponders at 30 days	3/6 (50%) with data (3 were not measured at 30 days)							
					30 days	Responders at baseline (n=29)	Responders at 30 days	14/18 (78%) with data (11 were not measured at 30 days)							

Appendix Table E119: Quality Assessment of studies assessing the predictive ability of miscellaneous platelet function tests in patients with ischemic heart disease

Author, year [ref] UID Country Study Name	Patients selection					Index test				Reference standard				Flow and timing				
	1	2	3	ROB (selection)	Applicability (selection)	4	5	ROB (index)	Applicability (index)	6	7	ROB (reference)	Applicability (reference)	8	9	10	11	ROB (flow & timing)
Smit , 2010{Smit, 2010 53 /id} 20889993 Netherlands ON-TIME-2	yes	yes	yes	low	low	NR	NO	high	low	yes	NR	unclear	low	no	yes	yes	yes	low
Dziewierze, 2005{Dziewierz, 118 216 /id} 15815794 Poland NR	yes	yes	yes	low	low	NR	no	high	high	yes	NR	unclear	low	no	yes	yes	yes	low
Breet, 2010{Breet, 2010 86 /id} 20179285 Netherlands POPULAR	yes	yes	yes	low	low	NR	no	high	low	yes	yes	low	low	yes	yes	yes	yes	low
Lindvall, 2009{Lindvall, 2009 119 /id} 19477870 Sweden None	yes	yes	yes	low	low	NR	yes	unclear	low	no	NR	high	high	no	yes	yes	yes	low
Gurbel, 2003{Gurbel, 2003 224 /id} 12714161 USA No	NR	yes	yes	low	low	NR	no	high	unclear	No	NR	high	yes	No (30 days)	yes	yes	No (many had no data at 30 days)	high
Kim, 2010{Kim, 2010 241 /id}	yes	yes	yes	low	low	NR	yes	unclear	high	Yes	NR	unclear	Low	no [6 months]	yes	yes	yes	Low

20449634 Korea NR																		
Mobley, 2004{Mobley, 2004 221 /id} 14969622 USA NONE	NR	yes	yes	low	low	NR	No	high	low	yes	NR	unclear	low	no	yes	yes	yes	low

Appendix F. Appendix Figures and Tables for Key Questions 4 and 4

Key Questions 3 and 4 – Figures

Appendix Figure F1: Assessment of Risk of Bias Items in Studies Providing Information on Effect Modification by CYP2C19 Variants

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Gladding PRINC, 2008 [19463375]	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	HIGH	UNCLEAR	HIGH	LOW	LOW	LOW	UNCLEAR	LOW	LOW	HIGH	LOW	HIGH
Mega, 2009 [19414633]	HIGH	LOW	HIGH	UNCLEAR	LOW	LOW	UNCLEAR	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW
Varenhorst, 2009 [19429918]	UNCLEAR	LOW	HIGH	UNCLEAR	LOW	HIGH	UNCLEAR	HIGH	UNCLEAR	LOW	LOW	LOW	LOW	UNCLEAR	HIGH	LOW	LOW
Hwang, 2010 [20823393]	UNCLEAR	LOW	HIGH	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	HIGH	LOW	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	LOW	LOW
Mega, 2010 [20801494]	HIGH	LOW	HIGH	UNCLEAR	LOW	LOW	UNCLEAR	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW	LOW	HIGH	HIGH	LOW
Pare (ACTIVE-A), 2010 [20979470]	HIGH	LOW	HIGH	UNCLEAR	LOW	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Pare (CURE), 2010 [20979470]	HIGH	LOW	HIGH	UNCLEAR	LOW	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Tantry, 2010 [21079055]	UNCLEAR	LOW	HIGH	UNCLEAR	HIGH	HIGH	UNCLEAR	HIGH	LOW	LOW	LOW	LOW	LOW	UNCLEAR	HIGH	HIGH	LOW
Wallentin, 2010 [20801498]	UNCLEAR	LOW	HIGH	UNCLEAR	LOW	LOW	UNCLEAR	LOW	LOW	LOW	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	HIGH
Kim, 2011 [21511217]	UNCLEAR	LOW	HIGH	UNCLEAR	UNCLEAR	LOW	UNCLEAR	HIGH	LOW	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Park, 2011 [21345843]	UNCLEAR	LOW	HIGH	UNCLEAR	LOW	HIGH	UNCLEAR	HIGH	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR

