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Intravascular Diagnostic Procedures and Imaging Techniques versus Angiography Alone: A Comparative Effectiveness Review

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Intravascular Diagnostic Procedures and Imaging Techniques Versus Angiography Alone: A Comparative Effectiveness Review

Structured Abstract

Background: Several intravascular diagnostic procedures and imaging techniques (collectively referred to here as intravascular diagnostic techniques) have been developed for the purpose of providing detailed anatomic and hemodynamic information regarding the narrowing (stenosis) of the lumen of coronary arteries. Intravascular diagnostic techniques are increasingly utilized in addition to angiography during percutaneous coronary intervention (PCI) and stent deployment to treat patients with coronary artery disease (CAD).

Purpose: To systematically review the comparative effectiveness of intravascular diagnostic techniques versus angiography alone or versus different intravascular diagnostic techniques in patients with CAD and undergoing PCI ─ for deciding whether a coronary lesion needs to be stented and, once a decision to stent has been made, guiding and optimizing stent deployment, and assessing whether stent placement was successful. The factors influencing the effect of intravascular diagnostic techniques compared to angiography alone or different intravascular diagnostic techniques on outcomes were also evaluated.

Data Sources: MEDLINE®, Cochrane Central Register of Controlled Trials, existing systematic and narrative reviews, recent conference proceedings, and ClinicalTrials.gov.

Study Selection: We included studies of any design and duration of followup, without any language or sample size restriction. We excluded studies that did not compare intravascular diagnostic directly with angiography alone or another intravascular diagnostic technique.

Data Extraction: We extracted details on design, patients, interventions, outcomes, and risk of bias. The outcomes of interest were first categorized as therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes. Outcomes were measured at three time points: short-term (up to 30-day of procedure), medium-term (>30 days to 1 year), and long-term (>1 year).

Data Synthesis: In total, 33 unique studies met eligibility criteria. The only two techniques evaluated in a comparative fashion were fractional flow reserve (FFR) and intravascular ultrasound (IVUS); all of the studies to determine which lesions require stenting involved FFR, while most of the studies that looked at optimizing stent placement (i.e., stent size and dilation) involved IVUS. There is a moderate strength of evidence (drawn from one randomized trial and one nonrandomized study) that the use of FFR during stenting, as compared with angiography alone, to decide whether an intermediate coronary lesion (≥50 percent stenosis) requires stenting can confer a lower risk of death or myocardial infarction (MI), decrease total costs, and lead to fewer stents implanted, without sacrificing freedom from angina and without a need for further revascularizations. However, these FFR studies also included patients with low risk lesions and lower grades of angina, and excluded left main coronary artery disease and acute MI. There is a moderate strength of evidence (drawn from 9 randomized trials and 18 nonrandomized studies)

that supports no significant difference in mortality and MI, but a significant reduction in target vessel revascularizations and restenosis with IVUS-guided stenting over stent placement guided by angiography alone. In randomized trials of IVUS-guided stent placement (most of which were conducted before 2000 using previous generation bare-metal stents) as compared with angiography alone, significantly decreased target vessel revascularizations and reduced the risk of restenosis in the medium-term, but these did not reach statistical significance in nonrandomized comparative studies. There is insufficient evidence regarding the use of FFR in optimizing stent placement (i.e., to determine stent size and dilation). There is insufficient evidence (from two nonrandomized studies of small sample size rated as being at high risk of bias for IVUS and no available studies for all other techniques) concerning the use of intravascular diagnostic techniques immediately after PCI to evaluate the success of stent placement as compared with angiography, or for direct comparisons between intravascular diagnostic techniques. There is a moderate evidence (on the basis of one large-sample-size nonrandomized study) that sex, diabetes mellitus status, lesion length and reference diameter, and interaction with IVUS- and angiography-guided stent placement did not show any significant association with individual components of or the composite outcome of major adverse cardiac events. There is insufficient evidence to evaluate the comparative effect of techniques other than FFR and IVUS on outcomes.

Limitations: We found comparative studies for only two techniques (FFR and IVUS). The majority of the available IVUS trials were conducted before 2000, a particularly important limitation given the rapid pace of technological advance in this domain. Across both FFR and IVUS studies, there was incomplete outcome reporting, heterogeneity in outcome definitions, infrequent enrollment of women, and a lack of data on patients with left main coronary artery disease, and acute MI.

Conclusions: In summary, there is a moderate strength of evidence that that the use of FFR to decide whether stenting for intermediate coronary lesions can confer to patients a lower risk of death or MI, decrease total costs and length of stay, and lead to fewer stents implanted, as compared with angiography alone. These findings are limited by the fact that there is only large RCT supporting them; further trials are needed to confirm and expand on these results. There is a moderate strength of evidence that supports a significant difference in TVR and restenosis, but no significant difference in clinical outcomes of mortality and MI during medium-term and long-term followup between IVUS-guided and angiography-guided stent placement. However, most of the IVUS trials were performed before the year 2000. Intravascular diagnostic techniques are quickly evolving, and further research is needed to evaluate the future use of hybrid and novel intravascular diagnostic techniques, as well as their relative impacts and resource utilization profiles. Future studies (regardless of technology or the current intervention of interest) will also need to focus on women and in patients with more serious CAD. These studies will also need to evaluate longer-term (years) patient outcomes to better appreciate real world effectiveness and any harms that could take years to manifest.

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Executive Summary

Background

Coronary artery disease (CAD), is a narrowing (stenosis) of one or more of the epicardial coronary arteries. It occurs most commonly due to a buildup of plaque (atherosclerosis) which impedes the ability of these blood vessels to deliver oxygenated blood to the heart muscle (myocardium). Revascularization is the standard treatment for CAD, and options vary according to the presentation of CAD, either as acute (myocardial infarction) or chronic (refractory chest pain, also known as angina). Percutaneous coronary intervention (PCI) with stent deployment is currently the most commonly performed revascularization procedure for CAD. In determining the proper treatment course for CAD patients, a number of treatment decisions must be made, including whether a particular lesion can be treated with medical therapy alone or whether it requires PCI or bypass grafting. If PCI is prescribed, the particulars of how to stent the lesion (stent size, length, material, and positioning) and, following the procedure, whether stenting was successful, must also be determined.

PCI with stent deployment has traditionally been based on coronary angiography, an imaging technique for visualizing the interior of blood vessels that can be analyzed either qualitatively (with visual inspection of the radiocontrast lumenogram) or quantitatively (with computer-based quantitation). While angiography is the standard technique for the anatomic imaging of coronary arteries, it only visualizes an outline of the interior of the luminal wall. It has a limited ability to determine the functional severity of intermediate ranges of coronary stenoses (40 to 70 percent), and therefore, using angiography alone in the diagnosis of lesions may lead to unnecessary stenting procedures. Furthermore, angiographic quantification is insufficient to map the detailed morphology of complex lesions—those appearing in left main coronary artery disease, in particular—and in providing information on the composition of coronary plaques. In addition, it is difficult to assess whether a stent was successfully placed as angiography alone often overestimates lumen dimensions, even after symmetric stent implantation.

In order to address these limitations, several adjunctive intravascular diagnostic procedures and imaging techniques (collectively referred to as intravascular diagnostic techniques in this report) have been developed to assist in treatment decisionmaking, by providing more detailed anatomic and hemodynamic information on coronary stenoses. Intravascular diagnostic techniques do not preclude the use of angiography but rather are complementary procedures.[1] Use of these techniques in tandem with angiography can aid practitioners in deciding whether a coronary lesion requires stenting, and once a decision to stent has been made, guiding and optimizing stent deployment, as well as assessing whether a stent was successfully placed. For example, fractional flow reserve (FFR) is used during coronary angiography to determine the physiological (functional) severity of coronary stenoses (as opposed to simply visualizing anatomy, as with angiography) by comparing blood flow at the distal and proximal ends of the coronary lesion. In this way, FFR can aid in deciding whether a lesion needs to be stented or whether stenting can be deferred. Other less common techniques used to determine the physiological severity of coronary stenosis include coronary flow reserve (CFR), as well as others which measure stenosis index and the index of microcirculatory resistance.

Other intravascular diagnostic techniques are used to guide treatment decisionmaking by enhancing visualization of coronary lesions. These have emerged as potentially important complementary tools to angiography, and are able to detect plaques at a much earlier stage of development, that is, before the plaques have attained maximum maturity.[2] Among such imaging

techniques, intravascular ultrasound (IVUS) is the most common. IVUS augments angiography by providing precise lesion characteristics, such as minimal and maximal lumen diameters, cross-sectional area, and plaque area. Other imaging techniques for visualizing coronary anatomy that are less commonly used or are still evolving include IVUS-virtual histology (VH-IVUS), integrated backscatter IVUS, optical coherence tomography (OCT), near-infrared spectroscopy (NIRS), angioscopy, thermography, and intravascular magnetic resonance imaging (IMRI). These techniques are described in detail in the main body of the report.

While intravascular diagnostic techniques do provide additional anatomic or hemodynamic information during PCI, they are invasive techniques, and their application can potentially result in procedure-related complications, increased procedural times, and high initial costs. The use of these adjunctive invasive procedures themselves can also lead to additional invasive tests or treatments that can adversely impact long-term clinical outcomes. Therefore, it is important to assess whether the additional diagnostic information actually translates into a benefit to the patient that outweighs the risks.

Currently available systematic reviews do not comprehensively examine the role of intravascular diagnostic techniques utilization in relation to the settings of interest (tertiary care and other hospital settings), and are not generally applicable to contemporary practice, as recent literature has not yet been thoroughly reviewed (e.g., application of intravascular diagnostic techniques during PCI and deployment of the newer drug-eluting stents). Furthermore, variation in how intravascular diagnostic techniques are adopted in clinical practice across catheterization laboratories reflects considerable uncertainty regarding the utility and role of these techniques.

Objectives

The purpose of this comparative effectiveness review (CER) is to systematically evaluate the effectiveness of intravascular diagnostic techniques versus angiography alone, as well as among different intravascular diagnostic techniques, in patients with CAD undergoing PCI with stent deployment. Also, this review aims to evaluate factors influencing the effect of intravascular diagnostic techniques compared to angiography alone (or different intravascular diagnostic techniques) on outcomes. The utility of a medical diagnostic technique is usually determined by its indirect effect on outcomes, that is, through its influence on therapeutic decision-making, intermediate outcomes, and subsequently, on patient-centered outcomes.

Methods

Input from Stakeholders

This project began with a topic refinement phase, in which the Key Questions were proposed and refined with a panel of Key Informants to better target the Key Questions. Key Informants included experts in interventional cardiology, interventional radiology, noninterventional cardiology, representatives from relevant specialty societies, payors, and a patient representative. Subsequently, during the CER phase, we formed a Technical Expert Panel (TEP), from those Key Informants who provided clinical and methodological expertise in translating the Key Questions into a research protocol. Key Questions were further refined with input from the TEP to help define the patient populations, interventions, comparators, outcomes, and study designs of interest that would be clinically relevant in the application of intravascular diagnostic

compared with angiography alone or other intravascular diagnostic techniques, in patients with CAD.

Key Questions

Our review focused on the following five Key Questions:

Key Question 1: In patients with CAD, what is the impact of using an intravascular diagnostic technique and angiography in deciding whether a coronary lesion requires intervention—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 2: For patients undergoing PCI, what is the impact of using an intravascular diagnostic technique and angiography to guide the stent placement (either immediately prior to or during the procedure)—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 3: For patients having just undergone a PCI, what is the impact of using an intravascular diagnostic technique and angiography to evaluate the success of stent placement immediately after the procedure—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 4: How do different intravascular diagnostic techniques compare to each other in their effects on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

a) During evaluation of the presence/extent of CAD and the potential necessity of coronary intervention?
b) During PCI to guide stent placement?
c) Immediately after PCI to evaluate the success of stent placement?

Key Question 5: What factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) influence the effect of intravascular diagnostic techniques and angiography—when compared to angiography alone (or among different intravascular diagnostic techniques)—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

a) During evaluation of the presence/extent of CAD and the potential need for coronary intervention?
b) During PCI to guide stent placement?
c) Immediately after PCI to evaluate the success of stent placement?

Data Sources and Selection

We conducted literature searches for studies in MEDLINE® (from inception to May 2011) and the Cochrane Central Register of Controlled Trials (through the 2nd quarter of 2011). Studies published in any language with adult human subjects were screened to identify articles relevant to each Key Question. We also screened the reference lists of selected narrative reviews and primary articles for additional articles. We retrieved and screened relevant abstracts from professional conferences and meetings that were available online through the following resources: Transcatheter Cardiovascular Therapeutics (TCTMD.com), the American Heart Association (AHA.org), and the American College of Cardiology (Cardiosource.com). We also searched the ClinicalTrials.gov Web site to identify ongoing trials.

We included studies conducted in adults (≥18 years) with CAD who were undergoing PCI with stent deployment. All forms of CAD presentation were included. For all Key Questions, we included any intravascular diagnostic technique that evaluates morphological or physiological parameters of coronary lesions and is presently employed in clinical care in the United States. The intravascular diagnostic techniques of interest included IVUS, FFR, and others that are primarily investigational at present, such as VH-IVUS, OCT, elastography, NIRS, thermography, angioscopy, intravascular MRI, and techniques measuring stenosis index and index of microcirculatory resistance.

For Key Question 5, the modifiers of treatment effect included patient or physician characteristics, availability of prior noninvasive testing, and the type of PCI performed. Coronary angiography alone was the comparison of interest for Key Questions 1–3 and 5. For Key Questions 4 and 5, head-to-head comparisons of two or more intravascular diagnostic techniques were included. The outcomes of interest were first categorized as therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes. Outcomes were measured at three time points: short-term (up to 30-day of procedure), medium-term (>30 days to 1 year), and long-term (>1 year).

We did not specify a minimum sample-size threshold or a minimum duration of followup. We included all comparative studies, including randomized controlled trials (RCTs) and nonrandomized comparative studies that provided data directly comparing intravascular diagnostic technique and angiography with angiography alone or one intravascular diagnostic technique with another. We excluded narrative reviews and case reports that included fewer than five patients.

Therapeutic decisionmaking

- *Key Question 1*: In patients with CAD, the change in the number of hemodynamically significant lesions after the application of intravascular diagnostic, and the change in the decision about an interventional therapy (e.g., if stenting is needed) after the application of intravascular diagnostic technique
- *Key Question 2*: During PCI, the change in the type of stent or number of stents or length of stent after the application of intravascular diagnostic technique
- *Key Question 3*: Immediately after PCI, the change in the decision about the need for reintervention planned before intravascular diagnostic changed after the test

Intermediate Outcomes

- Process outcomes (technical success rates assessed by quantitative coronary angiography [QCA], such as proportion of successful completion of attempted procedures or proportion of interpretable results in completed procedures, total procedural time required, fluoroscopy time, and volume of contrast medium used)
- Periprocedural complications (e.g., vessel dissection, bleeding, repeat PCI, or unplanned coronary bypass surgery, length of hospital stay)
- Resource utilization (e.g., number of guide catheters, wires, balloons, and stents)
- Stent-related complications (e.g., restenosis, stent thrombosis, dissection)
- Other measures (e.g., cardiac imaging findings [such as ventricular function or myocardial perfusion], electrocardiographic ischemia, biochemical markers, noninvasive assessment using magnetic resonance imaging, and a high-intensity signal on Doppler flow wire during PCI)

Patient-centered outcomes

- Clinical outcomes that directly affect patient well-being or clinical status (e.g., death, acute myocardial infarction [MI], repeat revascularization, composite endpoint of major adverse cardiac events [MACE], freedom from angina, quality of life, and quality-adjusted survival)

Data Extraction

Each study extraction was conducted by one investigator and reviewed by at least one other. Any disagreements were resolved by discussion in team meetings. We extracted data including basic demographics (such as age, sex, race), comorbidities (such as diabetes, hypertension), clinical characteristics (such as percent ejection fraction, location of stenosis, lesion type), and modifying factors associated with the application of intravascular diagnostic and outcomes.

Data Synthesis

To evaluate the effect of an intervention on outcomes, we performed DerSimonian and Laird random effects model meta-analyses of binary data or mean differences of continuous variables between interventions where there were at least three studies that were deemed to be sufficiently similar in population, had the same comparison of interventions, and the same outcomes. For each specific outcome of interest, we performed separate meta-analyses at pre-specified time points. When possible, we evaluated the net change of continuous outcomes (the difference between the intervention of interest and the control intervention in the changes between final and baseline values). However, a large number of studies did not report full statistical analyses of the net change. Where sufficient data were reported, we calculated the net change values and estimated their standard error (SE) from reported standard deviations (or standard errors) of baseline and final values. When necessary, we arbitrarily assumed a 50 percent correlation ($r = 0.5$) between baseline and final values. For outcomes that were reported as final measurements only, we conducted the weighted mean difference meta-analyses between final measurements. For each meta-analysis, the statistical heterogeneity was assessed with the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance. We performed sensitivity meta-analyses by excluding studies that were rated as being at a high risk of bias to see if these studies impacted inferences drawn from syntheses of studies with low and medium risk of biases only. We did not conduct statistical tests to assess publication bias.

Risk of Bias (Overall Methodological Quality) of Individual Studies

We assessed the risk of bias (methodological quality) for each individual study using the assessment instrument detailed by the AHRQ in its *Methods Guide for Effectiveness and Comparative Effectiveness Review*, hereafter referred to as "the Methods Guide."[3] Briefly, we rated each study as being at a high, medium, or low risk of bias on the basis of their adherence to well-accepted standard methodologies for studies, such as the Cochrane risk of bias tool for intervention studies, and assessed and reported each methodological quality item for all qualifying studies (Yes, No, or Unclear/Not reported). The overall judgment of risk of bias was based on the study conduct by evaluating selection, performance, attrition, detection, and selective outcome reporting. Two independent reviewers evaluated the risk of bias for each study, and all disagreements were resolved in consensus with a third reviewer.

Grading the Body of Evidence

We followed the Methods Guide to evaluate the strength of the body of evidence for each Key Question with respect to four domains: risk of bias, consistency, directness, and precision. Risk of bias (overall methodological quality) of individual study was assessed as described previously. We assessed the consistency of the data as either "no inconsistency" or "inconsistency present" (or "not applicable" if only one study). The direction, magnitude, and statistical significance of all studies were evaluated in assessing consistency, and logical explanations were provided in the presence of equivocal results. We also assessed the precision and sparseness of the evidence. We considered evidence to be sparse if only one study of a small sample size addressed the analysis. Because this review assessed many outcomes—therapeutic decisionmaking, intermediate, and patient-centered clinical outcomes—we assessed the strength of evidence based on these three broad categories; however, the overall strength of evidence evaluation was based on patient-centered clinical outcomes, which were defined as any outcome that affected the patient's well-being, such as survival, myocardial infarction, and quality-of-life.

We rated the strength of evidence (as per the AHRQ methods guide) as being High, Moderate, Low, or Insufficient. Ratings were assigned based on our level of confidence that the evidence reflected the true effect for the major comparisons of interest. The individual ratings were defined as follows:

- **High:** There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. No important scientific disagreement exists across studies.
- **Moderate:** There is moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. Little disagreement exists across studies.
- **Low:** There is low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. Underlying studies may report conflicting results.
- **Insufficient:** Evidence is either unavailable or does not permit a conclusion. There are sparse or no data. (In general, the evidence is considered insufficient when only one study has been published, unless the study was particularly large, robust, and of good quality.)

These ratings provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, they by necessity may oversimplify the many complex issues involved in the appraisal of a body of evidence. It is important to remember that the individual studies evaluated in formulating the composite rating differed in their design, reporting, and quality. The strengths and weaknesses of the individual reports, as described in detail in the text and tables, should also be taken into consideration.

Results

Our literature search yielded 3726 citations. From these, 558 articles were retrieved for further evaluation on the basis of the abstracts and titles. After full texts evaluation, 33 studies, published in 39 articles, met the inclusion criteria. A grey-literature search yielded no additional eligible studies, indicating no unpublished studies or presence of publication bias. The most common reason for article rejection was that there were no direct comparisons between

intravascular diagnostic techniques and angiography (276 articles). The other reasons for rejection included ineligible publication types, such as reviews or case reports (81 articles); irrelevant comparators (e.g., intravascular diagnostic compared with cardiac computed tomography; 55 articles); failing to address the Key Questions (46 articles); irrelevant outcomes (34 articles); no intravascular diagnostic techniques used (9 articles); within diagnostic technique comparisons (e.g. comparison between different criteria of the same diagnostic technique; 7 articles); irrelevant or incomplete measurement time points (e.g., comparison between intravascular diagnostic techniques and angiography only at followup; 9 articles); and no population of interest (3 articles). The 33 studies (in 39 articles) had data addressing at least one of the five Key Questions, and evaluated IVUS and FFR. No comparative studies were available for any technique other than IVUS and FFR.

Key Question 1: In patients with CAD, what is the impact of using an intravascular diagnostic technique and angiography in deciding whether a coronary lesion requires intervention—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Overall strength of evidence

Overall, there is a moderate strength of evidence favoring the adjunctive use of FFR during angiography in deciding to stent an intermediate coronary lesion (≥50 percent stenosis), using an FFR threshold <0.80. The evidence was derived from studies that focused on men with intermediate coronary disease and lower grade angina, and excluded patients with left main disease (LMD).

For therapeutic decisionmaking, there is a moderate strength of evidence that the adjunctive use of FFR during angiography aids in deciding whether to stent a coronary lesion, and which coronary vessels to stent, as compared with angiography alone. For intermediate outcomes, there is a moderate strength of evidence that the use of FFR reduces resource utilization in the short-term, as compared with angiography alone; however, the strength of evidence is insufficient for QCA and stent-related outcomes, as the reviewed studies did not report these outcomes at any time point. For patient-centered outcomes, there is a moderate strength of evidence that the use of FFR, as compared with angiography alone, improves combined clinical endpoints (e.g., death or MI and MACE) in the medium- and long-terms. There is insufficient reporting of patient-centered outcomes in the short-term.

There is insufficient evidence regarding the use of any techniques other than FFR to address Key Question 1, as none of the studies reviewed any other techniques.

Available evidence

Three studies, including one RCT (Fractional Flow Reserve versus Angiography for Multivessel Evaluation [FAME] trial in three publications) and two nonrandomized studies reported data comparing FFR-guided stenting with stent placement guided by angiography alone.

Therapeutic Decisionmaking

FFR was found to alter therapeutic decisionmaking as compared with angiography alone. The decision whether to stent a coronary lesion during PCI, or of what type of PCI to use, was made on the basis of an FFR threshold, which varied considerably across all three studies. Stent

implantation was conducted in 63 percent of the 1387 lesions with an FFR of 0.80 or less among patients randomly assigned to FFR-guided stenting in the FAME trial (no stents were placed in the remaining 37 percent of the lesions with FFR >0.80), as compared with stenting all or most of the lesions in the angiography alone group. In one of the two nonrandomized trials, a prospective nonrandomized comparative study, stenting was deferred in 75 vessels (58%) of the total 128 vessels (57 total number of enrolled patients; mean FFR of 0.86) in the FFR-guided stenting; the remaining 53 vessels (48 patients; mean FFR of 0.67) underwent stenting. In the other, a prospective nonrandomized comparative study with a historical comparator, stent implantation was performed in 40 lesions (FFR <0.94); the remaining 37 lesions (FFR≥0.94) underwent direct angioplasty without stenting. Similar information was not reported for angiography alone group.