Each row corresponds to a study (listed with first author surname, publication year [PMID]). Each column refers to a question (Q) about quality and reporting (see list below for the complete questions and **Appendix Table F1** for additional study-level information). "LOW," "HIGH," and "UNCLEAR" (green, red, and yellow circles, respectively) refer to whether the question was addressed and the salient information reported in the study in terms of risk of bias.

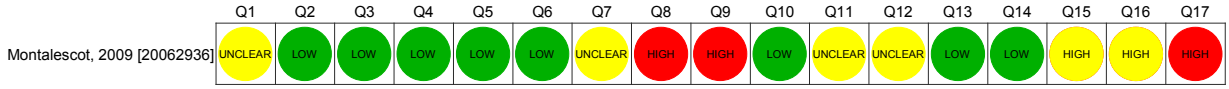
Q1 = Consecutive sample of patients enrolled
Q2 = Case–control design avoided
Q3 = Study avoided inappropriate exclusions, and post -hoc exclusions <5%
Q4 = Index test results interpreted without knowledge of outcomes?
Q5 = If a threshold used, was it prespecified?
Q6 = Reference standard likely to correctly classify the target condition (low if at least one clinical outcome assessed)?
Q7 = Reference standard results interpreted without knowledge of index test results?
Q8 = Appropriate interval between index test and reference standard (at least 12 mo of followup)?
Q9 = All patients received a reference standard (outcome data for >90% of patients)?
Q10 = All patients received the same reference standard?
Q11 = Random sequence generation
Q12 = Allocation concealment
Q13 = Blinding of participants and personnel
Q14 = Blinding of outcome assessment
Q15 = Incomplete outcome data (do they report enough data to estimate uncertainty for the primary outcome?)
Q16 = Selective reporting bias (do they report numerical results on the primary and secondary outcome; and are these identified in the methods?)
Q17 = Other bias (reported information on percutaneous coronary intervention delay and the difference was significant; or extreme numerical errors and inconsitencies)

Appendix Figure F2: Assessment of Risk of Bias Items in Studies of Alternative-Test-and-Treat Strategies Based on Phenotypic Testing

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Aleil, 2008 [19463377]	UNCLEAR	LOW	LOW	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	LOW	LOW	LOW	UNCLEAR	HIGH	HIGH	HIGH	HIGH	UNCLEAR
Bonello, 2008 [18387444]	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR	HIGH	LOW	LOW	UNCLEAR	UNCLEAR	HIGH	LOW	LOW	LOW	HIGH
Bonello, 2009 [19101221]	UNCLEAR	LOW	LOW	LOW	LOW	LOW	UNCLEAR	HIGH	LOW	LOW	UNCLEAR	UNCLEAR	HIGH	LOW	LOW	LOW	UNCLEAR
Tousek, 2011 [21663983]	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR	HIGH	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	UNCLEAR
Wang, 2011 [21538380]	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR	LOW	LOW	LOW	UNCLEAR	UNCLEAR	HIGH	LOW	LOW	LOW	HIGH

Layout is the same as for **Appendix Figure F1**.

Appendix Figure F3: Assessment of Risk of Bias in the Study Reporting on Effect Modification by Baseline Platelet Reactivity



Layout is the same as for **Appendix Figure F1**.

Appendix Figure F4: Assessment of Risk of Bias Items in Randomized Trials with Patient Selection Based on Phenotypic Testing

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Cuisset, 2008 [19463379]	UNCLEAR	LOW	LOW	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Valgimigli, 2009 [19528337]	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	HIGH	LOW
Gurbel, 2010 [20194878]	UNCLEAR	LOW	HIGH	LOW	LOW	HIGH	UNCLEAR	HIGH	LOW	LOW	LOW	UNCLEAR	LOW	UNCLEAR	LOW	LOW	LOW
Palmerini, 2010 [19604542]	UNCLEAR	LOW	HIGH	UNCLEAR	HIGH	HIGH	UNCLEAR	HIGH	LOW	LOW	LOW	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW	LOW
Price, 2011 [21406646]	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW

Layout is the same as for **Appendix Figure F1**.

Key Questions 3 and 4 – Tables

Appendix Table F1: Assessment of Risk of Bias Items in Studies Providing Information on Effect Modification by CYP2C19 Variants

Author Year Country PMID Study name (if available)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Pare[33] 2010 Multinational 20979470 CURE	High (selected patients from an RCT)	Low	High (included patients ~40% of the CURE trial population)	Unclear	Low (genotype grouping based on prior literature)	Low	Unclear	Unclear	Low	Low	Low (central, 24h, computerized randomization service)	Low (centralized computer generated randomization)	Low	Low (independent blind ascertainment)	Low	Low	Low
Pare[34] 2010 Multinational 20979470 ACTIVE-A	High (selected patients from an RCT)	Low	High (included patients ~15% of the ACTIVE-A population)	Unclear	Low (genotype grouping based on prior literature)	Low	Unclear	Unclear	Low	Low	Low (interactive phone system, varying blocks sizes)	Low (centralized, phone-based randomization)	Low	Low (independent blind ascertainment)	Low	Low	Low
Mega[35] 2009 Multinational 19106084[36] 19414633 TRITON TIMI – 38	High (selected patients from an RCT)	Low	High (included patients ~22% of the TRITON TIMI – 38 population)	Unclear	Low (genotype grouping based on prior literature)	Low	Unclear	Low	Low	Low	Unclear	Unclear	Low	Low (independent blind ascertainment)	Low	Low	Low
Mega[37] 2010 Multinational 20801494 TRITON TIMI – 38	High (selected patients from an RCT)	Low	High (included patients ~22% of the TRITON TIMI – 38	Unclear	Low (genotype grouping based on prior literature)	Low	Unclear	Low	Low	Low	Unclear	Unclear	Low	Low (independent blind ascertainment)	High (incomplete reporting in analyses relevant to this KQ)	High (missing numerical results for this KQ)	Low

[33] Some information extracted from Yusuf et al. 2001. [cite 11519503]
[34] Some information extracted from Connolly et al. 2009. [cite 19336502]
[35] Some information extracted from Wiviott et al. 2007. [cite 17982182]
[36] Detailed information on the clopidogrel treated arm of the TRITON TIMI 38 trial was provided in PMID 19106084; detailed information on the prasugrel treated arm was provided in PMID 19414633. Additional information extracted from 16996826 and 17982182.
[37] Some information on the patient selection criteria and the treatments compared in the parent trial were extracted from Wiviott et al. 2007 [cite 17982182] and Wiviott et al. 2006. cite16996826