Intermediate Outcomes

Intermediate resource utilization outcomes of contrast use (272 ml versus 302 ml; P<0.001), the number of stents implanted per patient (1.9 versus 2.7; P<0.001), and the number of hospital days (3.4 versus 3.7; P = 0.05) during procedure were significantly lower in the FFR group than in the angiography alone group in the FAME trial. In this trial, there were no significant differences in average procedure time between the groups, although a significantly lower number of stents were implanted per patient in the FFR group than in the angiography alone group. Only one of the two nonrandomized studies reported this outcome; in this study, no significant differences were found between groups in average procedure time, contrast use, and radiation exposure time. The number of stents implanted per patient was significantly lower in the FFR group than in the angiography alone group in this study (1.04 versus 1.28; P = 0.05), concurring with the FAME trial results. None of the nonrandomized comparative studies reported data on hospital days or data on medication use during the procedure. The cost of procedure, including materials used during PCI, was reported in all three studies, and was significantly lower with FFR-guided stenting as compared with stent placement guided by angiography alone, in all three studies.

Intermediate outcomes as measured by QCA were reported in the two nonrandomized comparative studies at short-term followup, but not in the FAME trial. Both studies reported net changes in the minimal lumen diameter (MLD) and percent diameter stenosis measurements, comparing the FFR and angiography alone groups from baseline to postprocedure. One study was rated as being at a medium risk of bias and reported no significant difference in either measurement between the two groups (MLD net difference 0.02 mm; NS and diameter stenosis net difference 1%; NS). The second (with a historical control and rated as being at a high risk of bias) reported an unfavorable effect in both measurements for FFR-guided stenting over stent placement guided by angiography alone, for this outcome (MLD net difference -0.3 mm; P < 0.001 and diameter stenosis net difference 9.0%; P<0.001).

The FAME trial and one nonrandomized study reported no stent-related intermediate outcomes. Nonsignificantly higher rates of reocclusion and restenosis were observed in the FFR group compared with angiography alone, in the other nonrandomized comparative study. All three studies reported no data on stent thrombosis.

Patient-centered Outcomes

Short-term patient-centered outcomes in the FAME trial included periprocedural MI (2.4% in the FFR group versus 3.2% in the angiography alone group) and MACE at hospital discharge

(absolute mean difference of -2.2 percent). In both these instances, this trial did not report statistical significance. The FAME trial did not report in-hospital complications such as emergent coronary artery bypass grafting (CABG) or revascularization, death, or acute stent thrombosis. Both nonrandomized studies reported nonsignificant differences in-hospital clinical outcomes of MI and MACE. There was no incidence of in-hospital complications of CABG or death reported in either of the nonrandomized studies. One nonrandomized study reported no statistical difference between groups in repeat target lesion revascularization during in-hospital stay. All three studies did not report patient-centered outcomes at 30 days after the procedure.

All three studies reported no significant difference between groups in either medium- or long-term all-cause mortality rates and the incidence of MI (only at 1-year in the FAME trial). In the FAME trial, the FFR group displayed a significant decrease in the risk of composite outcome of death or MI (Relative risk [RR] 0.66, 95 percent confidence interval [CI] 0.44, 0.98 at 1-year and RR 0.65, 95 percent CI 0.45, 0.94 at 2-year) and MI only at 2-year (RR 0.62, 95 percent CI 0.40, 0.95), as compared with the angiography-alone group. Both the FAME trial (at 1- and 2-year followup) and one prospective nonrandomized study (at more than 2-year followup) reported a favorable effect for repeat revascularization and MACE in the FFR, as compared with the angiography alone.

Only the FAME trial reported data on patient-reported outcomes, including the number of patients free from angina, the composite endpoint of the number of patients without an event and freedom from angina, and intake of antianginal medications at 1- and 2-year followup. The trial reported the European Quality of Life-5 Dimensions (EQ-5D) score only at 1-year followup. Although a higher proportion of patients were without an event and were free from angina (73% in the FFR group versus 68% in the angiography alone group), these differences did not reach statistical significance.

Key Question 2: For patients undergoing PCI, what is the impact of using an intravascular diagnostic technique and angiography to guide stent placement (either immediately prior to or during the procedure)—when compared to angiography alone—on the therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Most of the studies that looked at optimizing stent placement (i.e., stent size and dilation) involved IVUS. Only one prospective nonrandomized study (with a historical comparator; rated as being at a high risk of bias) reported data comparing FFR with angiography alone for additional therapy (dilation) after stent deployment. No studies involving techniques other than IVUS or FFR addressed Key Question 2.

IVUS-Guided Compared with Stent Placement Guided by Angiography Alone

Overall strength of evidence

Overall, there is a moderate strength of evidence that supports a significant reduction in target vessel revascularization (TVR) and restenosis, but no significant difference in mortality and MI, when using IVUS to guide stent deployment, as compared with angiography alone. The evidence was derived mostly from studies conducted before 2000 that focused on men, and excluded patients with LMD and acute MI, and used a previous generation of bare-metal stents. With regards to therapeutic decisionmaking, there is a moderate strength of evidence that the use of IVUS during PCI can aid the operator in optimizing stent deployment, as compared with

angiography alone. For intermediate outcomes, there is a moderate strength of evidence that the use of IVUS during PCI to optimize stent deployment increases resource utilization in the short-term, reveals statistically no significant differences in QCA outcomes in the short- and medium-terms, and lowers the risk of stent-related outcome of restenosis in the medium-term, as compared with angiography alone. For patient-centered clinical outcomes, there is a moderate strength of evidence that supports no significant difference in mortality, MI, and MACE, but reveals a significant benefit in decreasing TVR, when using IVUS to guide bare-metal stent deployment, as compared with angiography alone.

Available evidence

We identified nine RCTs (11 publications) and 18 nonrandomized studies comparing IVUS-guided stent placement and stent placement guided by angiography alone.

Therapeutic Decisionmaking

There was information to make a determination as to the comparative effectiveness of IVUS to guide stent deployment relative to angiography alone. Three RCTs and three nonrandomized comparative studies reported data on optimizing stent placement. In the RCTs, a significantly higher proportion of patients achieved optimal stent placement on the basis of IVUS guidance (82% in the IVUS versus 71% in the angiography alone, P<0.0001); almost one-third of the patients received further therapy for an unexpanded stent (37%) or received repeat balloon angioplasty in the IVUS group (46%), and more than one-third underwent overdilation due to not reaching the IVUS criterion(39% in the IVUS-guided stent placement group), though no similar data were provided for the angiography alone group.

Similar results were reported in three nonrandomized comparative studies of IVUS-guided optimized stent deployment, which included additional postdilation, debulking, and angioplasty, or a second stent deployment.

Intermediate Outcomes

Resource utilization in the short-term was reported in four RCTs and two nonrandomized comparative studies. Overall, procedural time was significantly longer, fluoroscopy time was increased, and the use of contrast medium was increased with IVUS-guided stent placement as compared with angiography-guided stent placement. Generally, there were no significant differences between groups for periprocedural complications or stent-related complications, use of glycoprotein IIb/IIIa inhibitor during the procedure, or utilization of other resources, including guidewires, stents, and balloons.

Meta-analyses of QCA outcomes in the short-term, including procedural MLD, reference vessel diameter, and percent diameter stenosis mostly revealed statistically nonsignificant results across RCTs and nonrandomized comparative studies (**ES Table 1**) The eligible studies reported QCA process outcomes heterogeneously (data reporting by lesion or by patients). Meta-analyses of QCA outcomes in the medium term, including MLD, diameter stenosis, reference diameter, and late loss found no statistically significant difference between groups (**ES Table 1**).

In-stent restenosis in the short-term was not significantly different between groups in one RCT and two nonrandomized comparative studies. With respect to the two nonrandomized comparative studies that reported data on subacute stent thrombosis, one reported no instance of subacute stent thrombosis, while the other reported no statistically significant difference between groups.

For the medium-term time point, reported stent-related outcomes included restenosis and stent thrombosis. Meta-analysis of six RCTs revealed a significantly 29 percent lower risk of restenosis in the IVUS-guided group as compared with the angiography-guided group (summary RR 0.71; 95 percent CI 0.52, 0.96), with high heterogeneity (I^2 = 54.7 percent). Although meta-analysis of five nonrandomized studies revealed a similar point estimate (summary RR 0.71; 95 percent CI 0.47, 1.09; I^2 = 42.1 percent), this finding did not reach statistical significance. In addition, two RCTs and three nonrandomized studies provided medium-term data on stent thrombosis, finding no consistent difference between the two groups.

There is insufficient evidence regarding long-term stent-related outcomes, as only two studies reported this outcome. Both of these studies (one RCT and one nonrandomized study) reported stent thrombosis rates, and found no significant difference between groups.

ES Table 1. Summary of QCA measures comparing IVUS-guided stent placement with angiography-guided stent placement

Outcomes	Time points	N RCTs (n participants)	Summary mean difference (95% CI)	N Nonrandomized Comparative Studies (n participants)	Summary mean difference (95% CI)
MLD (mm)	In-hospital (by patient)	6 (1694)	0.09 (0.0, 0.19)	6 (3989)	0.06 (0.0, 0.13)
	In-hospital (by lesion)	3 (659)	0.18 (-0.05, 0.42)	7 (1592)	0.29 (0.16, 0.43)*
	Medium-term (by patient)	4 (1025)	0.16 (0.06, 0.26)*	2 (339)	-0.04 (-0.30, 0.22)
	Medium-term (by lesion)	0		4 (820)	0.26 (-0.02, 0.54)
Diameter stenosis (%)	In-hospital (by patient)	5 (894)	-3.90 (-5.86, -1.94)*	5 (3862)	-0.59 (-1.64, 0.47)
	In-hospital (by lesion)	3 (659)	-5.39 (-12.45, 1.67)	7 (2972)	-2.90 (-6.28, 0.49)
	Medium-term (by patient)	4 (1025)	-3.46 (-7.47, 0.55)	1 (212)	-6.00 (-11.49, -0.51)*
	Medium-term (by lesion)	0		4 (820)	-6.60 (-13.94, 0.74)
Reference vessel diameter (mm)	In-hospital (by patient)	2 (307)	0.09 (-0.04, 0.22)	3 (3351)	0.04(-0.05, 0.12)
	In-hospital (by lesion)	2 (612)	0.02 (-0.06, 0.10)	5 (1188)	0.07 (0.01, 0.03)*
	Medium-term (by patient)	3 (870)	0.11 (-0.08, 0.30)	1 (212)	0.03 (-0,13, 0.19)
	Medium-term (by lesion)	0		3 (751)	0.08 (-0.04, 0.20)

CI = confidence interval, IVUS = Intravascular ultrasound, N = number, MLD = minimal lumen diameter, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, QCA = quantitative coronary angiography

A mean difference or confidence interval = 0 indicates no significant difference.
* Indicates statistical significance

Clinical Outcomes

Either no events occurred or no statistically significant differences in the risk between stenting guided by IVUS or angiography alone were observed in in-hospital clinical outcomes, including mortality, MI, and repeat revascularization (**ES Table 2**).

For the medium-term, both RCTs and nonrandomized studies reported no significant difference between IVUS-guided stent placement and stent placement guided by angiography alone, in the following clinical outcomes: all-cause mortality, or cardiac mortality, MI, and MACE. However, a meta-analysis of the RCTs revealed an 84 percent higher risk in mortality with IVUS as compared with angiography alone, while a meta-analysis of the nonrandomized studies found an 11 percent lower risk in mortality with IVUS versus angiography alone. Meta-analysis of TVR revealed a point estimate in the same direction, with inconsistent statistical

significance across RCTs and nonrandomized comparative studies. Meta-analysis of six RCTs, enrolling almost 1800 patients, found a significantly lower risk of TVR among patients who received IVUS-guided stenting, compared with those who received angiography-guided stenting (summary RR 0.70; 95 percent CI 0.51, 0.97; P = 0.03); however, meta-analysis of eight nonrandomized studies (enrolling almost 13,000 patients in total) found no statistical significance, with a point estimate in the same direction as the RCTs (summary RR 0.81; 95 percent CI 0.60, 1.08).

With respect to the long-term data, both RCTs and nonrandomized studies were in agreement, finding no significant difference between the IVUS and angiography alone groups for the following outcomes: all-cause mortality, MI, and MACE. Meta-analysis of the three RCTs found no significant difference in all-cause mortality, MI, and MACE, but a significant effect on TVR favoring IVUS-guided stent placement (summary RR 0.67; 95 percent CI 0.50, 0.90). Meta-analysis of all three nonrandomized studies found no significant difference in the risk of MACE between the IVUS and angiography alone groups. Two nonrandomized studies reported all-cause mortality, MI, and TVR, and found no significant difference between IVUS-guided stenting and stent placement guided by angiography alone (**ES Table 2**).

ES Table 2. Summary of clinical outcomes comparing IVUS-guided stent placement with angiography-guided stent placement

Outcomes	Time points	N RCTs (n participants)	Summary Relative Risk (95% CI)	N Nonrandomized Comparative Studies (n participants)	Summary Relative Risk (95% CI)
All-cause mortality	In-hospital	3 (925)	No events (3 RCTs)	2 (1802)	No events (1 study) No statistical significance (1 study)
	Medium-term	5 (1816)	1.84 (0.88, 3.85)	5 (12,342)	0.89 (0.68, 1.17)
	Long-term	3 (587)	1.06 (0.38, 2.94)	2 (1949)	Favorable with IVUS (1 study) No statistical significance (1 study
MI	In-hospital	3 (925)	No event (1 RCT) No statistical significance (2 RCTs)	3 (2227)	Favorable with IVUS (1 study) No statistical significance (2 studies)
	Medium-term	4 (1508)	0.66 (0.28, 1.56)	7 (11,643)	1.01 (0.75, 1.37)
	Long-term	3 (587)	0.37 (0.09, 1.50)	2 (1949)	No statistical significance (2 studies)
Repeat revascu-larization	In-hospital	5 (1238)	0.50 (0.20, 1.27)	3 (212)	No events (2 studies) No statistical significance (1 study)
	Medium-term	6 (1760)	0.70 (0.51, 0.97)*	8 (12,998)	0.81 (0.60, 1.08)
	Long-term	3 (587)	0.67 (0.50, 0.90)*	2 (1949)	No statistical significance (2 studies)

CI = confidence interval, IVUS = Intravascular ultrasound, N = number, PCI = percutaneous coronary intervention, RCT = randomized controlled trial

A relative risk <1 indicates a favorable effect with IVUS use.
* Indicates statistical significance

FFR-Guided Stenting Compared with Stent Placement Guided by Angiography Alone

Overall strength of evidence

There is insufficient evidence from one nonrandomized study regarding the use of FFR in determining the need for additional therapy (dilation) during stent deployment.

Available evidence

One prospective nonrandomized study (with a historical comparator; rated as being at a high risk of bias) used a cutoff FFR ≥0.94 reported data comparing FFR-guided stenting with angiography-guided stenting for additional therapy (dilation) during stent deployment. The net changes from baseline to postprocedure, in the minimal lumen diameter and percent diameter stenosis measurements revealed a favorable effect of FFR-guided stenting over angiography-guided stenting groups (MLD: 0.6mm, $P < 0.01$; percent diameter stenosis: 11 percent, $P < 0.01$). There was no incidence of in-hospital complications of CABG or death reported in this study. Nonsignificantly higher rates of reocclusion and restenosis in the FFR-guided stenting group over the angiography-guided stenting group were observed. The study did not report data on acute stent thrombosis, hospital days, and data on medication use during the procedure. No significant difference between groups was reported in long-term all-cause mortality rates.

Other intravascular diagnostic Techniques Compared with Angiography Alone

There is insufficient evidence for all techniques other than IVUS and FFR to answer Key Question 2, as no comparative studies evaluated techniques other than IVUS and FFR.

Key Question 3: For patients having just undergone a PCI, what is the impact of using an intravascular diagnostic technique and angiography to evaluate the success of stent placement immediately after the procedure—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Overall strength of evidence

There is insufficient evidence regarding the comparisons of interest in this Key Question, as data were drawn from two studies, both evaluating IVUS rated as being at a high risk of bias, each reporting on two different types of outcomes at different time points. There is insufficient evidence for any intravascular diagnostic technique, as none of the reviewed studies evaluated the effect of FFR or any other intravascular diagnostic technique on the success of PCI immediately after the procedure.

Available evidence

One study reported no significant differences in angiographic results either during short- or long-term and there were no significant differences in the incidence of restenosis between the two groups in the other study.

Key Question 4: How do different intravascular diagnostic techniques compare to each other in their effects on the therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Overall strength of evidence

There is insufficient evidence regarding the comparison of FFR versus IVUS, as only one study rated as being at a high risk of bias provided relevant data. There is insufficient evidence for all other comparisons, as none of the studies reviewed involving other intravascular diagnostic techniques addressed this Key Question.

Available evidence

One study with high risk of bias compared FFR-guided with IVUS-guided stent placement in patients with intermediate coronary lesions (40 percent to 70 percent diameter stenosis by visual assessment). The study compared FFR (cutoff 0.80) or IVUS (4 mm^2 derived minimal lumen area), and the use of FFR or IVUS was based on operator preference. Twenty-eight of 83 patients in the FFR group received stents, while 86 of 94 patients in the IVUS group received stents (33.7% vs. 91.5%, respectively; $P < 0.001$). The one-year composite outcome of MACE was not significantly different between FFR and IVUS (3.6% vs. 3.2%, respectively).

Key Question 5: What factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) influence the effect of intravascular diagnostic techniques—when compared to angiography alone (or among different intravascular diagnostic techniques)—on the therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Overall strength of evidence

There is a moderate strength of evidence that fails to support an association between IVUS and factors such as LMD, sex, diabetes mellitus status, lesion length and reference diameter, and its effect on outcomes. There were no studies to address this Key Question for any technique other than IVUS.

Available evidence

One prospective study with a medium risk of bias (9070 patients) and one retrospective with a high risk of bias (58 patients) evaluated factors influencing the comparative effectiveness of IVUS versus angiography. The studies enrolled patients with CAD who presented with angina, silent ischemia or left main coronary artery disease and were undergoing PCI procedure with or without stenting. Both studies used IVUS for the patients undergoing PCI or immediately after PCI, and compared them with patients whose stents were placed using only angiography alone. One study compared the use of IVUS with no IVUS on the subgroup of patients with distal LMD and nondistal LMD. Even though presence of distal LMD was significantly associated with adverse outcomes compared to those with nondistal LMD disease, the rate of events did not significantly differ between the IVUS or no IVUS, irrespective of variations in anatomic LMD. Evaluation of several factors such as sex, diabetes mellitus status, lesion length and reference

diameter and their interaction with stenting guided by IVUS or angiography alone did not show any significant association with individual components or composite outcome of MACE.

Other than these two studies of IVUS, we found no studies of other intravascular diagnostic techniques that evaluated factors influencing the effect of intravascular diagnostic techniques compared to angiography alone or different intravascular diagnostic techniques on outcomes. Therefore, the strength of evidence for all other intravascular diagnostic techniques was rated insufficient.

We found no studies evaluating additional subgroups of interest, including patients with and without diabetes, patients with chronic inflammation (e.g., systemic lupus erythematosus), and patients with atherosclerosis following heart transplantation.

Discussion

Key Findings and Strength of Evidence

Our review of the evidence found that the bulk of the available data addressed Key Question 1 (use of FFR, which measures the physiological severity of coronary stenosis, in deciding which coronary lesions require intervention) and Key Question 2 (use of IVUS, which visualizes coronary anatomy, in guiding PCI and optimizing stent deployment). There were insufficient data available to answer Key Questions 3 and 4. For Key Question 5, there is a moderate strength of evidence that fails to support an association between IVUS use and factors such as LMD, sex, diabetes mellitus status, lesion length and reference diameter, and its effect on the diagnostic thinking and therapeutic decisionmaking, or other outcomes. For all other intravascular diagnostic techniques as compared with angiography alone there were insufficient data to address this Key Question 5.

Our review suggests that the use of FFR in patients with intermediate coronary stenosis in order to decide which coronary lesions require intervention would confer a lower risk of the combined endpoint of death or MI, as compared with stent placement guided by angiography alone. Additionally, our review indicates that FFR-guided stenting would decrease total cost and length of stay, and would lead to fewer stents implanted, without sacrificing freedom from angina or without the need for further revascularization, as compared with stenting guided by angiography alone.

The study upon which these findings are primarily based, the FAME trial, found benefit in stent deployment in physiologically or functionally stenosed lesions, and we concluded that, in view of this RCT (rated as being at a low risk of bias) and one additional prospective nonrandomized study (rated as being at a medium risk of bias), there is moderate evidence favoring FFR-guided stenting over stent placement guided by angiography alone, in patients with intermediate coronary lesions, excluding left main disease and acute MI.

Our review also indicates that the use of IVUS compared with angiography alone to guide stent deployment achieved some measureable, though inconsistent, improvements in QCA outcomes, such as lumen diameter, in the short- and medium-term. The inconsistencies revealed in meta-analyses can be mostly attributed to the heterogeneity in outcome assessment (data reported by lesion or by patient). It should be noted that the gains achieved in intermediate outcomes with IVUS-guided stenting did not translate into significant differences in mortality or MI during followup. Nevertheless, there were significant reductions in TVR and restenosis rates during medium-term followup (>30 days to 1 year) with IVUS-guided stenting versus stent placement guided by angiography alone, with a reduction in TVR of about 30 percent (mostly

observed in RCTs of modest sample size). The lower TVR and restenosis rates reported with IVUS-guided stenting should be interpreted cautiously as these studies were conducted using a previous generation of bare-metal stents, and their results may no longer be applicable to current clinical practice with a widespread use of drug-eluting stents.

In the reviewed studies, IVUS-guided stenting appears to be associated with longer procedural times, greater radiation exposure, and greater contrast use than angiography-guided stenting, all factors that may be associated with short- and long-term risks of complications.

Context of Findings (Comparison with Other Reviews)

Our review concurs with three recently published systematic reviews comparing the effect of IVUS-guided PCI and non-IVUS-guided PCI, similarly finding no significant differences between groups for the clinical outcomes of mortality or MI, and a significant difference in TVR in randomized trials favoring IVUS-guided PCI over non-IVUS-guided PCI.[4-6] While these reviews also found a significant decrease in MACE with the use of IVUS for guiding PCI compared to non–IVUS-guided PCI,[4-6]our review, which included additional studies from recent literature, did not. The disparity in our findings could be explained by the differences in eligibility criteria, in the number of included studies, or the methods of analyses. The first review searched until 1999, but found only two RCTs overlapping with our review, because of differences in eligibility criteria;[4] the second review searched until 2001, and identified only five of the total nine RCTs included in our review;[5] and the third review combined medium- and long-term data, which resulted in a statistical significant results for MACE.[6]

In this review, we examine both older studies (examining PCI with bare-metal stents) and more recent studies (examining PCI with drug-eluting stents). Our review also comprehensively evaluates nonrandomized comparative studies of intravascular diagnostic techniques. Our analyses evaluate both intermediate and clinical outcomes at various time points (short-, medium-, and long-term). Such extensive assessments have not been carried out by prior reviews, which most often evaluated only the last reported time point. In addition, we conducted subgroup analyses, stratifying older versus newer studies (studies conducted before 2000 versus those conducted since 2000). Also in contrast to prior reviews, our review examined the impact of FFR in both RCTs and nonrandomized studies conducted in real-world settings. In addition, our review synthesizes data and analyzes gaps in the literature on the use of intravascular diagnostic techniques at various stages of the stenting (before, during, and after), and evaluated the role of these techniques in therapeutic decisionmaking. In summary, our review comprehensively examines both IVUS and FFR data and has identified a lack of comparative studies for all other emerging novel and hybrid techniques.

Applicability

Reviewed studies were conducted in tertiary care centers and were carried out mostly in Western Europe and North America. The majority of the included patients in reviewed studies were men. The majority of the studies specifically stated exclusion of individuals with LMD or acute MI. Minorities were underrepresented, although a few studies reported baseline data by race or ethnicity. These eligibility criteria likely selected groups of patients with intermediate coronary stenosis, better functional status, and higher socio-economic status, thus limiting applicability in patients with severe CAD. Most IVUS trials (seven of nine RCTs) reviewed were performed before the year 2000. Interventional techniques and technology have evolved considerably since then, not only in terms of high-pressure balloon inflation, but also in stent

design, composition, delivery systems, balloon technology, adjunctive pharmacotherapy, and other features. Current bare-metal stents are radically different than those used before 2000; and only two RCTs (both conducted in Eastern Europe) evaluated IVUS-guided stent placement in patients with a drug-eluting stent, and none evaluated second-generation drug-eluting stents. Thus, overall, there are several important groups of patients who have not been adequately represented in the available literature.

Implications for Clinical and Policy Decisionmaking

There is moderate strength of evidence favoring FFR-guided stenting over stent placement guided by angiography alone, in patients with intermediate coronary lesions; these findings are supported by only one large trial (FAME) and one nonrandomized study. Although the evidence was rated to be of moderate strength, there is the possibility that future studies will not support the favorable effect off FFR-guided stenting; this phenomenon, an initial effect that eventually dissipates through subsequent studies, has been well documented.[7] It is also worth noting that the FAME trial included patients with intermediate stenosis and lower grades of angina, patients who may otherwise not undergo stent implantation. The intrinsic risk of a non-ischemic stenosis may be lower than the risk of stent implantation itself. Treating low-risk lesions could lead to additional invasive tests or treatments that could adversely impact long-term clinical outcomes. Therefore, the use of stents in treating low-risk lesions should be weighed against this consideration. These decisions are, of course, not always straightforward in clinical practice. A further gap revolves around the role of FFR post intervention or stent deployment as FFR use has been primarily evaluated only in deciding whether revascularization is indicated.

Currently, IVUS is extensively applied in certain clinical situations and specific lesion subsets (e.g., LMD), without the backing of sufficient comparative data. Additionally, IVUS is used to assess stent apposition and adequate stent expansion, lesion coverage, and edge dissections when the operator is in doubt and cannot angiographically determine with certainty whether a potentially life-threatening technical complication exists (i.e., one that could lead to stent thrombosis and potentially death), despite the fact that the effectiveness of IVUS in these clinical scenarios has not been evaluated in comparative studies. IVUS cannot fully assess the physiological significance of lesions (in deciding if a coronary lesion needs intervention); therefore, operators may have to use additional techniques to evaluate physiological stenosis, especially in non-LMD lesions and small coronary arteries (<3.0 mm minimal lumen diameter).

Our review did not find comparative data correlating findings of OCT, IVUS-VH, NIRS, or any hybrid technique with subsequent outcomes and events, or on their relative impacts and resource utilization profiles.

Intravascular diagnostic techniques are quickly evolving, and differences in their learning curves and the skill with which they are employed can potentially influence outcomes. Additional study is necessary to figure out the implications of these factors on clinical and policy decisionmaking.

Limitations of this CER

Intravascular diagnostic techniques are rapidly evolving technologies, which likely explain why we found few comparative studies except for two established techniques, IVUS and FFR. There was insufficient evidence to answer all but the first two of the review's Key Questions. Our review included only direct comparisons and only studies that had two distinct comparison groups (intravascular diagnostic technique and angiography versus angiography alone). We

excluded studies that lacked a distinct group (at both intervention and followup) whose stents were placed using angiography alone.

Other restrictions included the focus of Key Questions on the short time-frame around PCI, thereby excluding studies evaluating the intravascular diagnostic techniques during followup only (but not during PCI). The reporting of timing of intravascular diagnostic technique application in reviewed studies was often unclear (e.g., during PCI or immediately after).

Limitations of the Evidence

Outcome reporting (primarily with respect to patient-centered outcomes) were not completely available in the included studies. There is also substantial heterogeneity in composite outcome definitions of MACE. None of the studies included in our review was itself sufficiently powered to address the effectiveness of IVUS to improve long-term outcomes, and few studies reported long-term outcome data.

Few studies evaluated the comparative effectiveness of these intravascular diagnostic techniques in patients undergoing drug-eluting stent implantation, specifically the latest generation of stents. And studies often did not evaluate the effect of training of operators and their variability in the application of these techniques on clinical outcomes. Studies did not report on the effect of evolution of intravascular diagnostic technique during study period.

Future Research Needs

This review has identified a number of substantial gaps in the intravascular diagnostic literature: the contemporary role of IVUS guidance in drug-eluting stent placement needs to be evaluated; the prognostic role of FFR should be confirmed in further trials; and hybrid and novel techniques need to be evaluated for comparative efficacy and safety. While early studies evaluating drug-eluting stents have used IVUS during stent placement, comparative studies, particularly RCTs of drug-eluting stents placed using IVUS or angiography alone, are lacking. Drug-eluting stents prevent neointimal hyperplasia, and profoundly reduce the rate of restenosis and TVR, as compared with bare-metal stents. The potential advantage of IVUS guidance in stent placement to reduce restenosis and TVR has become less significant with the widespread use of drug-eluting stents. However, IVUS continues to be used in small vessels, complex lesions, and long lesions. It is important, then, that additional studies in these populations are conducted to assess the comparative effectiveness of IVUS in the drug-eluting stent era.

The role of FFR after intervention or stent deployment, in side branches and other clinical situations, should be better defined in future trials. In addition, the role of FFR and IVUS needs to be better defined in other vascular territories, outside of the coronary circulation. Data correlating findings of investigational techniques such as OCT, IVUS-VH, and NIRS with subsequent outcomes and events are needed but not yet available. Catheters are currently deployed in combination with multiple imaging modalities for more comprehensive assessment, and variations or combinations of OCT or IVUS systems may further assist in the management of certain lesions. The future use of hybrid and novel intravascular diagnostic techniques may impact effectiveness and resource utilization. With an increase in availability, there will be increased utilization of hybrid and novel intravascular diagnostic techniques in the near future. The total cost and resources used for a combination of techniques may be less or more than those for any technique alone. Furthermore, the use of hybrid and novel intravascular diagnostic devices may decrease the total time required for imaging while also simultaneously providing data from multiple intravascular diagnostic techniques. At present, the absence of comparative

data available for hybrid and novel devices limits evaluations of their effectiveness in routine clinical practice.

Future research is needed to enrich our understanding of the comparative effectiveness of intravascular diagnostic techniques (both established and novel) and angiography in diverse ethnic populations, women, and patients with LMD and acute MI, as studies published in the past often excluded these populations while evaluating established techniques such as IVUS and FFR. There are no published comparative studies evaluating novel techniques. Furthermore, more studies with followup duration greater than 1 year may enhance our understanding of the long-term impact of the use of intravascular diagnostic techniques.

Consensus is needed among investigators in harmonizing outcomes assessment. Studies either reported procedural data by patients or by lesions, thereby making synthesis difficult across studies. Future research is also needed to assess the usefulness of how these procedural data are presented, for example, if data by patients is preferable over data by lesions. Until consensus is achieved, investigators should be encouraged to present data both by patients and by lesions.

Conclusions

In summary, there is moderate evidence that that the use of FFR-guided stenting to decide whether stenting for intermediate coronary lesions can confer to patients a lower risk of death or MI, decrease total costs and length of stay, and lead to fewer stents implanted, without sacrificing freedom from angina and without the need for further revascularizations, as compared with stenting guided by angiography alone. These findings are limited by the fact that the FAME trial is the only large RCT supporting them; further trials are needed to confirm and expand on these results. There is a moderate strength of evidence that supports a significant difference in TVR and restenosis, but no significant difference in clinical outcomes of mortality and MI during medium- and long-term followup between IVUS-guided and angiography-guided stent placement. However, most of the IVUS trials were performed before the year 2000. There are only two RCTs (both conducted in Eastern Europe) evaluating IVUS-guided drug-eluting stent placement, and none with second generation drug-eluting stents. These factors could affect the present-day applicability of the data, and the impact of current IVUS devices on TVR and restenosis must be reassessed in future studies of PCI with drug-eluting stent implantation. Furthermore, the majority of the eligible studies focused on men with lower grade disease and excluded patients with LMD; future studies (regardless of technology or the current intervention of interest) will also need to include women and patients with more serious coronary artery diseases. Future work will also need to evaluate longer-term (on the order of years) patient outcomes to better appreciate real-world effectiveness and to better account for harms that may take years to manifest.

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Introduction

Coronary artery disease (CAD) is a narrowing (stenosis) of one or more of the epicardial coronary arteries. It is most commonly due to a buildup of plaque (atherosclerosis), which impedes the ability of these blood vessels to deliver oxygenated blood to the heart muscle (myocardium). This form of arteriosclerosis is characterized by a hardening of the arterial walls, cholesterol deposition, local inflammation, fibrosis, and progressive narrowing (stenosis) of the lumen of these vessels.[1] It is a long-term health condition that affects populations with untreated or ineffectively treated risk factors, such as high blood pressure, high levels of cholesterol, diabetes, and smoking. Coronary atherosclerosis is a chronic disease with stable and unstable periods. Patients with stable angina usually experience effort-related symptoms. These symptoms arise because of an inability to augment myocardial blood flow in response to exertion, due to a fixed stenosis. During unstable periods, activated inflammation in the vascular wall may lead to atheromatous plaque rupture and thrombus formation, resulting in chest pain (unstable angina) or a heart attack (myocardial infarction).[2]

Burden of Disease

Cardiovascular disease is a leading cause of morbidity and mortality worldwide, accounting for 17.3 million (30 percent) of all deaths globally in 2005; of these, 7.3 million were due to coronary artery disease (CAD).[3] Although, there has been a steady decline in the age-adjusted mortality rates for CAD,[4] it is still the leading cause of death in the United States of both men and women.CAD is a major cause of disability and comprises a significant portion of the consumption of healthcare resources. In the United States alone, health care costs for management of CAD are projected to increase by 41 percent from $126.2 billion to $177.5 billion in 2040.[5] In the United States in 2010, the prevalence of CAD among men was 7.8 percent and among women was 4.6 percent. Elderly (≥65 years of age), American Indians/Alaska natives and persons with less than a high school education had the greatest prevalence of CAD that were 19.8 percent, 11.6 percent, and 9.2 percent, respectively.[6]

Challenges of Diagnosing Coronary Stenoses

Treatment options for CAD vary according to the disease presentation (i.e., acute or chronic). The management of acute coronary syndrome may include the use of thrombolytics ("clot busting" medications), urgent or emergent percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG) depending on clinical factors and the specific subtype (ST segment elevation and certain non-ST segment elevation syndromes, as defined by electrocardiogram). Adjunctive medical therapies in acute coronary syndromes include the use of antiplatelet and anticoagulant medications (blood thinners). For patients with stable CAD, mechanical revascularization (i.e., PCI or CABG) are indicated: 1) to improve survival in patients with high risk coronary anatomy (e.g., ≥50% left main coronary artery stenosis, or ≥70% stenoses in three major coronary arteries); 2) to improve symptoms in patients with unacceptable lifestyle limiting angina despite aggressive medical therapy, and with one or more significant (≥70% diameter) coronary artery stenoses amenable to revascularization. There are a number of details and variations of these revascularization guidelines, which are beyond the scope of the present review.[7,8]

PCI with stent deployment is currently the most commonly performed revascularization procedure for CAD. In determining the proper treatment course for CAD patients, a number of

treatment decisions must be made, including whether a particular lesion can be treated with medical therapy alone or whether it requires PCI or bypass grafting. If PCI is prescribed, the particulars of how to stent the lesion (stent size, length, material, and positioning) and, following the procedure, whether stenting was successful, must also be determined. PCI with stent deployment has traditionally been based on coronary angiography, an imaging technique for visualizing the interior of blood vessels that can be analyzed either qualitatively (visual inspection of the radiocontrast lumenogram) or quantitatively (computer-based quantitation). While angiography is the standard technique for anatomic visualization of coronary arteries, it only visualizes an outline of the luminal wall and, generally, has limited ability in determining the functional severity of stenoses. Because the outer wall of the artery enlarges to accommodate the growing plaque (positive remodeling),[9] angiographic evidence of stenosis is usually not detected until the plaque approaches 40 to 50 percent of the total cross-sectional area of the coronary artery. For intermediate ranges of coronary stenoses (40 to 70 percent), there is considerable variability between angiographic and physiologic assessments of stenoses severity, making it difficult to determine whether stenting will be needed.[10] In addition, angiography may not reveal the detailed morphology of complex lesions (e.g., ostial, graft, or bifurcation lesions) and lesions in left main coronary artery disease. Angiography also cannot provide information on the composition of the coronary plaque, which could be important in determining therapeutic choices.[9] Furthermore, it is difficult to assess whether a stent was successfully placed, as angiography alone often overestimates lumen dimensions, even after symmetric stent implantation.

In order to address these limitations, several adjunctive intravascular diagnostic procedures and imaging techniques (collectively referred to as intravascular diagnostic techniques in this report) have been developed for the purpose of providing more detailed anatomic and hemodynamic information in coronary stenoses. Intravascular diagnostic techniques do not preclude the use of angiography; rather, they are complementary in nature by assisting treatment decisionmaking.[11] Use of these techniques in tandem with angiography can aid practitioners in deciding whether a coronary lesion requires stenting, and once a decision to stent has been made, guiding and optimizing stent deployment, as well as assessing whether a stent was successfully placed.

One such intravascular diagnostic technique, fractional flow reserve (FFR), is used during coronary angiography to determine the physiological (functional) severity of coronary stenoses (as opposed to simply visualizing anatomy, as with angiography) by comparing blood flow at the distal and proximal ends of the coronary lesion. Other less common techniques used to determine the physiological severity of coronary stenosis include coronary flow reserve (CFR), as well as others which measure stenosis index and the index of microcirculatory resistance.

Among the intravascular diagnostic techniques used to visualize coronary anatomy, intravascular ultrasound (IVUS) is the most common. IVUS augments angiography by providing precise lesion characteristics, such as minimal and maximal lumen diameters, cross-sectional area, and plaque area. Other intravascular diagnostic techniques to visualize coronary anatomy that are less commonly used or are still evolving include IVUS-virtual histology (VH-IVUS), integrated backscatter IVUS, optical coherence tomography (OCT), near-infrared spectroscopy (NIRS), angioscopy, thermography, and intravascular magnetic resonance imaging (IMRI).

Proposed Advantages of intravascular diagnostic Techniques

Intravascular diagnostic techniques are potentially valuable in a number of clinical scenarios. For example, IVUS provides precise visualization of intracoronary anatomy, atherosclerotic plaque composition, and changes in vessel dimensions. It could be used in patients who have complex coronary lesions that might otherwise be missed, thereby improving long-term clinical outcomes. Conversely, FFR might help identify patients whose stenoses are not really impeding flow and thereby reduce the number of stents used and limit patient exposure to the risks of the initial or repeat revascularization procedures and antiplatelet agents.

While intravascular diagnostic techniques do provide additional anatomic and hemodynamic information during PCI, they are invasive techniques, and their application can potentially result in procedure-related complications or increased procedural times and high initial costs. The use of these adjunctive invasive procedures themselves could lead to additional invasive tests or treatments that can adversely impact long-term clinical outcomes. Therefore, it is important to assess whether the additional diagnostic information actually translates into a benefit to the patient that outweighs the risks. These decisions are not always straightforward. Invasive intravascular diagnostic modalities have emerged as potentially important complementary tools to angiography, as other available noninvasive imaging techniques for evaluating stenoses are inferior in a number of respects, such as having much lower resolutions than invasive techniques (e.g., cardiac computed tomography compared with IVUS). As such, noninvasive methods have been used primarily to detect well-formed plaques. In contrast, invasive intravascular diagnostic techniques are able to detect plaques at a much earlier stage than noninvasive techniques (e.g., IVUS vs. cardiac MRI), that is, before the plaques have attained maximum maturity. [12]

Current Uncertainties about Intravascular diagnostic Techniques

Recent clinical practice guidelines have indicated that FFR and IVUS can be useful in certain clinical contexts—specifically, FFR in determining the necessity of stenting in angiographically borderline-significant lesions, and IVUS for providing technical guidance during PCI and optimizing stent deployment results.[7,8] The systematic reviews currently available do not comprehensively examine the role of intravascular diagnostic techniques in relation to the settings of interest (tertiary care and other hospital settings), and are not generally applicable to contemporary practice, as recent literature has not yet been thoroughly reviewed (e.g., application of intravascular diagnostic techniques during PCI and deployment of the newer drug-eluting stents). Furthermore, variation in how intravascular diagnostic techniques are adopted in clinical practice across catheterization laboratories reflects considerable uncertainty regarding the utility and role of these techniques.[13] Thus, a comparative effectiveness review on the use of intravascular diagnostic applications in patients with CAD is timely and necessary to assess the clinical impact of incorporating such techniques into coronary revascularization procedures.

Narrative Description of Intravascular Diagnostic Techniques

Reference Diagnostic Technique: Angiography

Angiography is the current reference standard for identifying coronary artery lesions. It provides 2-dimensional silhouette image information about the luminal diameter and enables visualization of the luminal surface to diagnose atherosclerotic disease. The stenosis severity by angiography is reported as a ratio of the stenosis' minimal lumen diameter (MLD) to the adjacent "normal" reference segment. Computer-assisted, automated, edge-detection algorithm systems are often used to quantify coronary stenoses more accurately (e.g., quantitative coronary angiography [QCA]). Angiography may underestimate the degree of stenosis or atheroma burden, particularly in the setting of diffuse CAD, or because of the positive remodeling phenomenon with outward displacement of the external vessel wall that prevents plaque from encroaching into the lumen.

Index Diagnostic Techniques

Additional description of intravascular diagnostic-manufacturers and regulatory status are provided in **Appendix D**.

Intravascular Physiologic Testing Techniques

Coronary Flow Reserve

CFR utilizes invasive physiologic testing to assess the functional significance of a coronary stenosis. Measurements of CFR are obtained utilizing a Doppler-sensor-tipped intravascular wire to determine the ratio of hyperemia to basal mean flow velocity just distal to the coronary stenosis in question. This ratio is obtained from flow measurements before and immediately after the administration of a vasodilator, such as adenosine. The CFR decreases with increased lesion severity. A CFR <2.0 is typically used as a threshold to determine if an intermediate coronary lesion is physiologically significant (**Table 1**); however, CFR measurements have not been standardized for guiding stent placement during PCI.

The major limitation in assessing a coronary stenosis with CFR is the influence of microvascular impairment on CFR values. When microvascular circulation is compromised by ventricular hypertrophy or diabetes mellitus, then the CFR may be less than 2.0 (abnormal). An abnormal CFR does not differentiate whether an abnormality exists in the epicardial coronary artery or in the microcirculation. To overcome this limitation, the measurement of an adjacent "normal" coronary vessel has been proposed to provide values for a relative CFR. However, this requires interrogation of an additional vessel, which extends the procedural time and may result in additional complications. Because of these limitations, CFR has not gained wide-spread acceptance.

Fractional Flow Reserve

Coronary pressure wire-derived FFR is defined as the ratio of maximal blood flow achievable in a stenotic coronary artery relative to the maximal flow in the same vessel if it were normal. This index represents the fraction of the normal maximal myocardial flow that can be achieved despite coronary stenosis. Flow measurements are obtained readily by advancing a pressure sensor-tipped coronary angioplasty guide wire across a stenosis and recording the distal

pressure at rest and at maximal hyperemia induced with intracoronary or intravenous infusion of the vasodilator adenosine. The ratio between the mean distal pressure at maximal hyperemia and the mean aortic pressure is the FFR. Unlike CFR, FFR is independent of changes in heart rate, blood pressure, or prior infarction, and takes into account the contribution of collateral blood flow. The normal FFR for all vessels under all hemodynamic conditions is 1.0, regardless of the status of microcirculation. An FFR value >0.80 generally excludes ischemia related to a specific stenosis.[8] The presence of conditions that limit achievement of maximal hyperemia, such as small vessel, diffuse disease, infarcted myocardium, or left ventricular hypertrophy, diminish the reliability of FFR.

FFR can also accurately determine the hemodynamic significance of serial coronary lesions when performed via a slow "pull back method" during continuous intravenous infusion of adenosine, with avoidance of unnecessary procedures that may not provide additional hemodynamic benefit. Once a PCI is performed, adequacy of the PCI result can be assessed by FFR with established criterion for a successful stent placement an FFR value of >0.94 (**Table 1**).

Clinical adoption of FFR varies widely, influenced by geographic factors, physician preferences, provider settings (hospital-employed vs. private practice interventionists) and insurance coverage. FFR is currently covered by the Centers for Medicare and Medicaid (CMS) for reimbursement.

Intravascular Imaging Techniques

Intravascular Ultrasound

IVUS is a catheter-based technique that provides tomographic images perpendicular to the length of the coronary arteries. During PCI, IVUS provides high-resolution images of the vessel and lumen geometry, and enables analysis of plaque composition and distribution, as well as guidance of coronary stent implantation. IVUS can also be used to quantitatively assess revascularization success or diagnose stent-related complications.[14] However, it does not directly measure the hemodynamic effects of a stenosis. Limitations of the technique include the inability to discriminate between fibrous and lipid-rich plaques and the fact that thrombus formation cannot be easily detected. Modifications of IVUS using analysis of integrated backscatter and the radiofrequency envelope have been reported to improve resolution and sensitivity for the detection of lipid-rich plaques. IVUS elastography that combines ultrasound images with radiofrequency measurements may be able to better detect regions of increased strain prone to rupture. In an effort to improve plaque characterization, VH-IVUS was developed, which combined frequency and amplitude analysis and used an algorithm developed from known tissue types to detect plaques with vulnerability features.