			population)														
Varenhorst[38] 2009 Sweden 19429918 TABR	Unclear	Low	High (included ~90% of eligible patients)	Unclear	Low (genotype grouping based on prior literature)	High (no clinical outcomes)	Unclear	High (30 d)	Unclear	Low	Low (Interactive voice-response system; random permuted block randomization)	Low (centralized randomization)	Low	Unclear	High (inadequate data reported)	Low	Low
Tantry[39] 2010 USA and UK 21079055 ONSET/OFFSET and RESPOND Genotype Studies	Unclear	Low	High (included ~79% of the patients in the parent trial were included)	Unclear	High (multiple groupings of genotypes were evaluated)	High (no clinical outcomes)	Unclear	High (2-4 w)	Low	Low	Low (centralized, balanced block randomization)	Low (random allocation was performed as patients were entered in the study)	Low	Unclear	High (data only in graphical form)	High (incomplete reporting)	Low
Kim[40] 2011 S. Korea 21511217 ACCELAMI2C19	Unclear	Low	High (included ~90% of patients in the parent trial)	Unclear	Unclear (rationale for genotype grouping NR)	Low	Unclear	High (30d)	Low	Low	Low (computer-generated randomization sequence)	Unclear	Unclear	Unclear (study personnel assessed reactivity "blinded to the study protocol")	Low	Low	Low
Hwang[41] 2010 S. Korea 20823393 ACCEL-RESISTANCE, DM, and COMPLEX trials (ACEL-POLYMORPHISM)	Unclear	Low	High (included ~89% of patients in the parent trial)	Unclear	Unclear (the authors cited a previous publication from their team)	High (no clinical outcomes)	Unclear	High (30 d)	Low	Low	Low (computer-generated randomization sequence)	High (randomization sequence was provided in envelopes)	Unclear	Low (study personnel assessed reactivity "blinded to group assignment")	Low	Low	Low
Gladding[42] 2008 New Zealand 19463375 PRINC	Unclear	Low	Low (included 100% of patients in the parent trial)	Unclear	High (no rationale reported; data on some	High (no clinical outcomes)	Unclear	High (7 d)	Low	Low	Low (computed generated randomized sequence)	Unclear	Low	Low	High (some data only in graphical form)	Low	High (results not reported for all genotypes observed)

[38] Some information extracted from Wallentin et al. 2008 [PMID = 18055486].
[39] Some information extracted from Gurbel et al. 2008 [PMID = 19923168] and Gurbel et al. 2010 [PMID = 20194878].
[40] Some information extracted from Jeong et al. 2010 [PMID = 20118150].
[41] Some information extracted from Jeong et al. 2009 [PMID = 19324253].
[42] Some information extracted from Gladding et al. 2008 [PMID = 19463374].

					genotypes not presented)												
Wallentin 2010 Multinational 20801498 PLATO	Unclear	Low	High (included ~55% of patients in the parent trial)	Unclear	Low (genotype grouping based on prior literature)	Low	Unclear	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low	High (results not reported for all genotypes observed)
Park 2011 S. Korea 21345843 CILON-T	Unclear	Low	High (included ~85% of patients in the parent trial)	Unclear	Low (genotype and phenotypic grouping based on prior literature)	High (no clinical outcomes)	Unclear	High (until discharge)	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Quality items (a "yes" response = "low" risk of bias; "no" = "high," and "unclear" = "unclear")

Q1: Consecutive sample of patients enrolled
Q2: Case–control design avoided
Q3: Study avoided inappropriate exclusions, and *post -hoc* exclusions <5%
Q4: Index test results interpreted without knowledge of outcomes?
Q5: If a threshold used, was it prespecified?
Q6: Reference standard likely to correctly classify the target condition (low if at least one clinical outcome assessed)?
Q7: Reference standard results interpreted without knowledge of index test results?
Q8: Appropriate interval between index test and reference standard (at least 12 mo of followup)?
Q9: All patients received a reference standard (outcome data for >90% of patients)?
Q10: All patients received the same reference standard?
Q11: Random sequence generation
Q12: Allocation concealment
Q13: Blinding of participants and personnel
Q14: Blinding of outcome assessment
Q15: Incomplete outcome data (do they report enough data to estimate uncertainty for the primary outcome?)
Q16: Selective reporting bias (do they report numerical results on the primary and secondary outcome; and are these identified in the methods?)
Q17: Other bias (reported information on percutaneous coronary intervention delay and the difference was significant; or extreme numerical errors and inconsitencies)

Appendix Table F2: Assessment of Risk of Bias Items in Studies of Alternative-Test-and-Treat Strategies Based on Phenotypic Testing