IVUS has been used to guide and optimize stent implantation. It allows the operator to visualize how well the stent is deployed, quantify the residual luminal diameter, and detect complications of stent implantation that require immediate management, such as stent-edge dissections. IVUS offers optimal stent deployment with only minimal residual luminal stenosis. Attainment of a large luminal diameter minimizes the risk of both stent thrombosis and restenosis. IVUS may have potential value for the stenting of long lesions, bifurcation, ostial and undilatable lesions and for saphenous vein grafts. IVUS is currently covered by CMS for reimbursement.

Table 1. Catheter-based anatomic and physiologic criteria associated with clinical outcomes

Application	IVUS	CFR	FFR
Ischemia detection	<3-4 mm2	<2.0	<0.80
Deferred angioplasty	NA	>2.0	>0.80
Endpoint of stenting	>9mm2; >80% reference area; full apposition (depending on vessel size and volume plus morphology of plaque and target vessel segment)		>0.94 (depending on diffuse disease in persistent segment)

CFR=coronary flow reserve, FFR=fractional flow reserve, IVUS=intravascular ultrasound, NA=not applicable.

Optical Coherence Tomography

OCT measures the echo time delay and intensity of backscattered light due to internal microstructure in the tissue in order to create high-resolution (10 μm) cross-sectional images. Because of the short wavelength of OCT, it will reflect (and detect) very small objects, including blood cells. Therefore, in order for OCT to image the vessel wall, it requires a blood-free field. The original time-domain OCT technique requires continuous flushing with proximal balloon occlusion to displace the blood. Recently, faster data and image acquisition with optical frequency domain imaging (OFDI) has enabled rapid (i.e., 15 to 30 mm/s) imaging with only a 3 to 5 second contrast or saline injection through the guiding catheter (without the need for proximal balloon occlusion). The proposed advantages of OCT are that it provides a clearer picture of plaque structures than IVUS. The potential disadvantage of OCT is limited tissue penetration and, therefore, its inability to consistently image the adventitia and assess plaque burden. The diagnostic information provided by OCT pertains to the very detailed anatomic imaging of plaques, thus making the technique potentially useful for the detection and treatment plaques that are at risk of rupture and also for the assessment of stent apposition. No potential role of OCT in helping to make treatment decisions for intermediate lesions has been described. Recent data suggest that OCT imaging can be performed with similar safety profile as IVUS. The United States Food and Drug Administration (FDA) has recently cleared an OCT device (LightLab Imaging, Inc., Westford MA) for high resolution vessel and lumen morphology, but CMS does not currently reimburse OCT imaging.

Angioscopy

Intracoronary angioscopy facilitates direct visualization of the plaque surface, color of the luminal surface, presence of thrombus, and macroscopic features of the arterial wall. Angioscopy can assess plaque color and detect red and white thrombus and surface characteristics, such as ulcerations, fissures and flaps. Angioscopy visualizes the luminal surface but is insensitive to subtle differences in plaque. Therefore, the major role of angioscopy is limited to the assessment of the lumen structure before and after interventions. However, angioscopy is rarely used in clinical practice, because it requires a blood-free field of view. The technique, nevertheless, remains valuable for research purposes, with most use occurring in Japan. This imaging modality is not currently covered by CMS.

Near Infrared Spectroscopy

NIRS employs a catheter containing an optic fiber that is used to measure diffuse reflectance signals with near infrared light as an energy source. NIRS yields information about the plaque chemical composition via the pattern of absorption of the light in relation to the wavelength. This pattern is unique for lipid and each of the other plaque elements. A NIRS device (Lipiscan) has been recently cleared by the FDA for the detection of lipid-rich plaque. The clinical premise of

NIRS is that lipid-rich plaques could be detected before performing PCI and thus therapeutic decisions could be tailored to the chemical composition of the plaque (e.g., use of embolic protection devices, selection of stent type). The major limitation of NIRS is that it provides compositional but not structural information. This imaging modality is not currently covered by CMS.

Thermography

Thermography is a catheter-based technique to detect heat released by activated inflammatory cells of atherosclerotic plaques. Temperature differences correlate positively with cell (macrophage) density, which may predict plaque disruption and thrombosis. However, there is no clear evidence that temperature differentials correlate with specific plaques that are at risk of rupture, and without the structural definition obtained from high-resolution imaging techniques, the role of thermography is limited. This imaging modality is not currently covered by CMS.

Intravascular Magnetic Resonance Imaging

Plaque characterization by IMRI may be useful in the detection of plaques with necrotic core and intraplaque hemorrhage. In this technique, an intravascular coil is inserted into the artery or the adjacent vein. IMRI yields adequate resolution to discriminate plaque components, including lipid, collagen, thrombus, and calcium on the basis of biochemical properties. Technical limitations exist in the IMRI coil designs, however, requiring multiple catheter manipulations and repeated imaging. Image quality is also reduced significantly as the intravascular coil moves off axis from the external magnet field. This imaging modality is not currently covered by CMS.

Scope of the Review

The purpose of this review is to systematically evaluate the comparative effectiveness of intravascular diagnostic techniques versus angiography alone, as well as among different intravascular diagnostic techniques, in patients with CAD undergoing PCI with stent deployment. Also, this review aims to evaluate factors influencing the effect of intravascular diagnostic techniques compared to angiography alone (or different intravascular diagnostic techniques) on outcomes. The utility of a medical diagnostic technique is usually determined by its indirect effect on outcomes, that is, through its influence on therapeutic decisionmaking, intermediate outcomes, and subsequently, on patient-centered outcomes.

Key Questions

Our review focused on the following five Key Questions:

Key Question 1: In patients with CAD, what is the impact of using an intravascular diagnostic technique and angiography in deciding whether a coronary lesion requires intervention—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 2: For patients undergoing PCI, what is the impact of using an intravascular diagnostic technique and angiography to guide the PCI procedure (either immediately prior to or during the procedure)—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 3: For patients having just undergone a PCI, what is the impact of using an intravascular diagnostic technique and angiography to evaluate the success of PCI immediately after the procedure—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 4: How do different intravascular diagnostic techniques compare to each other in their effects on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

a) During evaluation of the presence/extent of CAD and the potential necessity of coronary intervention?
b) During PCI to guide stent placement?
c) Immediately after PCI to evaluate the success of stent placement?

Key Question 5: What factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) influence the effect of intravascular diagnostic techniques and angiography —when compared to angiography alone (or among different intravascular diagnostic techniques)—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

a) During diagnostic coronary angiography for the evaluation of the presence/extent of CAD and the potential need for coronary intervention?
b) During PCI to guide the procedure?
c) Immediately after PCI to evaluate the success of PCI?

Methods

This comparative effectiveness review (CER) evaluates the effects of intravascular diagnostic technique (intravascular diagnostic) applications compared with angiography alone in patients with coronary artery disease (CAD). The Evidence-based Practice Center (EPC) reviewed the existing body of evidence on the effects of intravascular diagnostic applications compared with angiography alone on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes in the management of patients with CAD and undergoing PCI with stent placement. This report is based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) *Methods Guide for Comparative Effectiveness Reviews*.[15]

AHRQ Task Order Officer

The AHRQ Task Order Officer (TOO) assigned to this project was responsible for overseeing all aspects of this report. The TOO facilitated a common understanding among all parties involved in the project, resolved ambiguities, and fielded all EPC queries regarding the scope and processes of the project. The TOO and other staff at AHRQ reviewed the report for consistency, clarity, and to ensure that it conforms to AHRQ standards.

External Expert Input

During a topic refinement phase, the initial questions that had previously been nominated for this report were refined with input from a panel of Key Informants. Key Informants included experts in interventional cardiology, interventional radiology, noninterventional cardiology, and representatives from relevant specialty societies, payors, and a patient representative. After a public review of the proposed Key Questions, the clinical experts were reconvened to form the Technical Expert Panel (TEP), which served in an advisory capacity to help translating the Key Questions into a research protocol, identify important issues, and define parameters for the review of evidence. Discussions among the EPC, TOO, and Key Informants (and subsequently, the TEP) occurred during a series of teleconferences and via email. In addition, input from the TEP was sought during preparation of the report when questions arose concerning the scope of the review.

Key Questions

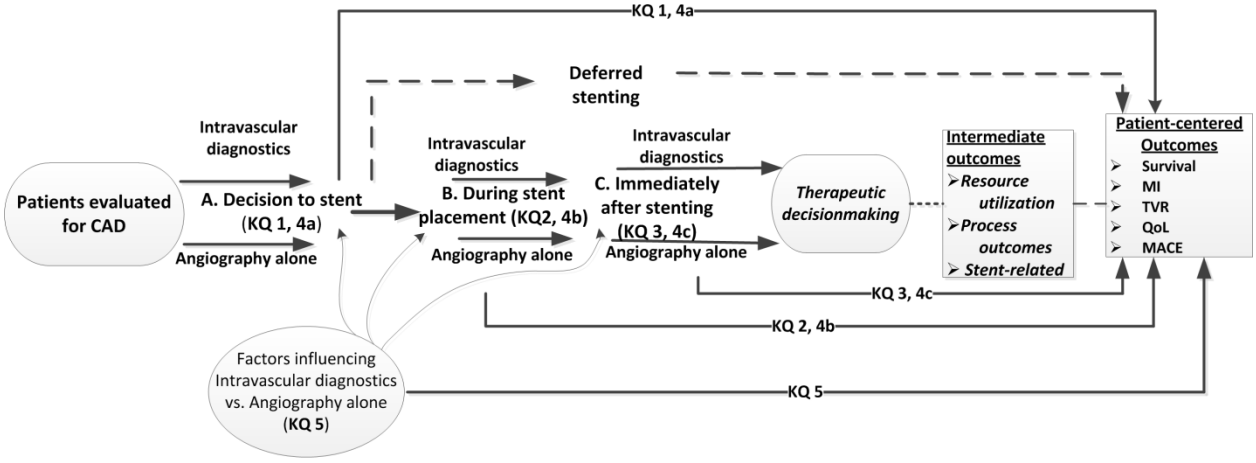
Five Key Questions were posed. Four pertained to outcomes in patients with CAD on the use of intravascular diagnostic applications when compared to angiography (Key Questions 1-3), or different intravascular diagnostic techniques (Key Questions 4), and one (Key Question 5) addressed associations between factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) that could influence the effect of intravascular diagnostic techniques compared to angiography (or among different intravascular diagnostic techniques) on outcomes. The exact wording of the Key Questions has been described in the Introduction.

Analytic Framework

We developed an analytic framework (**Figure 1**) that maps the Key Questions within the context of the populations of interest, the interventions, comparator, and the outcomes of interest,

and the chain of logic that evidence must support to link the interventions to improved health outcomes. The figure illustrates how intravascular diagnostic techniques— compared with angiography alone—may aid in decisions to stent coronary lesions (**A** in **Figure 1**), allow optimization of stent placement during PCI (**B** in **Figure 1**), and assessment of immediate results in patients after stent deployment to decide the need for additional procedures (**C** in **Figure 1**), and improve short-term (in hospital or discharge to 30 days), medium-term (>30 days to 1 year), and long-term (>1 year) outcomes. Angiography alone is the comparator for Key Questions 1–3. For Key Question 4, the comparator is a different intravascular diagnostic technique from the index intravascular diagnostic technique of interest (head-to-head comparisons of intravascular diagnostic techniques). For Key Question 5, the modifiers of treatment effect included patient/physician characteristics, availability of prior noninvasive testing, and the type of PCI performed.

Figure 1. Analytic framework



CAD = coronary artery disease; KQ = key question; MACE = major adverse cardiac events, MI = myocardial infarction, QoL = quality of life, TVR = target vessel revascularization.

Literature Search

We conducted literature searches for studies in MEDLINE® (from inception to May 19, 2011) and the Cochrane Central Trials Registry® (through the 2nd quarter of 2011) without any language restriction. All studies conducted in adult human subjects were screened to identify articles relevant to each Key Question. Our search included terms for intravascular diagnostic techniques, myocardial ischemia, revascularization, stents, and relevant research designs (see **Appendix A** for complete search strings). We also reviewed the reference lists from recently published systematic reviews on intravascular diagnostic techniques for potentially eligible studies. We excluded narrative reviews, editorials, and letters to the editor.

With input from the TEP, we compiled a list of professional organization meetings that published oral presentations and poster abstracts on intravascular diagnostic techniques addressing our Key Questions. We retrieved and screened relevant abstracts from professional

and summit conference meetings that were available online through the following resources: Transcatheter Cardiovascular Therapeutics (TCTMD.com) indexed until November 2011, the American Heart Association (AHA.org) indexed from 2009 through November 2011, and the American College of Cardiology (Cardiosource.com) indexed from 2009 through November 2011. We also searched the ClinicalTrials.gov Web site to identify ongoing trials.

Study Selection and Eligibility Criteria

We screened titles and abstracts of citations identified from our literature search using the predefined eligibility criteria. The titles and abstracts were initially screened by one investigator; rejected abstracts were rescreened by a second investigator. Abstracts equivocal for inclusion would trigger an automatic full-text review. Full-text articles of abstracts that met screening criteria were retrieved and examined by two investigators to confirm their eligibility. All disagreements were resolved in consultation with a senior investigator. Full-text articles published in non-English languages were translated using Google™ Translate (http://translate.google.com). We focused only on direct comparative studies for this review. We excluded studies of indirect comparisons or that lacked a distinct comparator group. Eligibility criteria for inclusion were as follows.

Populations and Conditions of Interest

We included studies conducted in adults (≥18 years) with CAD who were undergoing PCI with stent deployment. We included the following conditions of interest, if reported in individual studies: CAD due to intermediate coronary stenoses (40 to 70 percent), either ischemic or nonischemic; left main artery lesions; any type of complex coronary lesions (e.g., long diffuse lesions, tandem lesions, bypass conduit vessel lesions, bifurcation lesions, total occlusions, ostial lesions, stent thromboses, thrombotic and nonthrombotic lesions); types of acute coronary syndrome (ST segment elevation myocardial infarction [STEMI] and non-STEMI); unstable and stable angina; in-stent restenosis; and stent fractures.

Additional subgroups of interest for all Key Questions included: patients with and without diabetes; patients with chronic inflammation (e.g., systemic lupus erythematosus); patients with atherosclerosis following heart transplantation.

Interventions

For all Key Questions, we included intravascular diagnostic techniques that evaluate morphological or physiological parameters of coronary lesions and are presently employed in clinical care. The most commonly employed intravascular diagnostic techniques included FFR and IVUS. If available, also included were interventions that are primarily investigational at present, such as VH-IVUS, OCT, elastography, NIRS, thermography, angioscopy, and intravascular MRI, and techniques measuring stenosis index and index of microcirculatory resistance.

For Key Question 5, the modifiers of treatment effect included patient/physician characteristics, availability of prior noninvasive testing, and the type of PCI performed.

Comparators

Coronary angiography was the comparison of interest for Key Questions 1–3 and 5. For Key Questions 4 and 5, head-to-head comparisons of two or more intravascular diagnostic techniques were included.

Outcomes

The outcomes of interest were first categorized as either changes in therapeutic decisionmaking, intermediate outcomes, or patient-centered outcomes. Outcomes were measured at three time points: short-term (up to 30-day of procedure), medium-term (>30 days to 1 year), and long-term (>1 year).

- Therapeutic decisionmaking *Key Question 1*: In patients with CAD, the change in the number of hemodynamically significant lesions after the application of intravascular diagnostic, and the change in the decision about an interventional therapy (e.g., if stenting is needed) after the application of intravascular diagnostic
- *Key Question 2*: During PCI, the change in the type of stent or number of stents or length of stent after the application of intravascular diagnostic
- *Key Question 3*: Immediately after PCI, the change in the decision about the need for reintervention planned before intravascular diagnostic changed after the test

Intermediate Outcomes

- Process outcomes (technical success rates assessed by quantitative coronary angiography [QCA], such as proportion of successful completion of attempted procedures or proportion of interpretable results in completed procedures, total procedural time required, fluoroscopy time, and volume of contrast medium used)
- Periprocedural complications (e.g., vessel dissection, bleeding, repeat PCI, or emergency coronary bypass surgery)
- Resource utilization (e.g., number of guide catheters, wires, balloons, and stents)
- Stent-related complications (e.g., restenosis, acute stent thrombosis, and dissection)
- Other measures (e.g., cardiac imaging findings [such as ventricular function or myocardial perfusion], electrocardiographic ischemia, biochemical markers, noninvasive assessment using magnetic resonance imaging, and a high-intensity signal on Doppler flow wire during PCI)

Patient-centered outcomes

- Clinical outcomes that directly affect patient well-being or clinical status (e.g., death, MI, revascularization or composites of major adverse cardiac events [MACE], freedom from angina, quality of life, and quality-adjusted survival)

Sample Size and Timing

We did not specify a minimum sample-size threshold. We included studies of any duration of followup.

Eligible Study Designs

We included all comparative studies, including randomized controlled trials (RCTs) and nonrandomized comparative studies that provide data directly comparing intravascular diagnostic technique and angiography with angiography alone or one intravascular diagnostic technique with another. We excluded narrative reviews and case reports that included less than five patients.

Settings

Application of intravascular diagnostic techniques and use in the following settings were considered: tertiary care centers or community hospitals; in-hospital or stand-alone catheterization laboratories; and emergency or nonemergency catheterizations.

Data Extraction

Each study extraction was conducted by one investigator and reviewed by at least one other. Any disagreements were resolved by discussion in team meetings. Data were extracted into standard forms in Microsoft® Word. The basic elements included fields that addressed population characteristics, sample size, study design, analytic details, and outcomes.

We extracted data including basic demographics (such as age, sex, race); comorbidities (such as diabetes, hypertension); clinical characteristics (such as percent ejection fraction, location of stenosis, lesion type); and modifying factors associated with the application of intravascular diagnostic and outcomes. We tested the extraction form on several studies and revised the form as necessary before commencing full data extraction of all articles.

Data Synthesis

To evaluate the effect of an intervention on outcomes, we performed DerSimonian and Laird random effects model meta-analyses of the risk ratio of binary data or mean differences of continuous variables between interventions where there were at least three studies that were deemed to be sufficiently similar in population and had the same comparison of interventions and the same outcomes. For each specific outcome of interest, we performed separate meta-analyses at specific time points (i.e., in-hospital, ≤1 year, and >1 year), chosen based on available relevant data. We sought input from the clinical expert (cardiologist) on our team to assess whether studies were too clinically heterogeneous for meta-analysis to be appropriate. For example, if target vessel revascularization was not reported, we used target lesion revascularization.

When possible, we preferentially evaluated the net change of continuous outcomes (the difference between the intervention of interest and the control intervention in the changes between final and baseline values). However, a large number of studies did not report full statistical analyses of the net change. Where sufficient data were reported, we calculated the net change values and estimated their standard error (SE) from reported standard deviations (or standard errors) of baseline and/or final values. For outcomes that were reported as final measurements, we conducted the weighted mean difference meta-analyses between final measurements. For each meta-analysis the statistical heterogeneity was assessed with the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance. We performed sensitivity meta-analyses by excluding studies that were rated

to have high risk of bias to see if these studies impacted inferences drawn from syntheses of studies with low and medium risk of biases only.

The findings of the report were presented according to the order of the Key Questions. Within each Key Question, findings were presented separately for therapeutic decisionmaking, intermediate, and patient-centered outcomes. They were further categorized by specific time periods: short term (in hospital, discharge to 30 days), medium-term (>30 days to 1 year), and long-term (>1 year). Outcome data were presented in evidence tables and were summarized in the full text and the Executive Summary of the report. All included studies were summarized in narrative form and in summary tables, which tabulated the important features of the study populations, design, intervention, outcomes, and results. We did not conduct statistical analyses to assess publication bias.

Summary Tables

Summary tables succinctly report measures of the main outcomes evaluated. We included information regarding study design, intravascular diagnostic technique, country, age data, gender data, sample size, study duration, patients' medical characteristics, and study quality. For continuous outcomes, we included the mean outcome values, their 95 percent confidence intervals (CI), standard deviations (SD) or other measures of variability, and when available, the mean difference (between groups) and its corresponding P value or CI, as appropriate. For categorical (dichotomous) outcomes, we reported the number of events and total number of patients for each intervention and relative risk metrics (odds ratios, risk ratios or hazard ratios) with their corresponding 95 percent CI and associated P value. We created separate summary tables based on the type of interventions and the type of outcomes.

Risk of Bias (Overall Methodological Quality) of Individual Studies

We assessed the risk of biases (methodological quality) for each individual study using the assessment instrument detailed by the Agency for Healthcare Research and Quality in its *Methods Guide for Effectiveness and Comparative Effectiveness Review,* hereafter referred to as "the Methods Guide."[15] Briefly, we rated each study as being of high, medium, or low risk of bias on the basis of their adherence to well-accepted standard methodologies for studies such as Cochrane risk of bias tool for intervention studies, and assessed and reported each methodological quality item for all qualifying studies (Yes, No, or Unclear/Not reported). The overall judgment of risk of bias was based on study conduct by evaluating selection, performance, attrition, detection, and selective outcome reporting. Two independent reviewers evaluated the risk of bias for each study, and all disagreements were resolved in consensus with a third reviewer.

Grading the Body of Evidence

We graded the strength of the body of evidence for each analysis within the Key Questions as per the Methods Guide[15] and an updated methods paper,[16] with modifications as described below. Risk of bias (overall methodological quality) of individual study was assessed as described previously. We assessed the consistency of the data as either "no inconsistency" or "inconsistency present" (or "not applicable" if only one study). The direction, magnitude, and statistical significance of all studies were evaluated in assessing consistency, and logical explanations were provided in the presence of equivocal results. We also assessed the precision

and sparseness of the evidence. We considered evidence to be sparse if only one study of a small sample size addressed the analysis. Because this review assessed many outcomes (surrogate, stent-related, and clinical outcomes), the overall strength of evidence evaluation was based on patient-centered clinical outcomes, which we broadly define here as any outcomes that affect the patient's well-being.

We rated the strength of evidence with one of the following four strengths (as per the AHRQ methods guide): High, Moderate, Low, and Insufficient. Ratings were assigned based on our level of confidence that the evidence reflected the true effect for the major comparisons of interest. Ratings were defined as follows:

High: There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. No important scientific disagreement exists across studies.

Moderate: There is moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. Little disagreement exists across studies.

Low: There is low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. Underlying studies may report conflicting results.

Insufficient: Evidence is either unavailable or does not permit a conclusion. There are sparse or no data. (In general, the evidence is considered insufficient when only one study has been published, unless the study was particularly large, robust, and of good quality.)

These ratings provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, they by necessity may oversimplify the many complex issues involved in the appraisal of a body of evidence. It is important to remember that the individual studies evaluated in formulating the composite rating differed in their design, reporting, and quality. The strengths and weaknesses of the individual reports, as described in detail in the text and tables, should also be taken into consideration.

Assessing Applicability

We assessed applicability of studies using the individual study eligibility criteria and baseline characteristics of the included population. Characteristics that could affect applicability to a wide population included narrow study eligibility criteria (e.g., narrow range of demographics) and dated studies using practices that are no longer applicable to contemporary practices. We also summarized how well the evidence applies to clinical practice. We provided an overall summary table describing key conclusions about applicability of bodies of evidence, and also provided comments on specific issues that affected applicability.

Protocol Registration

A comparative effectiveness review protocol was submitted and published on the AHRQ Effective Health Care Program Web site on August 29, 2011 (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-

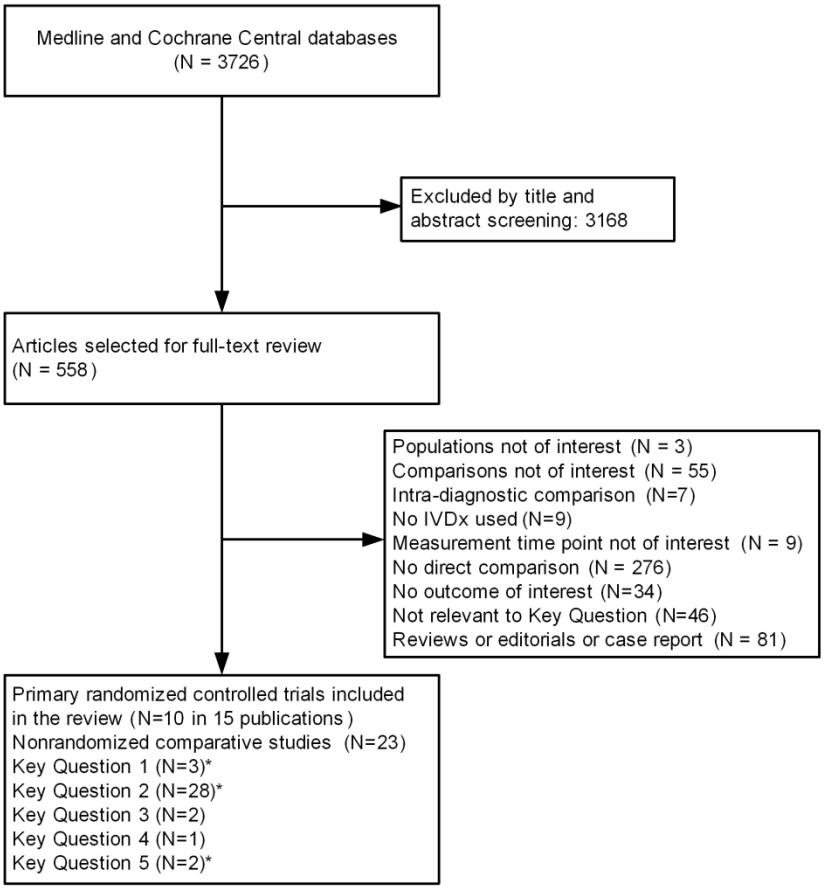
reports/?pageaction=displayproduct&productid=766). Some minor amendments to the posted protocol were made at the time of preparation of this draft. These included a slight rewording of the Key Questions (e.g., PCI replaced by stenting), and a restructuring of the outcome categories (short-, intermediate-, and long-term outcomes were changed to therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes).

Results

The literature search yielded 3726 citations. From these, 558 articles were provisionally accepted for review on the basis of the abstracts and titles (**Figure 2**). After screening their full texts, 33 studies, published in 39 articles, were judged to have met the inclusion criteria. The grey literature search yielded no additional studies. The most common reason for article rejection was that there were no direct comparisons between intravascular diagnostic techniques and angiography (276 articles). The other reasons for rejection included ineligible publication types, such as reviews or case reports (81 articles); irrelevant comparators (e.g., intravascular diagnostic compared with cardiac computed tomography; 55 articles); failing to address the Key Questions (46 articles); irrelevant outcomes (34 articles); no intravascular diagnostic techniques used (9 articles); within diagnostic technique comparisons (e.g., comparison between different criteria of the same diagnostic technique; 7 articles); irrelevant or incomplete measurement time points (e.g., comparison between intravascular diagnostic techniques and angiography only at followup; 9 articles); and no population of interest (3 articles). See **Appendix B** for a list of the excluded studies with the reason for exclusion.

The 33 accepted, nonoverlapping studies (in 39 articles) had data addressing at least one of the five Key Questions are available for IVUS and FFR, and no comparative studies are available for the remaining investigational intravascular diagnostic techniques. Summary Tables with the descriptions and results of each study are in **Appendix C**.

Figure 2. Literature flow diagram



* Indicates some overlapping studies across Key Questions

Key Question 1

In patients with CAD, what is the impact of using an intravascular diagnostic technique and angiography in deciding whether a coronary lesion requires intervention–when compared to angiography alone–on therapeutic decisionmaking, intermediate outcomes and patient-centered outcomes?

Key Points

- Three studies, including one RCT (Fractional Flow Reserve versus Angiography for Multivessel Evaluation [FAME] trial in three publications) and two nonrandomized studies reported data comparing FFR-guided stenting with stenting guided by angiography alone.
- There is a moderate strength of evidence favoring the adjunctive use of FFR during angiography in deciding to stent an intermediate coronary lesion (≥50 percent), using an FFR threshold <0.80.

- The evidence supporting the adjunctive use of FFR during angiography in deciding to stent an intermediate coronary lesion was derived from studies that focused on men with intermediate coronary disease and lower grade angina, and excluded patients with left main disease.
- There is insufficient evidence regarding the use of any techniques other than FFR, as none of the studies reviewed techniques other than FFR to decide whether a coronary lesion required stenting.

Overall strength of evidence

Overall, there is a moderate strength of evidence favoring the adjunctive use of FFR during angiography in deciding to stent an intermediate coronary lesion (≥50 percent), using an FFR threshold <0.80. The evidence was derived from studies that focused on men with intermediate coronary disease and lower grade angina, and excluded patients with left main disease.

For therapeutic decisionmaking, there is a moderate strength of evidence that the adjunctive use of FFR during angiography aids in deciding whether to stent a coronary lesion, and which coronary vessels to stent, as compared with angiography alone. For intermediate outcomes, there is a moderate strength of evidence that the use of FFR reduces resource utilization in the short-term, as compared with angiography alone; however, the strength of evidence is insufficient for QCA and stent-related outcomes, as the reviewed studies did not report these outcomes at any time point. For patient-centered outcomes, there is a moderate strength of evidence that the use of FFR, as compared with angiography alone, improves combined clinical endpoints (e.g., death or MI and MACE) in the medium- and long-terms. There is insufficient reporting of patient-centered outcomes in the short-term.

With respect to Key Question 1, there is insufficient evidence regarding the use of any technique aside from FFR, as none of the studies reviewed any other technique.

Available evidence

We identified three studies evaluating the use of FFR to decide whether a coronary lesion needs intervention, as compared with angiography. No eligible studies on other intravascular diagnostic techniques were found to address this Key Question. Three studies in five publications compared the use of FFR-guided stenting with stenting guided by angiography alone.[17-21] One RCT (with three publications), the FAME trial, followed 1005 adult patients with at least a ≥50% diameter stenosis in two or more major epicardial vessels, over 2 years.[17,19,20] Also included were patients with a recent nonST-segment elevation MI for less than 5 days if their peak CK-MB was <1000 IU or if they had undergone PCI in the past. Excluded were patients with left main coronary artery disease, previous CABG, or a recent ST-segment elevation MI within 5 days. The average age of these patients was 64 years, and the proportion of included men was 74 percent. The proportion of patients with diabetes was 25 percent, hypertension 67 percent, and dyslipidemia 73 percent. The majority of patients had Canadian Cardiovascular Society angina grade I to III; less than 20 percent of the included patients had grade IV angina. After randomization, patients in the FFR-guided PCI group had drug-eluting stent implantation only if the FFR was 0.80 or less in epicardial vessels that demonstrated a ≥50% diameter stenosis by angiogram. In the angiography-guided PCI group, all patients underwent drug-eluting stent implantation. The choice of stent implantation was at the discretion of the surgeon. The FAME trial was rated as being at a low risk of bias.

Two nonrandomized studies compared the use of FFR-guided stenting with stenting guided by angiography alone.[18,21] One followed 137 patients prospectively for more than 2 years.[21] In this study, patients who had stable angina with stenoses in two or more coronary arteries were included; excluded patients were those who had undergone a previous CABG, experienced a recent acute MI, or those with an ejection fraction <50 percent. The average age of included patients was 62 years; the majority were men (77 percent). The proportion of patients with diabetes was 38 percent, hypertension 74 percent, and dyslipidemia 63 percent. The study lacked data on other baseline characteristics. The study was rated as being at a medium risk of bias due to the lack of adjusted analyses.

The second nonrandomized study followed 154 consecutive first-time acute MI patients with totally occluded lesions (142 of the 155 total stenotic lesions).[18] Patients in the intervention group were prospectively followed for 2 years; however, the comparison group was a historical cohort from the same single-center. The average age of included patients was 63 years; the majority were men (76 percent). The proportion of patients with diabetes was 16 percent and dyslipidemia 23 percent. The proportion of patients with LAD culprit stenoses was significantly higher in the FFR-guided stenting compared with stenting guided by angiography alone. The proportion of patients with hypertension was not documented, and the study lacked data on other baseline characteristics. The study was rated as being at a high risk of bias due to comparisons to a historical control and the lack of adjusted analyses.

Therapeutic Decisionmaking

All three studies included for KQ1[17-21] reported data for therapeutic decisionmaking outcomes comparing FFR-guided stenting with stenting guided by angiography alone.

The diagnostic and therapeutic decisions with regards to changing the type of PCI were made on the basis of FFR threshold, which varied considerably across all three studies. Stent implantation was conducted in 63 percent of the 1387 lesions with an FFR of 0.80 or less among patients randomly assigned to FFR-guided PCI in the FAME trial (no stents were placed in the remaining 37 percent of the lesions with FFR >0.80).[20] In the prospective nonrandomized comparative study, PCI was deferred in 75 vessels (58%) of the total 128 vessels (57 total number of enrolled patients; mean FFR of 0.86) in the FFR-guided PCI group; the remaining 53 vessels (48 patients; mean FFR of 0.67) underwent PCI and stenting.[21] In the prospective nonrandomized comparative study with a historical comparator, stent implantation was performed in 40 lesions (FFR <0.94); the remaining 37 lesions (FFR≥0.94) underwent direct angioplasty without stenting.[18]

Intermediate Outcomes

Resource Utilization

In the FAME trial, the number of hospital days at baseline admission was significantly lower in the FFR-guided group, as compared with the group who received stenting guided by angiography alone (3.4 versus 3.7 days; P = 0.05).[20] The remaining two nonrandomized comparative studies did not report this outcome.[18,21]

None of the included studies reported data on medication use during the procedural time period. The number of stents implanted per patient was significantly lower in the FFR-guided group, as compared with the group receiving stenting guided by angiography alone, in both the FAME trial[20] and in one prospective nonrandomized comparative study.[21] The number of stents

implanted per patient was 1.9 versus 2.7in the FAME trial,[20] and 1.04 versus 1.28 in the prospective nonrandomized study.[21] The second prospective nonrandomized study (with a historical control) did not report this outcome.[18]

The cost of procedure was reported in all three studies.[18,20,21] The total cost of the procedure, including materials used during PCI, was significantly lower in the FFR-guided group, as compared with the group who received stenting guided by angiography alone, in all three studies. Both the FAME trial and one prospective nonrandomized study reported cost individually per material used during PCI.[17,21] In the FAME trial, individual cost per material was lower with FFR-guided stenting than in with angiography-guided stenting, although no formal statistical comparisons of individual cost per material were reported between groups. In the prospective study, the cost of the guidewires was significantly higher in the FFR-guided stenting group; however, this was off-set by the increased use and cost of balloons and stents in the group whose stents were guided by angiography alone.[21]

There were no significant differences in procedure time between the groups, based on the findings of the FAME trial[20] and one prospective nonrandomized comparative study.[21] In the FAME trial, contrast use was significantly lower in the FFR-guided stenting than in the angiography-guided stenting (272 ml versus 302 ml; P<0.001). However, no significant difference in the use of contrast was observed between the two groups in the nonrandomized comparative study. Radiation exposure time was similar between the two groups in this study.

QCA Process Outcomes

Two nonrandomized comparative studies, reported data for in-hospital process outcomes comparing FFR-guided stenting with stenting guided by angiography alone.[18,21] The FAME trial did not report process outcomes assessed by QCA.

The net changes in the minimal lumen diameter measurements of the FFR and angiography alone groups, from baseline to postprocedure, reported in two prospective nonrandomized comparative studies, was inconsistent.[18,21] One was rated as being at a medium risk of bias, and reported no significant difference between the two groups ((MLD net difference 0.02 mm; NS and diameter stenosis net difference 1%; NS).[21] The second, with a historical control and rated as being at a high risk of bias, reported an unfavorable effect for FFR-guided stenting over stenting guided by angiography alone (MLD net difference -0.3 mm; P<0.001 and diameter stenosis net difference 9.0%; P<0.001).[18]

The net changes in percent diameter stenosis measurements between the FFR-guided group and the group who received stenting guided by angiography alone, from baseline to postprocedure (reported in two prospective nonrandomized studies), were inconsistent.[18,21] One (rated as being at a medium risk of bias) reported no significant difference in percent diameter stenosis between the groups. The second (with a historical control; rated as being at a high risk of bias) reported a favorable effect for FFR-guided stenting over stenting guided by angiography alone (percent diameter stenosis net difference -0.3 mm; P<0.001).[18]

Stent-Related Outcomes

One prospective nonrandomized comparative study with a historical control reported nonsignificantly higher rates of reocclusion and restenosis with FFR-guided stenting, as compared with stenting guided by angiography alone.[18] None of the included studies reported data on acute stent thrombosis.

Patient-centered Outcomes

There was no incidence of in-hospital complications of CABG or death reported in any of the three included studies.[18,20,21] Only one study (nonrandomized) reported data on repeat target lesion revascularization during in-hospital stay, and found no statistically significant difference between groups.[21]

The FAME trial did not report in-hospital death.[20] The trial reported periprocedural infarctions diagnosed on the basis of increases in creatinine kinase (CK)-MB (three to five times the upper limit of normal) as 2.4 percent in the FFR-guided stenting versus 3.2 percent angiography-guided stenting.[19] The FAME trial reported the absolute mean difference of MACE at discharge as -2.2 percent between the two groups (no statistical significance was provided).[19] One of the nonrandomized comparative studies, reported a nonsignificantly lower proportion of in-hospital non-Q wave MI and cumulative MACE with FFR-guided stenting, as compared with stenting guided by angiography alone.[21] The prospective nonrandomized comparative study (with a historical comparator) reported no cardiac deaths during in-hospital stay.[18]

All three studies reported no significant difference between groups in long-term all-cause mortality rates.[18,20,21] The incidence of MI was similar and showed no significant difference between groups in the FAME trial (at 1-year) and in one prospective nonrandomized study.[20,21] In the FAME trial, the FFR-guided stenting group displayed a significant decrease in the composite outcome of death or MI (Relative risk [RR] 0.66, 95 percent confidence interval [CI] 0.44, 0.98 at 1-year and RR 0.65, 95 percent CI 0.45, 0.94 at 2-year) and MI only at 2-year (RR 0.62, 95 percent CI 0.40, 0.95), as compared with the group receiving stenting guided by angiography alone.[19,20] Both the FAME trial (at 1-year followup,[20] but not at 2-year) and one prospective nonrandomized study[21] (at more than 2-year followup) reported a point estimate indicating a favorable effect for FFR-guided stenting, as compared with stenting guided by angiography alone, for the outcomes of repeat revascularization and MACE. However, at 2-year followup of the FAME trial, relative risk was nonsignificant for both of these outcomes.[19]

Only the FAME trial reported data on patient-reported outcomes, including the number of patients free from angina, composite endpoint of the number of patients without event and free from angina, and intake of antianginal medications at 1- and 2-year followup.[19,20] The trial also reported the European Quality of Life-5 Dimensions (EQ-5D) score, but only at 1-year followup. Although a higher proportion of patients were without an event and were free from angina (73% in the FFR-guided stenting group versus 68% in the group receiving stenting guided by angiography alone), there was no significant difference between the groups for all patient-reported outcomes.

Key Question 2

For patients undergoing PCI, what is the impact of using an intravascular diagnostic technique and angiography to guide stent placement (either immediately prior to or during the procedure)—when compared to angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Points

- Nine RCTs (11 publications) and 18 nonrandomized studies compared IVUS-guided stent deployment to stenting guided by angiography alone.
- When using IVUS to guide stent deployment, there is a moderate strength of evidence that supports a significant reduction in target vessel revascularization (TVR) and restenosis, but no significant difference in mortality and MI, as compared with angiography alone.
- The evidence supporting adjunctive use of IVUS during angiography to guide stent deployment was derived mostly from studies conducted before 2000 that focused on men, excluded patients with left main disease (LMD) and acute MI, and used a previous generation of bare-metal stents.
- There is insufficient evidence for all techniques other than IVUS (one available study regarding the use of FFR, and no studies for all other techniques) to guide and optimize stent deployment.

Overall strength of evidence

Overall, there is a moderate strength of evidence that supports a significant reduction in target vessel revascularization (TVR) and restenosis, but no significant difference in mortality and MI, when using IVUS to guide stent deployment, as compared with angiography alone. The evidence was derived mostly from studies conducted before 2000 that focused on men, excluded patients with left main disease (LMD) and acute MI, and used a previous generation of bare-metal stents. With regards to therapeutic decisionmaking, there is a moderate strength of evidence that the use of IVUS during PCI can aid the operator in optimizing stent deployment, as compared with angiography alone. For intermediate outcomes, there is a moderate strength of evidence that the use of IVUS during PCI to optimize stent deployment increases resource utilization in the short-term, reveals no statistically significant differences in QCA outcomes in the short- and medium-terms, and lowers the risk of stent-related outcome of restenosis in the medium-term, as compared with angiography alone. For patient-centered clinical outcomes, there is a moderate strength of evidence that supports no significant difference in mortality, MI, and MACE, but reveals a significant benefit in decreasing TVR, when using IVUS to guide bare-metal stent deployment, as compared with angiography alone.

There is insufficient evidence from one nonrandomized study regarding the use of FFR in determining the need for additional therapy (dilation) after stent deployment. There is insufficient evidence for all other techniques to answer Key Question 2, as no comparative studies evaluated techniques other than IVUS and FFR.

Available evidence

We identified 28 studies reporting direct comparisons of two intravascular diagnostic techniques, IVUS (27 studies) and FFR (1 study), with angiography alone in optimizing stent deployment.

IVUS Versus Angiography Alone in Stent Deployment

We identified nine RCTs (in 11 publications)[22-32] and 18 nonrandomized comparative studies[33-50] comparing IVUS-guided stent deployment with stenting guided by angiography alone.

Two RCTs were rated as being at a low risk of bias,[28,31] six at a medium risk of bias,[22,24-26,30,32] and one at a high risk of bias.[27] Among the RCTs, sample sizes ranged from 42 to 800, and the average ages of patients ranged from 55 to 66 years. Followup durations ranged from 6 months to 2.5 years. The proportion of men ranged from 62 to 100 percent. The proportion of patients with diabetes ranged from 7.5 to 100 percent (9 RCTs). The proportion of patients with dyslipidemia ranged from 42 to 94.5 percent (9 RCTs), and those with hypertension ranged from 22 to 69.5 percent (9 RCTs). All but one RCT[26] excluded patients with left main coronary artery disease or AMI. All but two RCTs recruited patients before the year 2000;[25,26] both were conducted in Eastern Europe. One RCT evaluated PCI with long stent implantation.[30]

Among the18 included nonrandomized comparative studies, eight nonrandomized comparative studies were rated as being at a high risk of bias,[36-39,45,46,48,50] while the rest at a medium risk of bias.[33-35,40,41,43,44,47-49] Five were conducted prospectively[34,37,40,44,49] and eight retrospectively,[33,35,36,38,41,42,46] four were registry-based (two single center and two multicenter),[39,43,47,48] and one was cross-sectional.[50] Sample sizes ranged from 34 to 9070, and the average ages of patients ranged from 55 to 66 years (15 studies). Followup durations ranged from 30 days to 3 years. The proportion of patients with diabetes ranged from 7.1 to 47.1 percent (18 studies). The proportion of patients with dyslipidemia ranged from 25.5 to 91.2 percent (17 studies[33-48,50]). The proportion of patients with hypertension ranged from 19 to 91.2 percent (17 studies[33-48,50]). Three of the 18 total nonrandomized comparative studies excluded patients with left main coronary artery disease (LMD) or acute MI.[34,46,47] One evaluated patients with only acute MI;[39] one compared patients with distal and nondistal LMD;[46] and two others included patients with only unprotected LMD.[42,48]

In total, 27 studies reported data for in-hospital outcomes (nine RCTs and 18 nonrandomized comparative).[22,24-28,30-50] Reported in-hospital outcomes of interest included clinical outcomes, diagnostic and therapeutic decisionmaking, process outcomes, periprocedural complications, and stent-related outcomes. Short-term outcomes (30 day outcome) was reported in four studies (two RCTs[28,30] and two nonrandomized comparative[39,43]). Medium-term outcomes (>30 days to 1 year) were reported in 20 studies (seven RCTs[22,23,25,28,30-32] and 13 nonrandomized comparative studies[33-45]), and long-term outcomes (>1 year) were reported in 6 studies (three RCTs[22,24,26,29] and three nonrandomized comparative studies[46-48]).

Therapeutic Decisionmaking

Three RCTs[28,31,32] and three nonrandomized comparative studies[37,42,46] reported data on optimizing stent placement. In the RCTs, a significantly higher proportion of patients achieved optimal stent placement on the basis of IVUS guidance;[28] almost one-half of the patients received further therapy for an unexpanded stent and repeat balloon angioplaty;[31]and more than

one-third underwent overdilation due to not reaching the IVUS criterion[32] in the IVUS-guided PCI group as compared with the angiography-guided PCI group.

Similar IVUS-guided-optimized-stent-deployment results were reported in three nonrandomized comparative studies, which included additional postdilation, debulking, and angioplasty, or a second stent deployment.[37,42,46]

Intermediate Outcomes

Resource Utilization

Meta-analysis of these four RCTs[25,26,28,30] revealed a nonstatistically significant increase in the use of glycoprotein IIb/IIIa inhibitor in the IVUS-guided PCI group (summary RR 1.27; 95 percent CI 0.76, 2.12), with statistically significant heterogeneity (I^2 = 42.3 percent).

Across four RCTs[22,24,26,28] and two nonrandomized comparative studies[35,50] reporting data on procedure time, two RCTs[22,24] and one nonrandomized comparative study[50] reported significantly longer procedure time in IVUS-guided stenting compared with stenting guided by angiography alone, while two other RCTs[18,20] and a nonrandomized comparative study reported no significant difference between groups.[35]

Three RCTs[22,26,28] and one nonrandomized comparative study[50] reported significantly longer fluoroscopy time in IVUS-guided stenting over stent deployment guided by angiography alone, while the other nonrandomized comparative study reported no significant difference between the two groups.[35]

Two RCTs[22,24] reported a significantly increased volume of contrast medium used in IVUS-guided stenting over stenting guided by angiography alone, while the remaining RCT[22] and both nonrandomized comparative studies[35,50] reported no significant difference between groups.