Author Year Country PMID Study Name (if available)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Wang 2011 China 21538380	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Unclear	Unclear	High	Low	Low	Low	High (numerous discrepancies between results and reported methods)
Bonello 2009 Italy 19101221	Unclear	Low	Low	Low	Low	Low	Unclear	High	Low	Low	Unclear	Unclear	High	Low	Low	Low	Unclear
Bonello 2008 Italy 18387444	Low	Low	Low	Low	Low	Low	Unclear	High	Low	Low	Unclear	Unclear	High	Low	Low	Low	High (statistically significant difference between groups in time-to-PCI may impact results)
Tousek 2011 Czech Republic 21663983	Low	Low	Low	Low	Low	Low	Unclear	High	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Aleil 2008 France 19463377 VASP-02	Unclear	Low	Low	Unclear (timing of outcomes and testing NR)	Low	Low	Unclear	High	Low	Low	Low (sequence provided by central lab)	Unclear (no details reported on how the random assignment information was provided to investigators)	High (“open”)	High (“open”)	High	High	Unclear

NR=not reported, PCI=percutaneous coronary intervention.
Item definitions as in Appendix Table F1.

Appendix Table F3: Assessment of Risk of Bias in the Study Reporting on Effect Modification by Baseline Platelet Reactivity

Author Year Country PMID Study name (if available)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Montalescot 2009 France 20062936 ACAPULCO	Unclear	Low	Low (93% of eligible patients received baseline testing)	Low	Low	Low	Unclear	High (2 w on each treatment)	High (only 73% of patients completed the trial)	Low	Unclear	Unclear	Low	Low	High (incomplete outcome reporting for items relevant to this review)	High	High (study terminated early with unequal number of terminated subjects in each arm)

Item definitions as in Appendix Table F1.

Appendix Table F4: Assessment of Risk of Bias Items in Randomized Trials with Patient Selection Based on Phenotypic Testing

Author Year Country UID Study name (if available)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17
Price 2011 Multinational 21406646 GRAVITAS	Unclear	Low	Low	Low	Low (protocol-specified)	Low	Low	High (6 mo)	Low	Low	Low (centralized, interactive voice-response system)	Low (encrypted reactivity values; central randomization)	Low (encrypted reactivity values and placebo-controlled design)	Low (blinded clinical events committee)	Low	Low	Low
Palmerini 2010 Italy 19604542 DOUBLE	Unclear	Low	High	Unclear	High (cut-off for response was based on prior literature; unclear choice of cut-off for selection of patients)	High (patients with AEs were excluded from analyses of reactivity; no other clinical outcomes assessed)	Unclear	High (1 mo)	Low	Low	Low (computer-generated random sequence)	Unclear	Unclear	Unclear	Low	Low	Low
Valgimigli 2009 Italy 19528337 3T/2R	Low ("all patients")	Low	Low	Low	Low (threshold based on prior literature)	Low	Low	High (1 mo)	Low	Low	Low (block of 6, stratified (stable or unstable CAD; and response status) by a local nurse using sealed envelopes)	High (local randomization using envelopes)	Low	Low	Low (uncertainty in estimates was reported)	High (only limited outcomes were reported in the clopidogrel non-responsive patients)	Low
Cuisset 2008 France 19463379	Unclear	Low	Low	Unclear	Low (threshold based on prior literature)	Low	Unclear	High (1 mo)	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Gurbel[43] 2010 Multinational (N. America and Europe) 20194878 RESPOND	Unclear	Low	High (>5% dropout)	Low	Low (single threshold used for stratification; unclear rationale)	High (no clinical outcomes)	Unclear	High (30 d)	Low	Low	Low (centralized block randomization)	Unclear	Low	Unclear	Low	Low	Low

[43] Despite including both responders and non-responders, this study was categorized as a study of randomized treatment after test-based selection because patients were assigned to different treatments during the course of the study based on their original response status.

AE = adverse event; CAD = coronary artery disease; mo = month; PMID = PubMed identification number.
Item definitions as in Appendix Table F1.