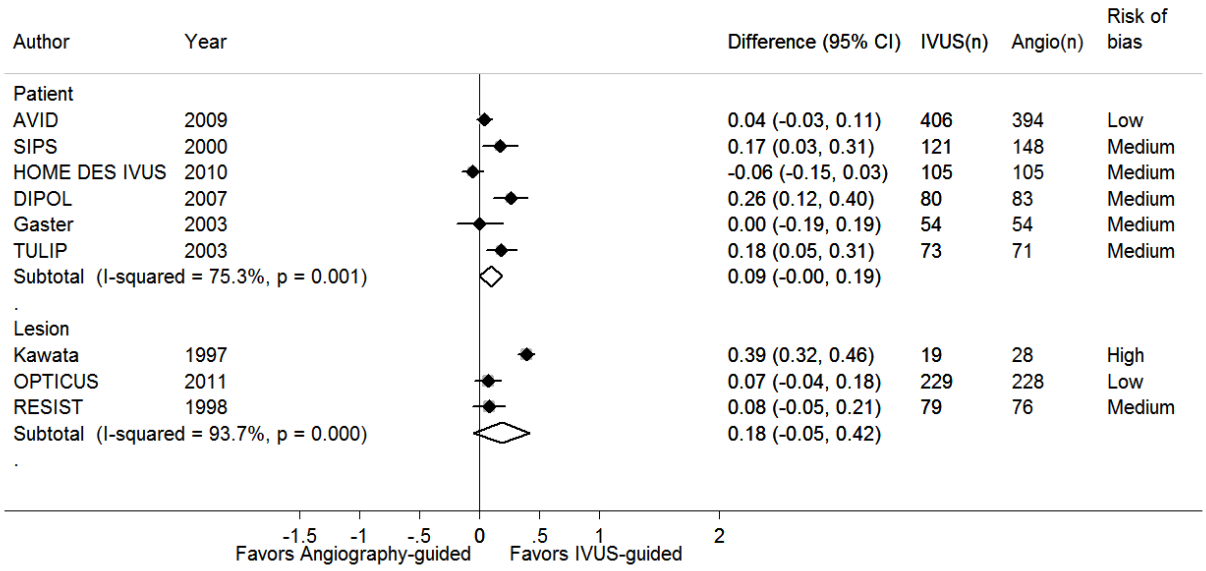
The number of guidewires used was similar in both groups in one RCT[28] and one nonrandomized comparative study.[35] The use of stents was similar in both groups in four RCTs,[22,24,26,28] and seven nonrandomized comparative studies, with two exceptions: more stents per patient were used in the IVUS-guided stenting group, compared with the group who received stents guided by angiography alone, in one RCT[30] and one nonrandomized study.[33] The average number of balloons utilized during procedure was similar between groups in two RCTs[22,24] and one nonrandomized comparative study,[35] while one RCT[28] and one nonrandomized comparative study[43] showed the IVUS-guided group utilizing significantly more balloons compared with the group who received stents guided by angiography alone.

One RCT[23] and two nonrandomized comparative studies[35,50] reported an increase in initial cost in the IVUS group relative to the angiography alone group, owing to the extra procedure time and increased utilization of catheters, balloons, and stents. The hospitalization stay was similar between groups in the one RCT reporting data on hospitalization after procedure.[28] No other studies reported data on this outcome.

QCA Process Outcomes

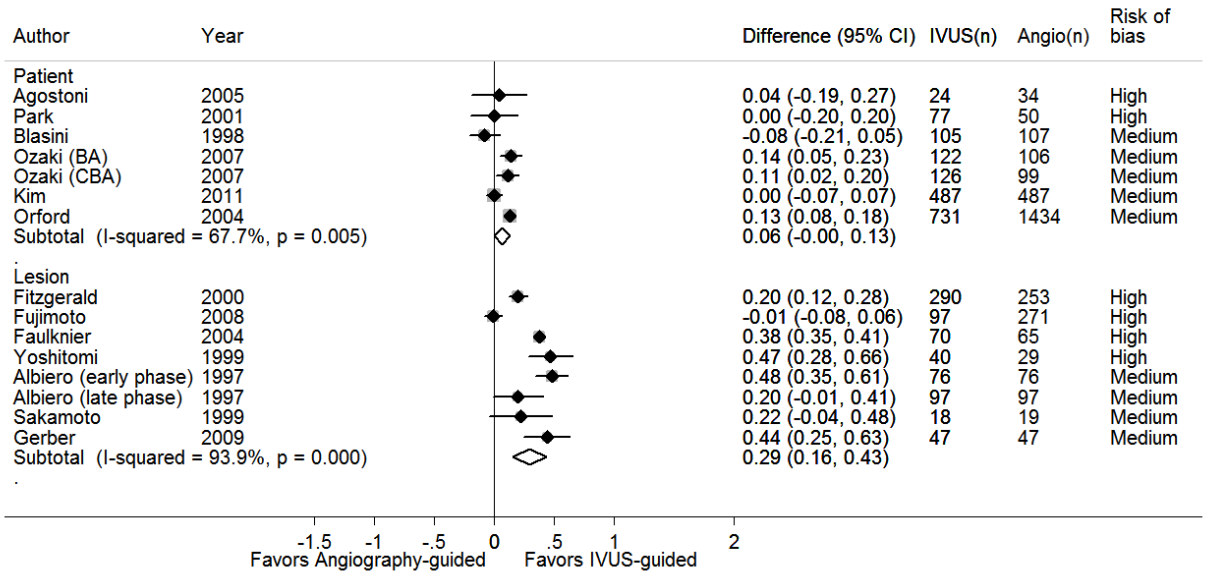
Meta-analyses of the net changes in MLD measurements between IVUS-guided stenting and stent deployment guided by angiography alone, from baseline to postprocedure, conducted across nine RCTs[22,24-28,30-32] and six nonrandomized comparative studies reporting data by patient,[34,40-42,46,47] revealed consistent small gains favoring IVUS, but no statistically significant difference between IVUS-guided stent placement and stenting guided by angiography alone (**Figures 3** and **4**).

Figure 3. Forest plot of RCTs of in-hospital minimal lumen diameter



However, meta-analysis of seven nonrandomized comparative studies reporting lesion-level data[33,36-38,44,45,49] revealed a significant difference, indicating a favorable effect for IVUS-guided stenting over stent placement guided by angiography alone (**Figure 4**), with significant statistical heterogeneity (I^2 = 94%).

Figure 4. Forest plot of nonrandomized comparative studies of in-hospital minimal lumen diameter



Meta-analysis of the net changes in MLD between IVUS-guided and angiography-guided stent placement groups, from baseline to medium-term (up to 1 year), across four RCTs[22,28,30,32] found a significant favorable effect with IVUS over angiography alone (**Figure 8**). No subgroup analysis by risk of bias or recruitment year was performed due to the small number of available

studies per subgroup. Meta-analysis of the nonrandomized studies (four lesion-level [33,38,44,45] and two patient-level[34,42]) revealed no significant difference between groups (**Figures 5 and 6**).

Figure 5. Forest plot of medium-term minimal lumen diameter (data reported by patients)

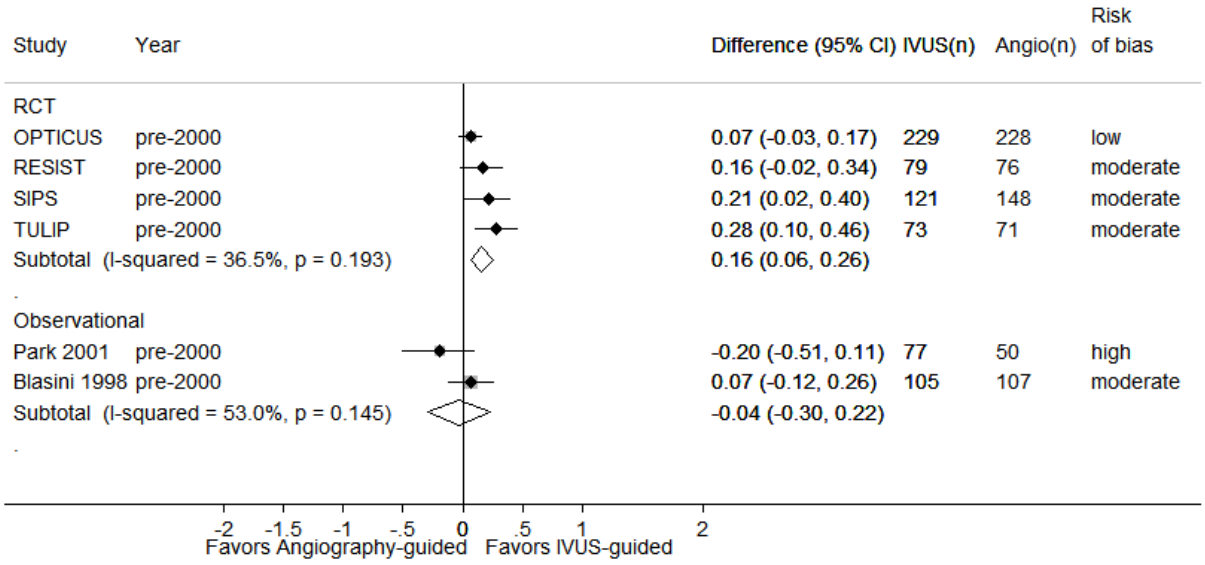
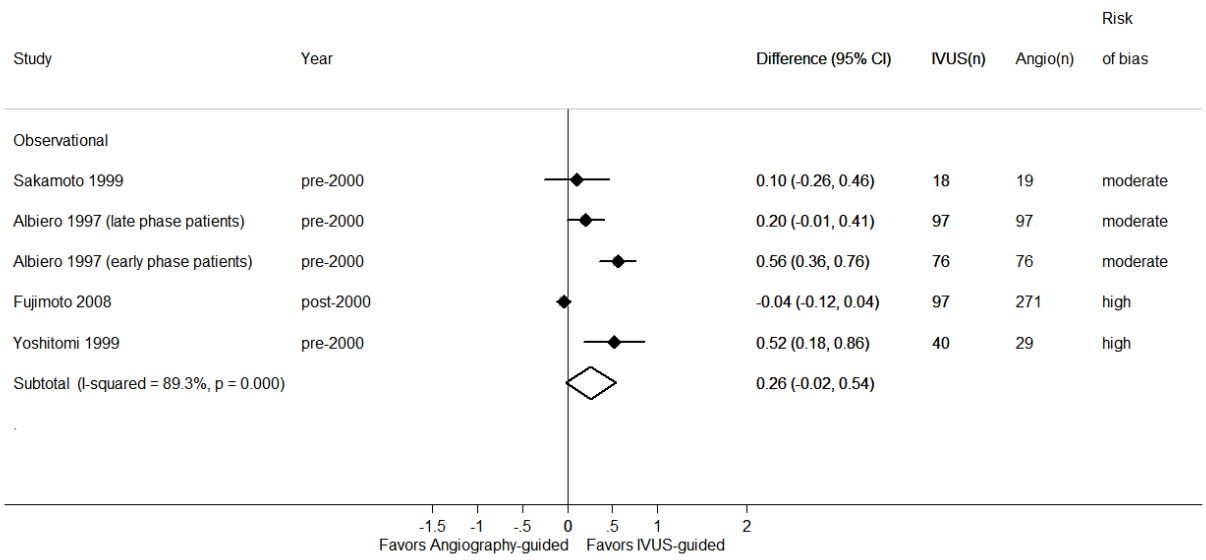


Figure 6. Forest plot of medium-term minimal lumen diameter (data reported by lesions)



Among eight RCTs,[22,24-28,30,32] meta-analysis of the five RCTs[22,24-26,30] reporting data by patient revealed a significant difference in the net changes in percent diameter stenosis, indicating a favorable effect for IVUS-guided over angiography-guided stent placement (**Figure 5**). Meta-analysis of either the three RCTs that reported lesion-level data,[27,28,32] or the 12 nonrandomized comparative studies (either patient- or lesion-level),[33,34,36-41,44-47] revealed

consistent small gains favoring IVUS, but there was no significant difference between groups (**Figures 7** and **8**).

Figure 7. Forest plot of RCTs of in-hospital percent diameter stenosis

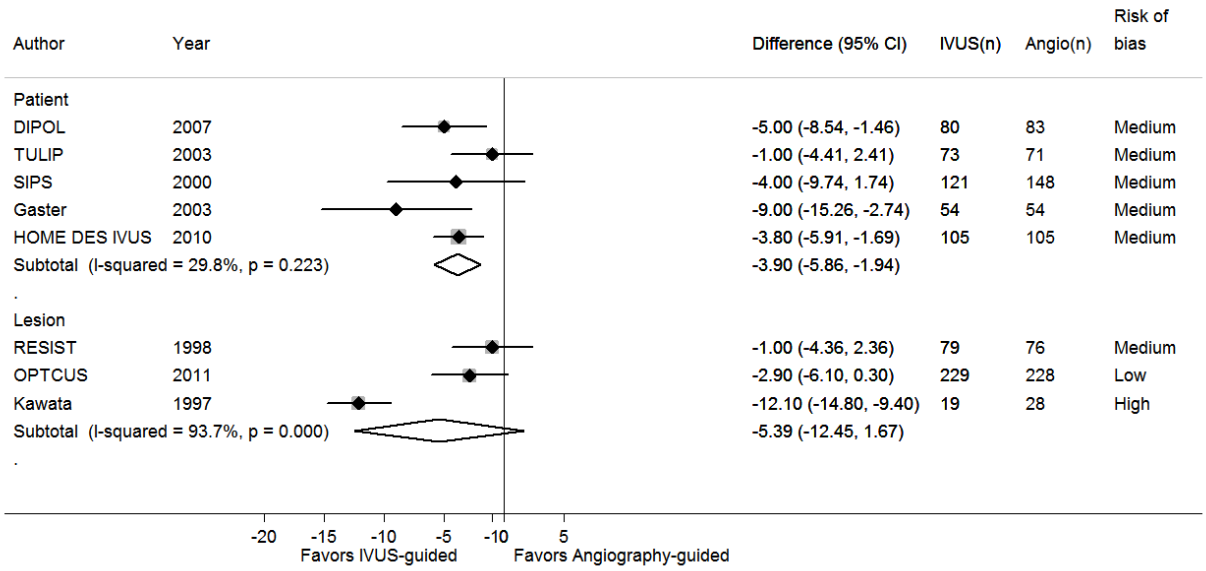
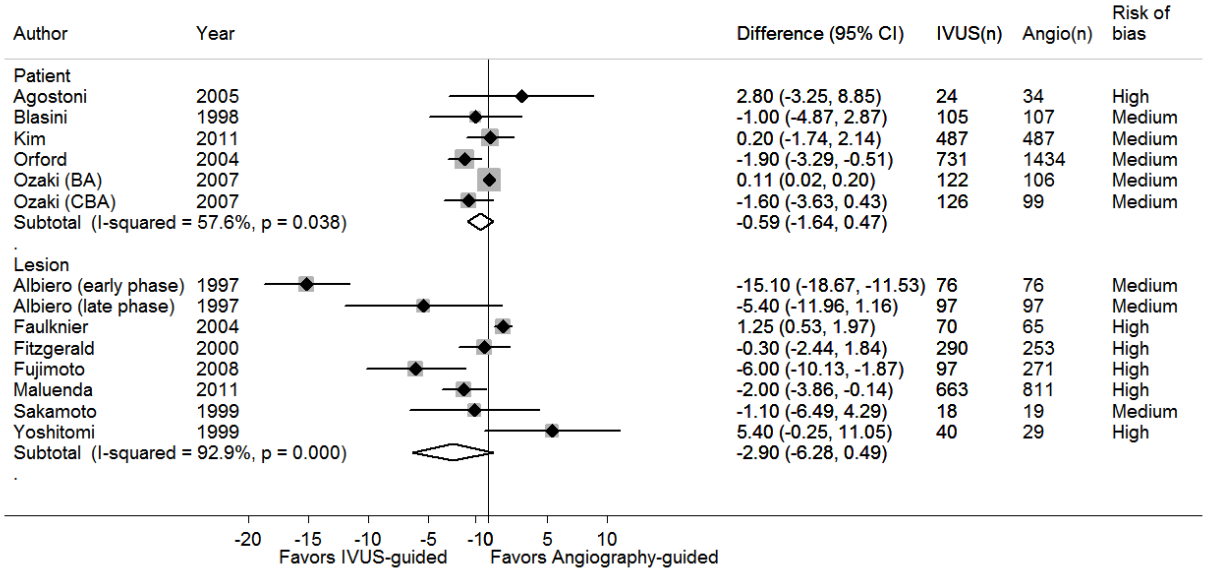


Figure 8. Forest plot of nonrandomized comparative studies of in-hospital percent diameter stenosis



Meta-analysis of the net changes in percent diameter stenosis between the IVUS-guided stenting group and the group receiving stenting guided by angiography alone, from baseline to final measurements, across four RCTs[22,28,30,32] and four nonrandomized studies (lesion-level data)[33,38,44,45] revealed no significant difference between groups (**Figures 9** and **10**). The lone

study analyzing data by patient reported a significant favorable effect of IVUS-guided stenting over angiography alone.[34]

Figure 9. Forest plot of medium-term percent diameter stenosis (data reported by patients)

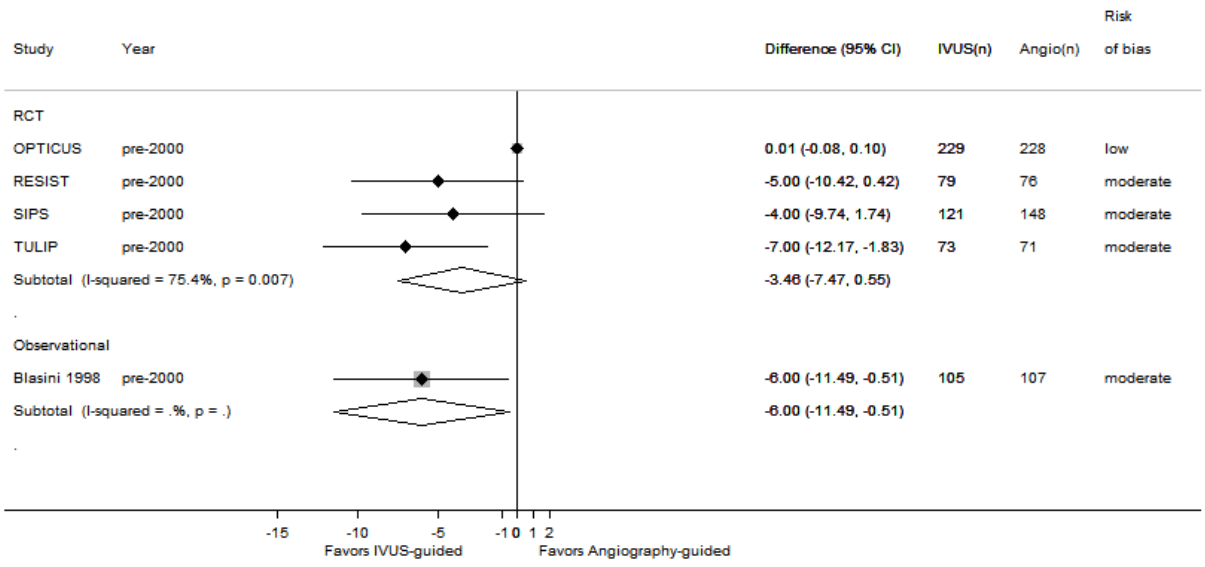
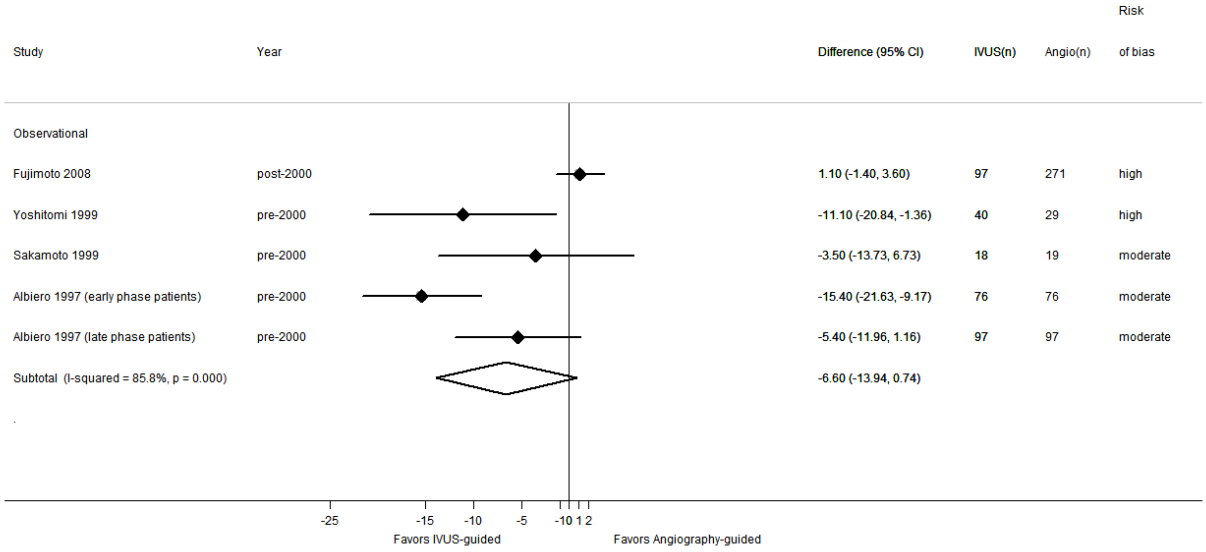


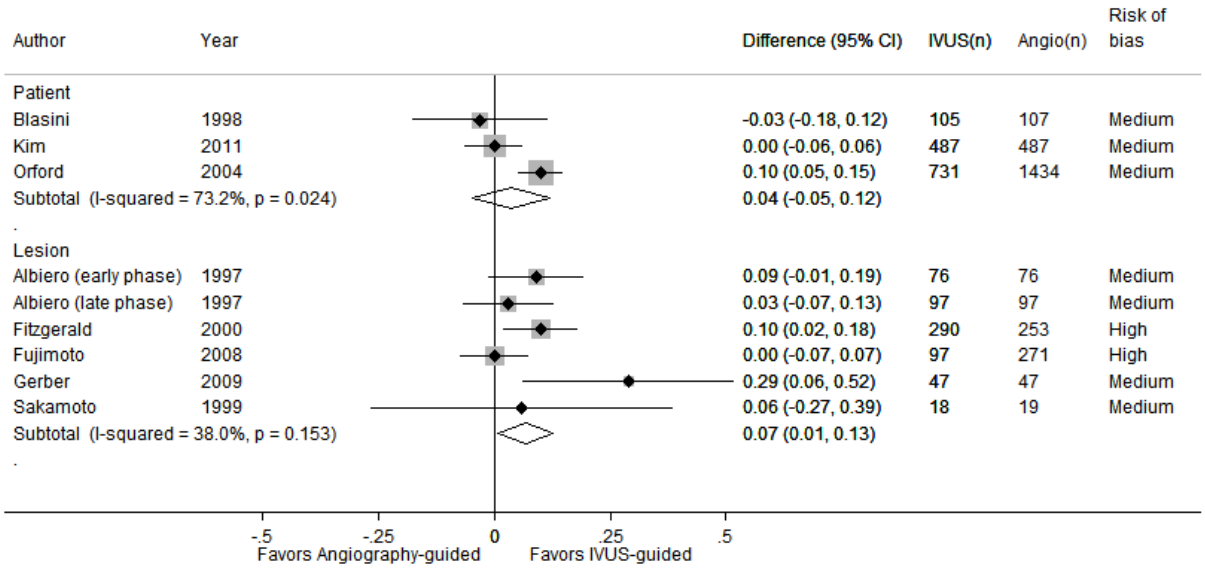
Figure 10. Forest plot of medium-term percent diameter stenosis (data reported by lesions)



Small but non-significant gains favoring IVUS were found in the net changes in reference vessel diameter between the IVUS-guided and angiography guided stent placement groups, from baseline to postprocedure, in the four RCTs examined.[21,24,26,28] No meta-analysis was performed due to the small number of RCTs per category (patient- or lesion-level). Of the eight nonrandomized comparative studies,[29,30,33,34,36,40,43,45] the five reporting lesion-level

data[29,33,34,40,45] revealed a significant difference indicating a favorable effect for IVUS-guided stenting over stent procedures guided by angiography alone (**Figure 11**). Meta-analysis of the three patient-level nonrandomized comparative studies revealed no statistically significant difference between groups (**Figure 11**).