Appendix G. List of Ongoing Studies

CT.gov NCT number [study names]	Population	Targeted enrollment	Tests assessed	Study design	Current status
NCT00827411 [ARCTIC]	Coronary Artery Disease; Acute Coronary Syndrome	2500	VerifyNow	Four arm, double randomization study of a monitoring adjusted antiplatelet treatment versus a common antiplatelet treatment for DES implantation, and interruption versus continuation of double antiplatelet therapy.	Active, not recruiting
NCT00774475 [DANTE]	UA/NSTEMI undergoing PCI with stent implantation	442	VerifyNow	Two arm, randomized study of dual antiplatelet therapy (arm1: clopidogrel 75 mg/day versus clopidogrel 150 mg/day); (arm 2: doubled therapy clopidogrel 150 mg/day) tailored on the extent of platelet function inhibition.	Unknown
NCT00638326 [DOSER]	Stable Angina Pectoris Ad Hoc Percutaneous Coronary Intervention	500	VASP	Three arm, randomized study in patients with high on-clopidogrel platelet reactivity compared to 75 mg clopidogrel after elective percutaneous coronary intervention. (Arm 1: no intervention, patients with adequate response to 600 mg LD of clopidogrel receiving 1x75 mg of clopidogrel); (Arm 2: patients with suboptimal response to 600mg LD of clopidogrel receiving 1x150 mg for 28d.); (Arm 3: patients with suboptimal response to 600mg LD of clopidogrel receiving 1x75 mg clopidogrel).	Terminated
NCT00992420 [GIFT]	Coronary Artery disease	2000	VerifyNow	A prospective observational cohort study in patients with CAD assessing which genes influence residual platelet reactivity on standard dose clopidogrel therapy, whether certain genes influence the incremental change in platelet reactivity with high-dose clopidogrel maintenance dosing in patients who have high residual platelet reactivity on standard dosing. Groups/cohorts: GRAVITAS Arms A,B,C	Completed
NCT00910299 [TRIGER-PCI]	Coronary Artery Disease	426	VerifyNow	Two arm, randomized, interventional study testing platelet reactivity in patients undergoing elective stent placement on clopidogrel to guide alternative therapy with prasugrel	Terminated due to the low rate of primary endpoint events experienced in the study to date
NCT01184300 [RAPID GENE]	Stable Coronary Artery Disease Acute Coronary Syndrome Percutaneous Coronary Intervention	200	CYP2C19*2	Two arm, randomized interventional study of point-of-care genetic screening with subsequent prasugrel administration to CYP2C19*2 carriers (Arm 1) and genotyping at the time of percutaneous coronary intervention followed by clopidogrel 75 mg daily for 1 week with CYP2C19*2 carrier status verified at the end of the 1 week period (Arm 2).	Completed; results published after our last search date; to be included in updated report
NCT01174693 [MAESTRO]	Cerebral Infarction	1080	CYP2C19	Two arm, randomized interventional study comparing the preventive effect of stroke between triflusal and clopidogrel	Recruiting