Figure 11. Forest plot of nonrandomized comparative studies of in-hospital reference vessel diameter



Meta-analysis of the net changes in reference diameter between the IVUS-guided and angiography-guided stent placement groups, from baseline to medium-term, across three RCTs[22,28,30] and three nonrandomized comparative studies (lesion-level data),[33,38,44] revealed no significant difference between groups (**Figures 12** and **13**). The only nonrandomized comparative study analyzing data by patient reported no significant difference between groups.[34]

Meta-analysis of three RCTs[22,28,30] (summary mean difference in late lumen loss -0.001 mm [95 percent CI -1.13, 0.13; NS]) and one nonrandomized comparative study[44] revealed no significant difference between groups in late lumen loss.

Figure 12. Forest plot of medium-term reference vessel diameter (data reported by patients)

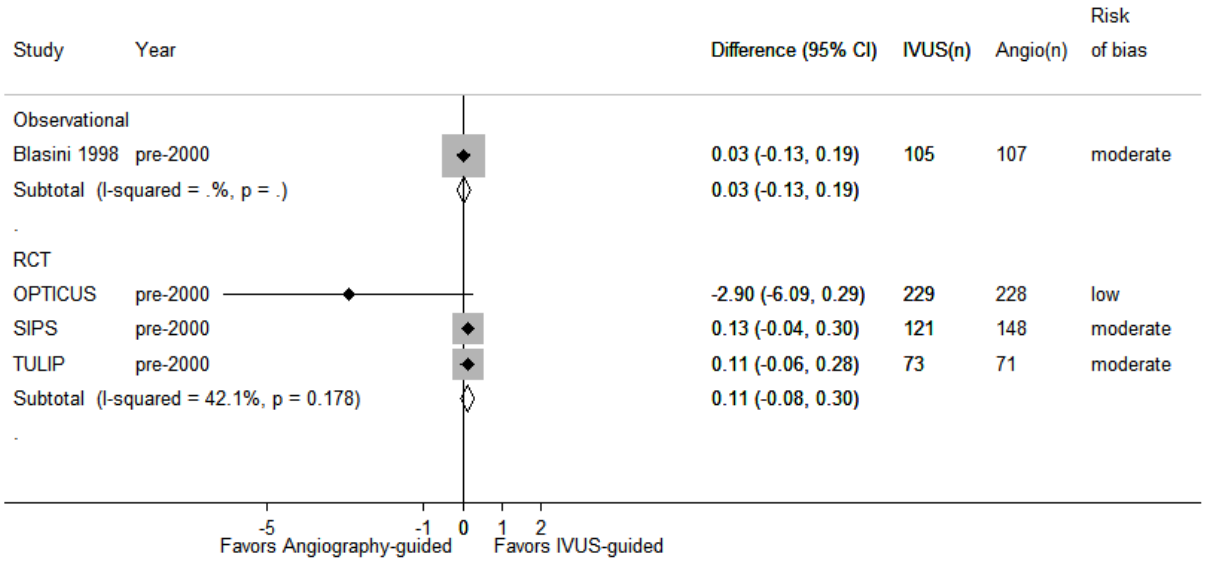
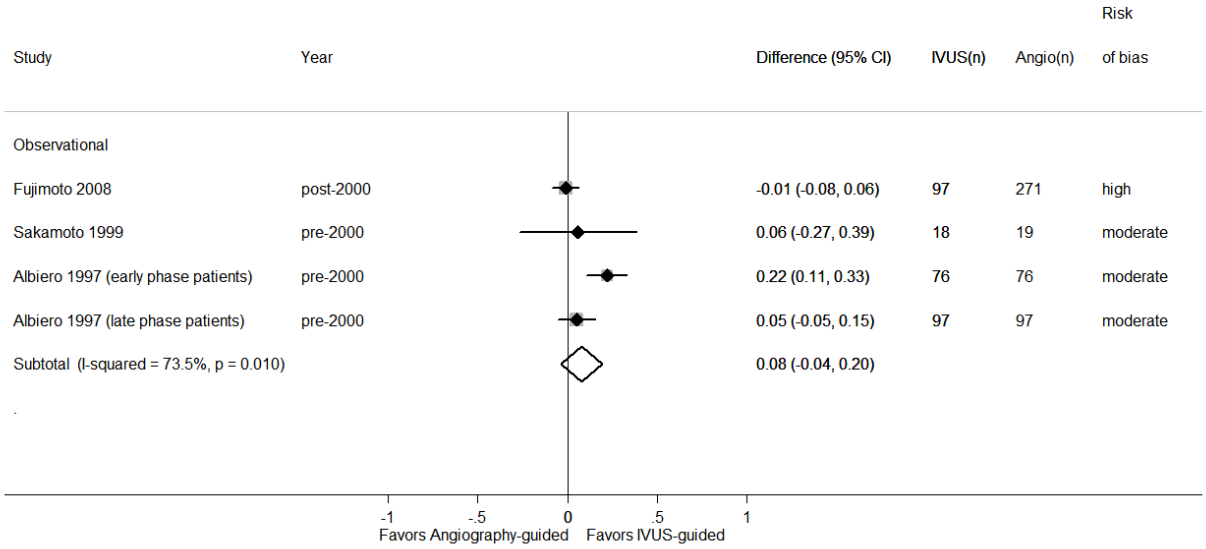


Figure 13. Forest plot of medium-term reference vessel diameter (data reported by lesions)



We did not identify any studies that reported intermediate outcomes of QCA measures greater than 1 year of followup.

Stent-Related Outcomes

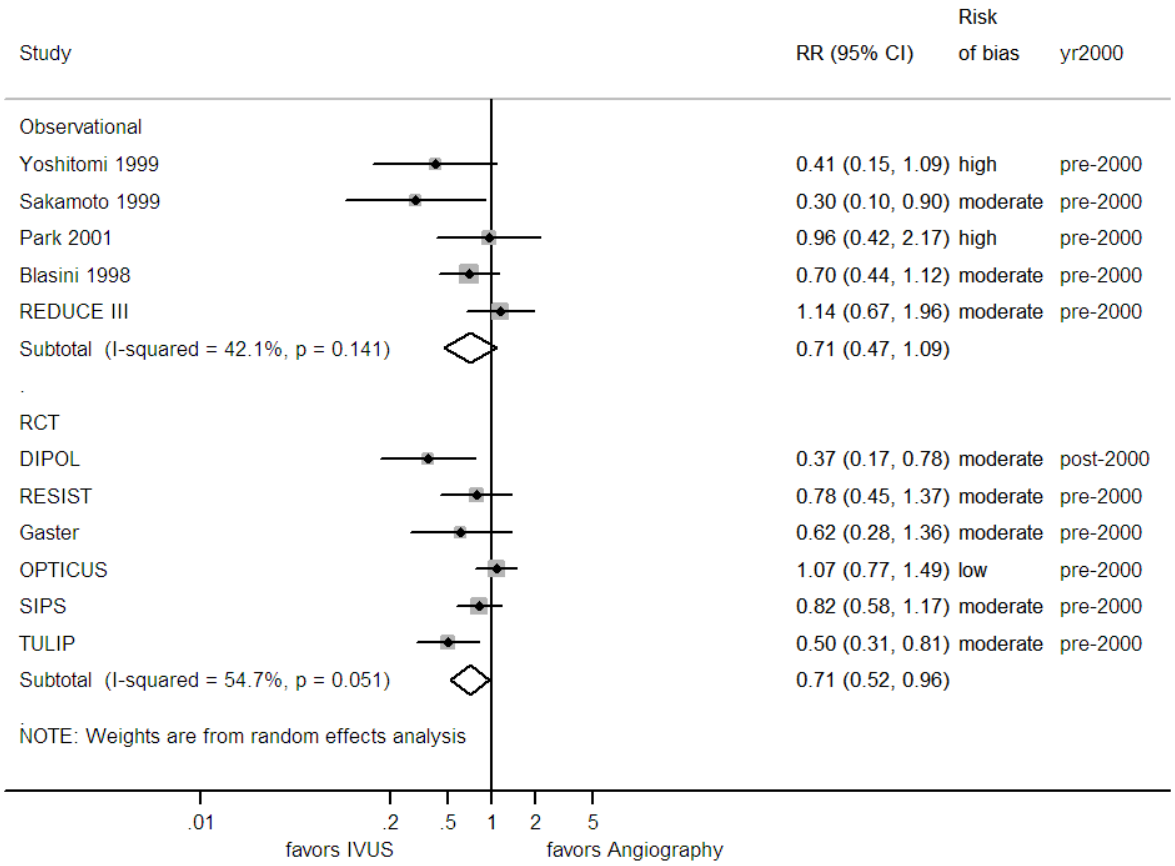
In-hospital restenosis rates were not significantly different between groups in one RCT[28] and two nonrandomized comparative studies.[33,42]

Six RCTs provided data for binary restenosis at 6-month followup. Meta-analysis of six RCTs[22,23,25,28-30,32] revealed a significantly lower risk (29 percent) of restenosis in the IVUS-guided group compared with the angiography alone group (**Figure 14**), with high heterogeneity

(I^2 = 54.7 percent). Recruitment closure year was not a source of heterogeneity (P = 0.24) in meta-regression analyses. In contrast, meta-analysis of five nonrandomized comparative studies (data by patients)[34,41,42,44,45] found a 29 percent lower (though nonsignificantly so) risk of restenosis in the IVUS-guided group compared with the angiography alone group (**Figure 14**).

We did not identify any studies that reported restenosis rates with greater than 1 year of followup.

Figure 14. Forest plot of medium-term restenosis



No RCTs reported data on in-hospital subacute stent thrombosis. Of the two nonrandomized comparative studies that reported data on in-hospital subacute stent thrombosis, no instance of subacute stent thrombosis was reported in one,[33] while the other reported no statistically significant difference between groups.[47]

Stent-related thromboses at 30-days were reported in two nonrandomized comparative studies; one study reported no difference between groups,[39] while the other identified a significantly higher incidence of cumulative stent thrombosis in the IVUS-guided group compared with the angiography alone group.[43]

Of the two RCTs that provided data for stent thrombosis in the medium duration timeframe,[25,31] one reported no events in either of the groups,[25] and the other reported no significant difference between groups at 1-year followup.[31] Of the three nonrandomized comparative studies that provided data on stent thrombosis,[38,39,43] one reported no events in either of the groups at 8 months,[38] one reported no difference at 6 months,[39] and one reported a

significant favorable effect of IVUS-guided stenting over stents placed using angiography alone, over 1 year of followup.[43]

One RCT[26] and one nonrandomized comparative study[47] reported no significant difference in stent thrombosis between groups in the long-term followup.

Other periprocedural complications (reported in three RCTs) during stent placement included: prolonged spasm after stent implantation (only in the IVUS-guided stent placement group);[28] more vessel dissection requiring additional therapy in the IVUS group relative to the angiography alone group;[31] and vessel dissection, intima peeling off the lumen, suboptimal stenting results, and nonQ wave MI (only in the angiography alone group).[23] Among the nonrandomized studies, four reported no significant differences in dissection or abrupt closure between groups,[33,43-45] though one reported a significantly lower rate of abrupt closure with IVUS compared with angiography alone.[35]

Patient-centered Outcomes

Among the five studies,[22,24,28,39,40] in-hospital all-cause mortality was observed in only one. A lone nonrandomized comparative study reported event rates of 0.5 percent in the IVUS group versus 0.8 percent in the angiography alone group, with no statistically significant difference between groups.[43]

In the medium timeframe, meta-analysis of five RCTs[25,28,30-32] and five nonrandomized comparative studies[36,37,39,40,43] found no statistical significance in the risk of all-cause mortality between groups (**Figure 15**). However, the meta-analysis of RCTs revealed 84 percent higher risk in mortality with IVUS use as compared with angiography alone, while the meta-analysis of nonrandomized studies found 11 percent lower risk in mortality with IVUS versus angiography alone during stent deployment.

We identified no RCT that reported cardiac mortality in the medium timeframe. Meta-analysis of four nonrandomized comparative studies[35,38,39,43] found 16 percent lower risk, but no statistical significance in the risk of cardiac mortality between groups (**Figure 16**).

Figure 15. Forest plot of medium-term all-cause mortality

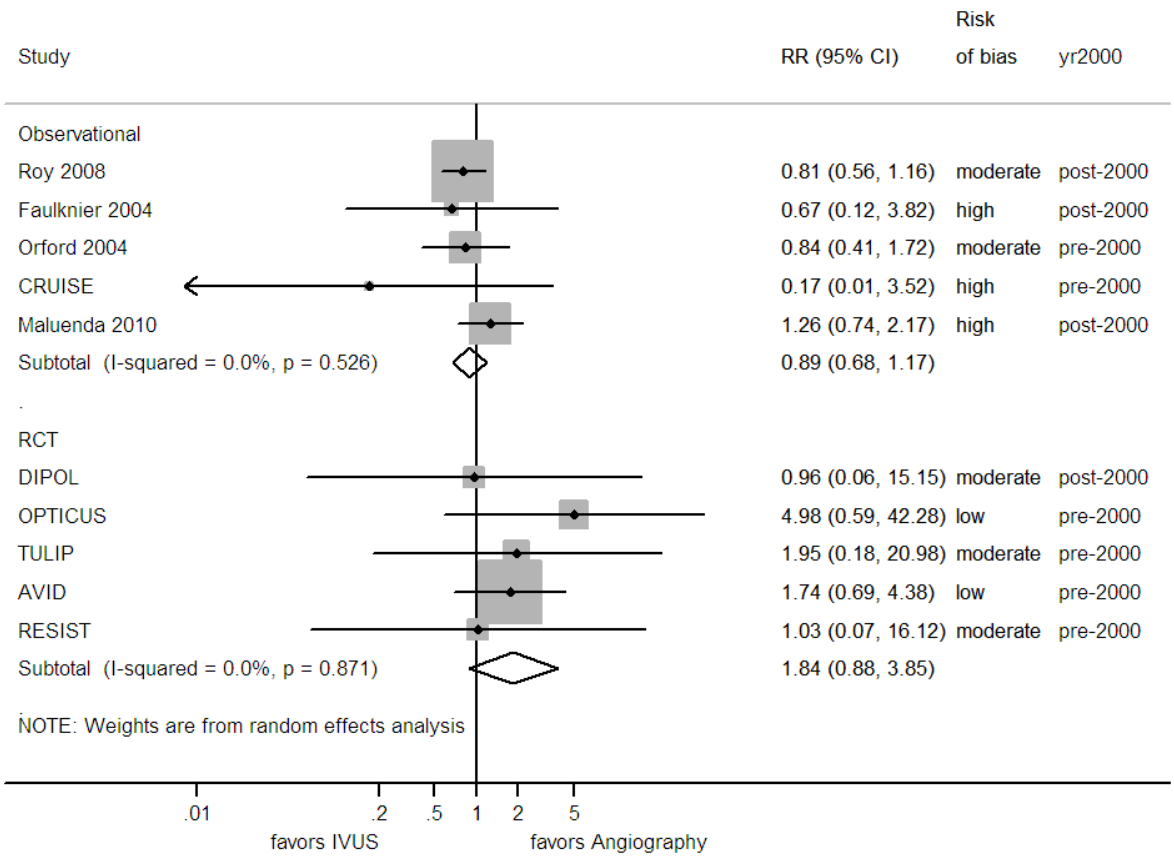
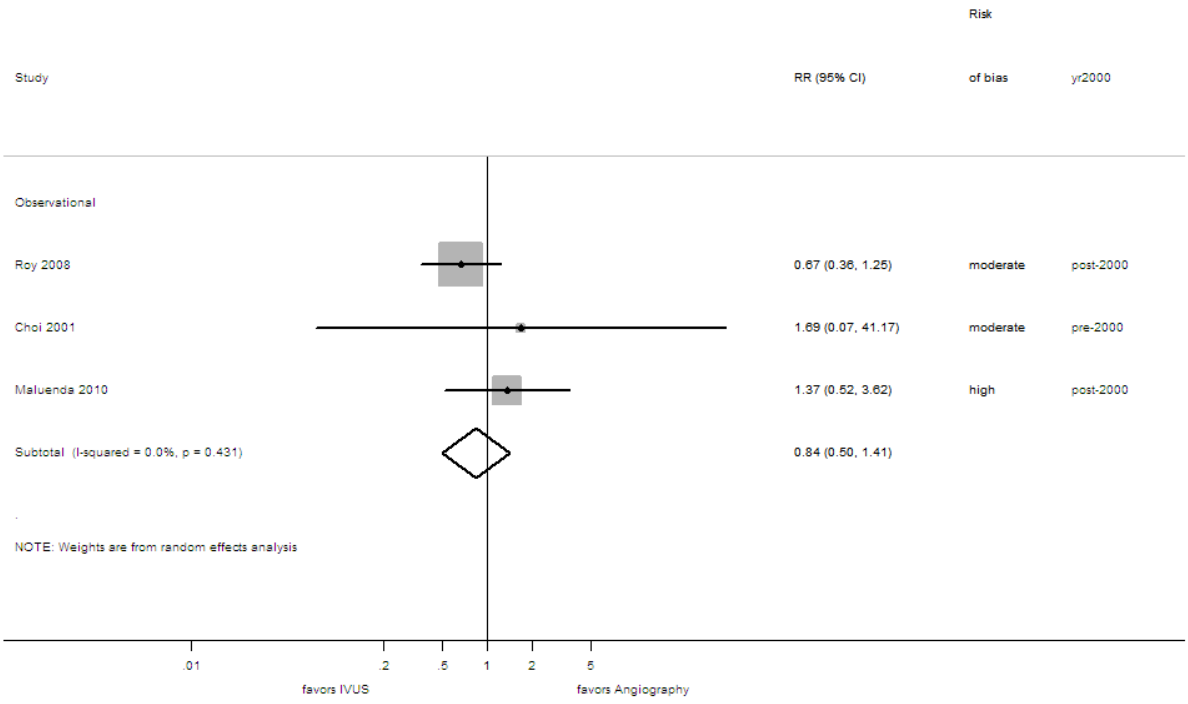


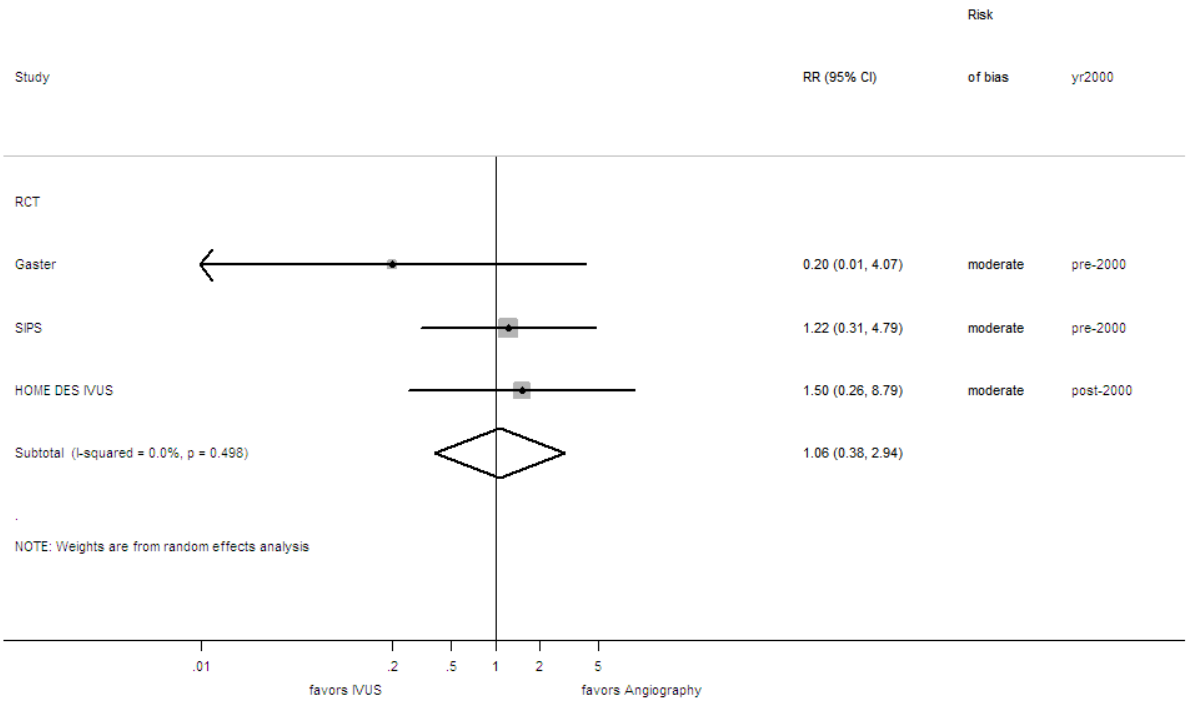
Figure 16. Forest plot of medium-term cardiac mortality



During long-term followup, meta-analysis of three RCTs[18,20,22] found a 6 percent higher (though nonsignificantly so) risk of all-cause mortality with IVUS-guided stenting than with angiography-guided stent placement (**Figure 17**). Of the two nonrandomized comparative studies that evaluated this outcome,[47,48] both reported a point estimate indicating a favorable effect of IVUS-guided stent placement, but statistical significance was reached in only one.[48].