CT.gov NCT number [study names]	Population	Targeted enrollment	Tests assessed	Study design	Current status
				in ischemic stroke patient based on the cytochrome P450 2C19 (CYP2C19) polymorphism. (Arm 1, active comparator clopidogrel); (Arm 2- Experimental: Triflusal).	
NCT01360437	Coronary Artery Disease Acute Coronary Syndrome	44	VerifyNow assay (platelet reactivity units PRU≥235)	Two arm, single-center, randomized, single-blind, investigator-initiated pharmacological study with a crossover design of ticagrelor versus prasugrel in acute coronary syndromes presenting resistance to the usual clopidogrel dose after PCI.	Completed
NCT01452152 [PAPI-2]	Cardiovascular Diseases Acute Coronary Syndrome	7200	CYP2C19	Three arm, randomized, interventional study of genotype-directed (G-D) versus Standard of Care (SOC) anti-platelet therapy. (Arm 1, Experimental: Genotype-directed, clopidogrel); (Arm 2, Experimental: Genotype-directed, prasugrel); (Arm 3: No intervention: Standard of Care, no CYP2C19 genotype analysis performed, patients will receive dual anti-platelet therapy).	Recruiting
NCT01475552	Diabetes Mellitus	100	VerifyNow	Two arm, randomized interventional study of tailored antiplatelet therapy during PCI in patients with diabetes mellitus. (Arm 1: Experimental- patients treated with abciximab in addition to conventional antiplatelet treatment (aspirin+clopidogrel); (Arm 2: active comparator, patients that were randomized to control group treated with conventional antiplatelet therapy (aspirin+clopidogrel).	Recruiting
NCT01097343	Resistance to clopidogrel therapy	200	VerifyNow	Two arm, randomized, unblinded cross-over comparison of two clopidogrel dosing strategies. (Arm 1: 75 mg clopidogrel); (Arm 2: 150 mg clopidogrel).	Unknown
NCT01512953 [GENIOUS]	Coronary Stenting	522	LTA after 20 µmol/l ADP	Two arm, randomized, intervaentional study comparing the use of PPI versus no PPI on top of the standard dose of clopidogrel in patients stratified based on CYC2C19 activity. (Arm 1: No intervention, no PPI); (Arm 2: Experimental, PPI).	Recruiting
NCT01538446 [ANTARCTIC]	Acute Coronary Syndrome	962	VerifyNow	Two arm, randomized, interventional study for the assessment of a normal versus tailored dose of prasugrel after stenting in patients >75 years of age. (Arm 1: Monitoring, modification of prasugrel based on a biological assay); (Arm 2: Active comparator, prasugrel / clopidogrel).	Not yet open for participant recruitment.
NCT01505790	Acute Coronary Syndrome	188	VASP	Two arm, randomized interventional study on the impact of clopidogrel dose adjustment to compare the biological	Ongoing, but not recruiting participants.

CT.gov NCT number [study names]	Population	Targeted enrollment	Tests assessed	Study design	Current status
				efficacy of tailored clopidogrel therapy according to the VASP index (Arm 1) and prasugrel (Arm 2) standard therapy in acute coronary syndromes patients undergoing PCI.	
NCT01155765	Hemodialysis Chronic Renal Failure	70	VerifyNow	Two arm, randomized, interventional study of prasugrel (Arm 1, Experimental) in comparison to high clopidogrel dose (Arm 2, Active comparator) for inhibition of platelet reactivity in patients undergoing chronic hemodialysis presenting resistance to the usual clopidogrel dose	Completed
NCT01109784	Coronary Artery Disease Acute Coronary Syndrome	70	VerifyNow	Two arm, randomized, interventional (crossover assignment) study of prasugrel (Arm 1) vs high dose (150 mg) clopidogrel (Arm 2) in clopidogrel resistant patients post PCI.	Completed
NCT01543932 [TRIPLETE RESET]	Coronary Artery Disease	30	CYP2C19*2	Three arm, randomized interventional (dual crossover assignment) study of the comparison of switching therapy with ticagrelor, prasugrel and high clopidogrel dose in PCI patients with high on treatment platelet reactivity and genotype variation.	Not yet open for participant recruitment.
NCT00822666 [CLOVIS2]	Coronary Artery Disease	120	LTA (RPA with 5µM and 50 µM of ADP)	Two arm, randomized, interventional (crossover assignment) study of the role of the genetic variant 2C19*2 on the pharmacodynamic response and the pharmacokinetic response following an oral administration of a loading dose of 300/900mg of clopidogrel in patients with established coronary artery disease. (Arm 1: patients homozygous for the 2C19*1 genetic variant); (Arm 2: carriers of the 2C19*2 genetic variant, homozygous or heterozygous)	Unknown
NCT01338909 [STEMI] [PRO-GR-4]	Myocardial Infarction	35	VerifyNow	Two arm, randomized, interventional (parallel assignment) study of prasugrel (Arm 1) in comparison to clopidogrel (Arm 2) for inhibition of platelet reactivity in patients with STEMI undergoing PCI after 600mg clopidogrel loading dose.	Completed
NCT01452139 [STEMI] [RAPID STEMI]	STEMI	100	VerifyNow	Three arm, randomized, interventional (parallel assignment) study. (Arm 1: experimental, at-risk genetics arm: Prasugrel treatment of STEMI patients carrying at least 1 at-risk genetic variant with prasugrel 10mg daily for 1 month); (Arm 2: active comparator, at-risk genetics arm: Clopidogrel treatment of STEMI patients carrying at least 1 at-risk genetic variant with clopidogrel 150mg daily for 1 week followed by 75mg daily); (Arm 3: active comparator, low risk genetics arm: clopidogrel treatment of STEMI patients with no at-risk genetic variants with	Recruiting

CT.gov NCT number [study names]	Population	Targeted enrollment	Tests assessed	Study design	Current status
				clopidogrel 75mg daily).	
NCT01135667 [TAILOR]	Coronary Artery Disease Percutaneous Coronary Intervention Acute Coronary Syndromes	200	Multiplate	Two arm, randomized, interventional (parallel assignment) study of double dose clopidogrel (Arm 1) versus prasugrel (Arm 2) to treat clopidogrel low-responsiveness post PCI.	Recruiting
NCT01493999 [PECS-HPR]	High Platelet Reactivity	100	Multiplate-assessed ADP-reactivity	Two arm, randomized, interventional (factorial assignment) study of prasugrel antiplatelet efficacy (Arm 1) compared to clopidogrel adjusted loading doses (Arm 2) in patients with high platelet reactivity after stenting	Recruiting
NCT01509365 [PLATO-dose]	Cardiovascular Disease Overweight	150	VerifyNow	Three arm, randomized, interventional (parallel assignment) study for the evaluation the effect of the double maintenance dose of clopidogrel versus single dose in patients with CAD with a BMI ≥ 27 kg.m^2. (Arm 1,no intervention, loading dose of clopidrogrel); (Arm 2, active comparator: simple dose); (Arm 3, active comparator: double dose).	Recruiting
NCT01304472	Coronary Artery Disease	25	VerifyNow	Two arm, randomized, interventional (crossover assignment) study of prasugrel (Arm 1, experimental) versus high dose clopidogrel (Arm 2, active comparator) in patients with stable CAD and high platelet reactivity while on Chronic Clopidogrel Treatment.	Completed
NCT01463150	Platelet Reactivity	26	VerifyNow	Two arm, randomized, interventional (crossover assignment) study of high dose clopidogrel (Arm 1, active comparator) versus prasugrel 5mg (Arm 2, experimental) in clopidogrel resistant patients ≥75 years of age and/or weighing <60 kg post PCI.	Recruiting
NCT01575795	STEMI	130	VerifyNow	Two arm, randomized, interventional (parallel assignment), multi-center, single-blind study of standard-180mg loading dose of Ticagrelor (Arm 1, active comparator) versus double-360mg loading dose of ticagrelor (Arm 2, experimental) in atients with STEMI undergoing PCI.	Recruiting
NCT01177592 [TARGET-PCI]	Coronary Artery Disease	1500	VerifyNow P2Y12, Verigene	Two arm, prospective, single-center, randomized, interventional (parallel assignment) study of guided antiplatelet therapy (Arm 1, experimental, n=750) or standard therapy (Arm 2, no intervention, n=750).	Terminated (lack of financial support)
NCT01235351 [ELEVATE-TIMI56]	Myocardial Infarction Percutaneous Coronary Intervention	275	CYP2C19	Four arm, double-blind, randomized interventional (crossover assignment) study of escalating dose of clopidogrel (Arm 1, active comparator, clopidogrel 75 mg daily); (Arm 2, experimental,	Ongoing, but not recruiting participants

CT.gov NCT number [study names]	Population	Targeted enrollment	Tests assessed	Study design	Current status
				clopidogrel 150 mg daily); (Arm 3, experimental, clopidogrel 225 mg daily); (Arm 4, experimental, clopidogrel 300 mg daily) to assess whether higher as compared with lower doses of clopidogrel can adequately improve the degree of platelet inhibition in carriers of a reduced-function CYP2C19 allele.	

CAD = coronary artery disease; LD = loading dose; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation Myocardial Infarction; UA = unstable angina