None of the three RCTs reported data for cardiac mortality. One retrospective nonrandomized comparative study enrolling 975 patients reported a significantly lower rate of 3-year cardiac mortality in the IVUS-guided compared with the angiography-guided stent placement group (RR 0.32; 95 percent CI 0.18, 0.56; P < 0.0001).[48]

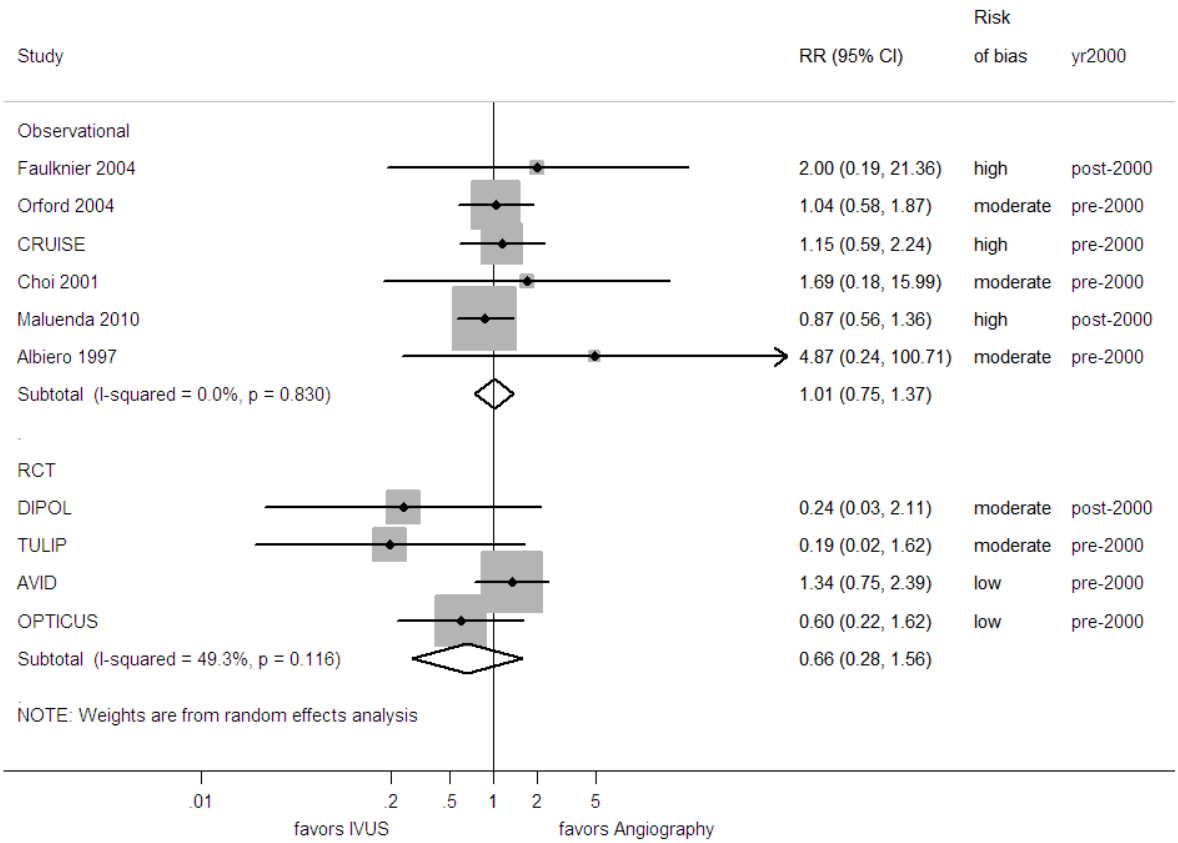
Figure 17. Forest plot of long-term all-cause mortality



One RCT reported no instances of in-hospital acute MI[24] while the other two RCTs[22,28] and two of the nonrandomized comparative studies[33,44] found no statistically significant difference between groups. The remaining nonrandomized comparative study reported significantly lower rates of Q-wave MI in the IVUS than in the angiography alone group (0.1 percent in the IVUS group versus 0.9 percent in the angiography alone group; P<0.02).[43]

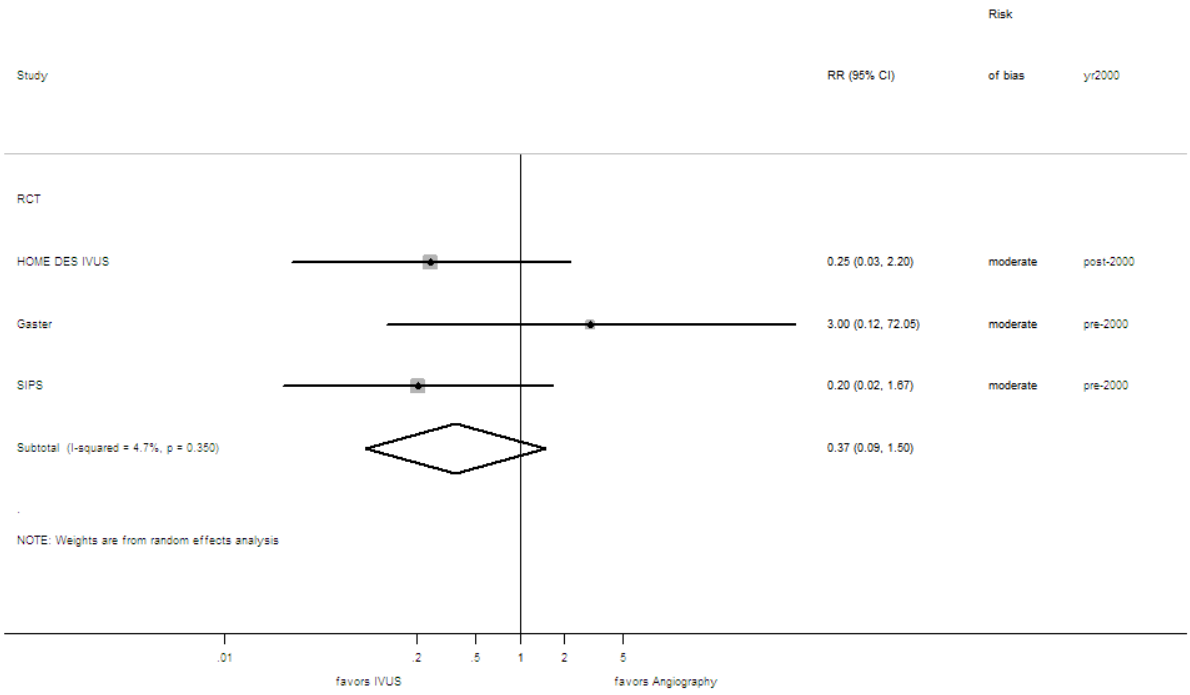
Meta-analysis of four RCTs[25,28,30,31] (34 percent lower risk) and six nonrandomized comparative studies[33,35-37,39,40] (no difference) that provided data for MI in the medium timeframe found no statistical significance in the risk of MI between groups (**Figure 18**).

Figure 18. Forest plot of medium-term myocardial infarction



During long-term followup, meta-analysis of the three included RCTs[18,20,22] found 63 percent lower risk of MI in the IVUS group compared with angiography alone group, but this did not reach statistical significance (**Figure 19**). Two nonrandomized comparative studies also reported no significant difference in the risk between the IVUS and angiography alone groups.[47,48]

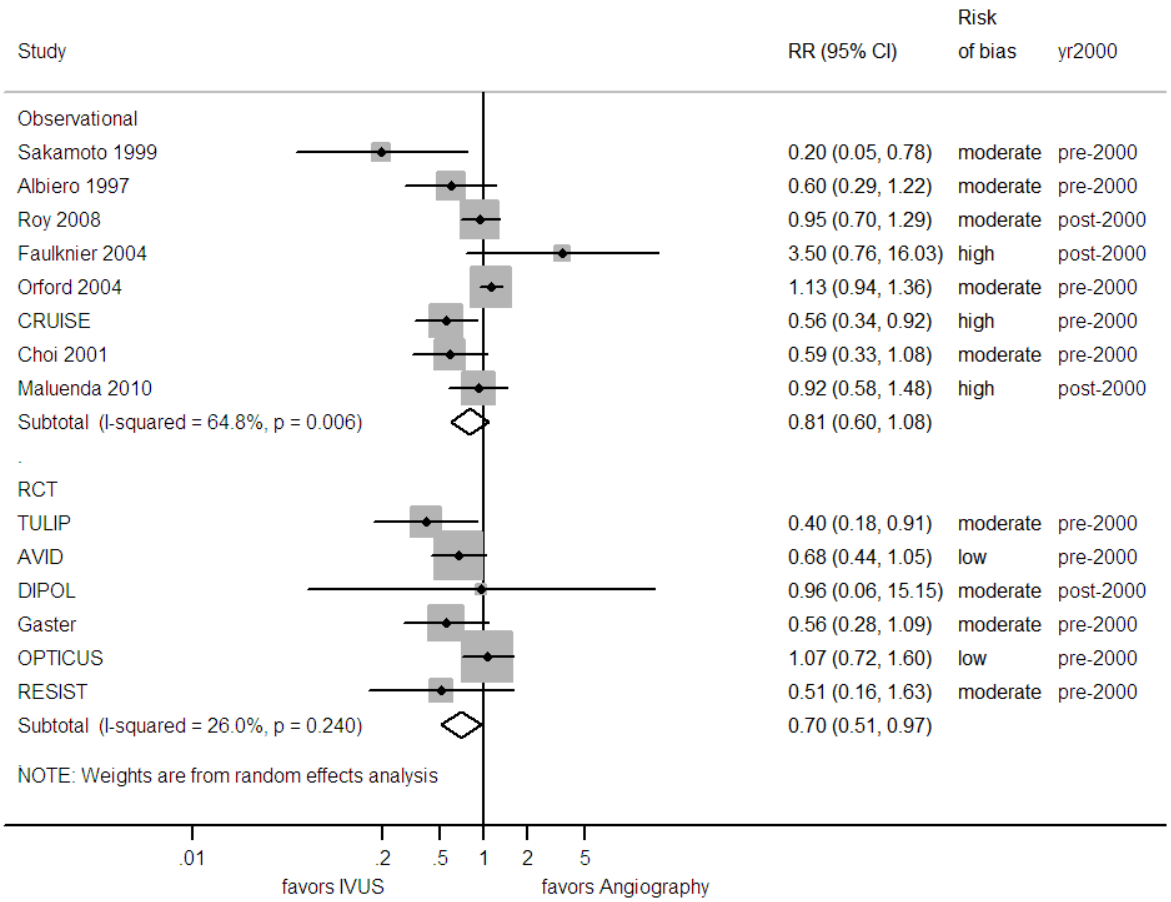
Figure 19. Forest plot of long-term myocardial infarction



Data on repeat revascularization during in-hospital stay was reported in five RCTs[22,23,25,28,30] and in three nonrandomized comparative studies.[33,43,44] Meta-analysis of all five RCTs revealed a nonstatistically significant decrease in repeat revascularization during in-hospital stay in the IVUS group compared with the angiography alone group (summary relative risk [RR] 0.50; 95 percent confidence interval [CI] 0.20, 1.27), without statistical heterogeneity (I^2 = 0 percent). Among the nonrandomized comparative studies, two reported no patients undergoing repeat revascularization,[33,44] and one reported similar rates in the need for emergent CABG in both groups.[43]

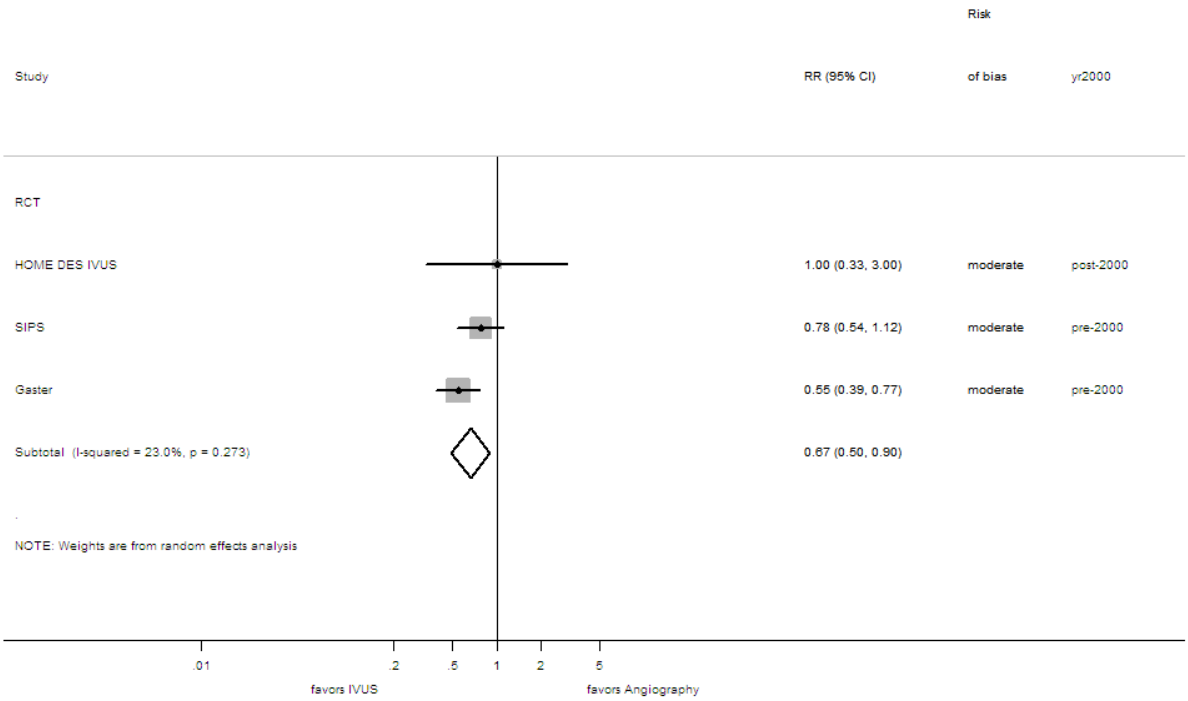
During medium-term followup, meta-analysis of all six RCTs[23,25,28,30-32] with almost 1800 patients revealed 30 percent significantly lower risk of TVR among patients who received IVUS-guided stent placement compared with those who received stents guided by angiography alone (**Figure 20**). In contrast, meta-analysis of eight of the nonrandomized comparative studies (data by 13,000 patients)[33,35-37,39,40,43,44] found 19 percent lower risk, but no statistical significance in the risk of TVR between groups (**Figure 20**).

Figure 20. Forest plot of medium-term repeat revascularization



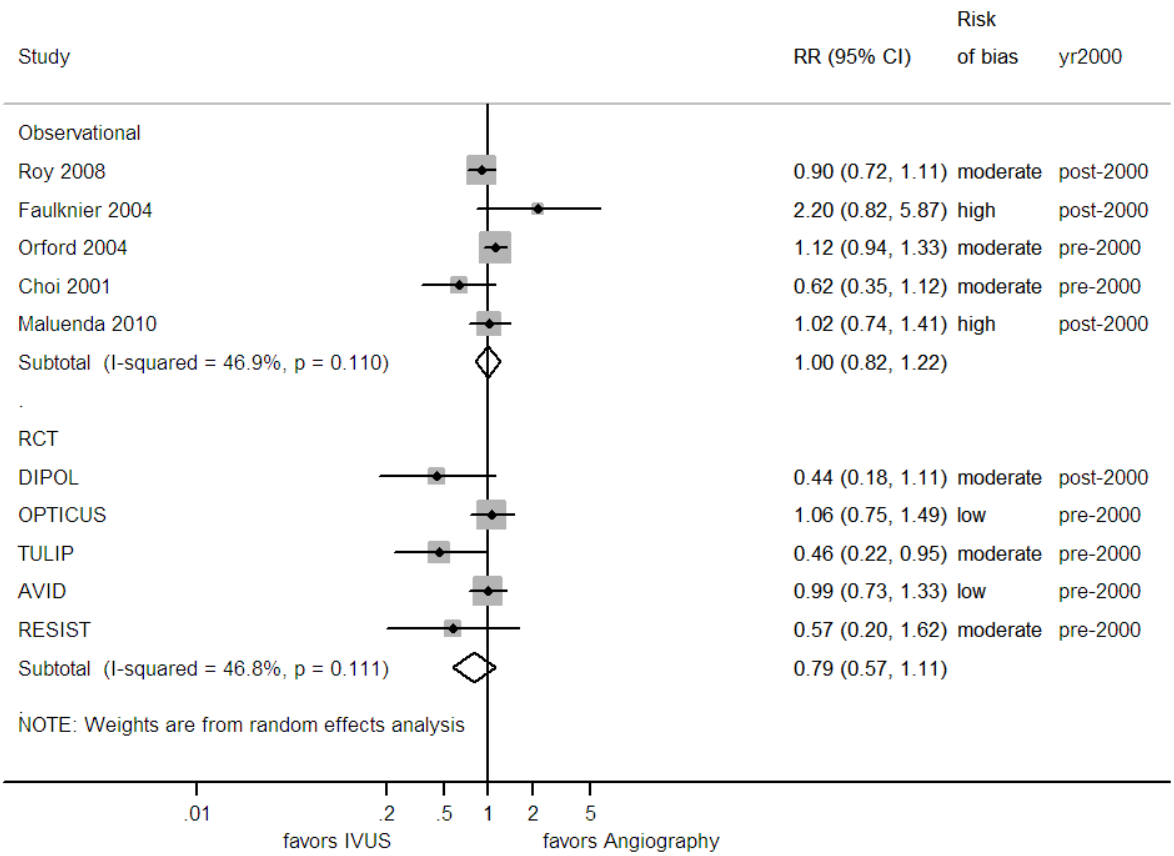
During long-term followup, meta-analysis of the three included RCTs found a significantly 33 percent lower risk of TVR among patients who received IVUS-guided stent placement compared with those who received stents guided by angiography alone (**Figure 21**). Of the two nonrandomized comparative studies that provided data for TVR, neither reported a significant difference between groups.[47,48]

Figure 21. Forest plot of long-term repeat revascularization



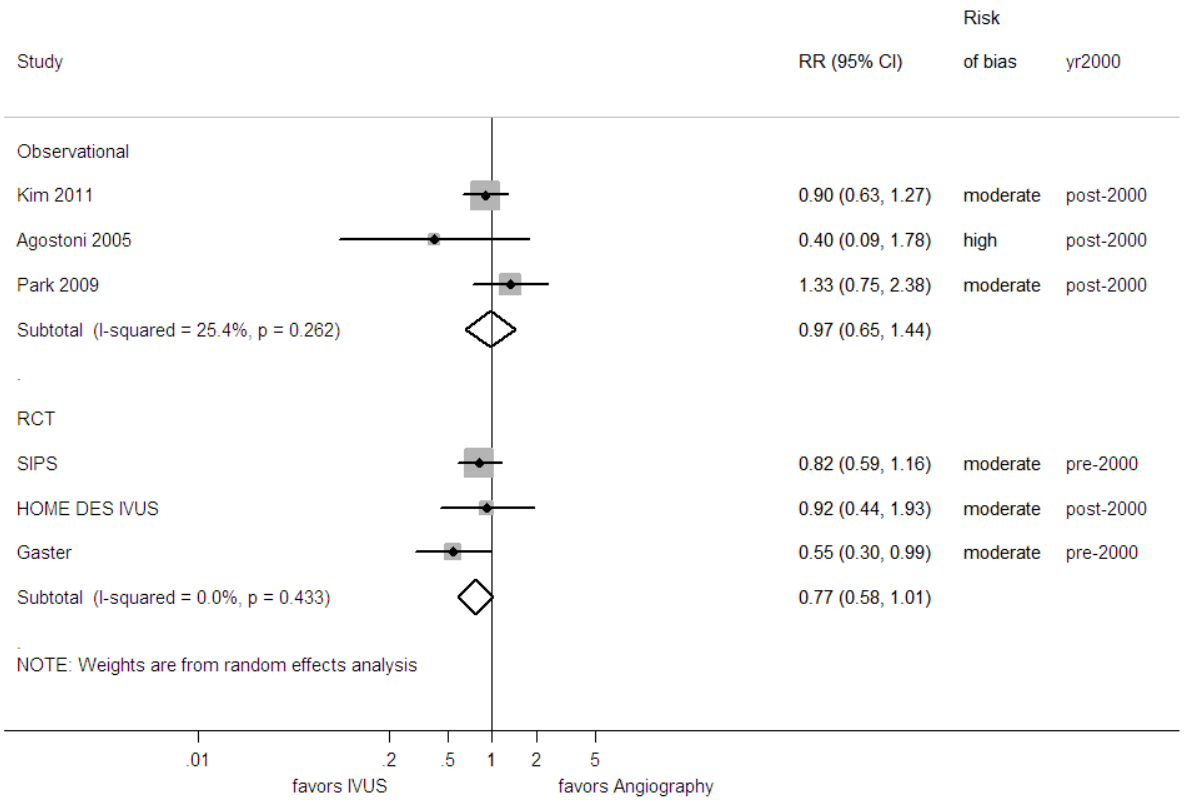
The overall rates of in-hospital MACE and its individual components of death, MI, and TVR were reported as similar between groups in two RCTs.[28,30] One nonrandomized comparative study reported similar findings,[39] while another identified a significantly lower incidence of MACE, mortality (both all-cause and cardiac), and target lesion revascularization in the IVUS group compared with the angiography alone group.[43] Meta-analysis of five RCTs[25,28,30-32] revealed a nonsignificantly lower risk (21 percent) of MACE during medium-term followup, and five nonrandomized studies[35,36,39,40,43] found no significant difference in the risk of MACE between IVUS-guided stenting and stent placement guided by angiography alone (**Figure 22**). The definition of MACE varied considerably among studies (see **Appendix C**).

Figure 22. Forest plot of medium-term MACE



Meta-analysis of all included studies with long-term followup found no statistically significant risk of MACE (23 percent lower risk in RCTs and 3 percent lower risk in nonrandomized studies) in the IVUS group compared with the angiography alone group (**Figure 23**).

Figure 23. Forest plot of long-term MACE



FFR-Guided Compared With Stenting Guided by Angiography Alone

Only one nonrandomized comparative study evaluated the use of FFR versus angiography alone to guide and to optimize stent deployment.[18] In addition to the diagnostic and therapeutic decisions (with regards to changing the type of PCI) that were made on the basis of threshold of FFR, this study used high-pressure dilatation following suboptimal stent implantation. The outcomes of this study are described under Key Question 1.

Other intravascular diagnostic Techniques Compared with Angiography Alone

There is insufficient evidence regarding the use of all other intravascular diagnostic techniques, due to a lack of data available to answer Key Question 2.

Key Question 3

For patients having just undergone a PCI, what is the impact of using an intravascular diagnostic technique and angiography to evaluate the

success of stent placement immediately after the procedure—when compared to angiography alone—on therapeutic decisionmaking, intermediate, and patient-centered outcomes?

Key Points

- There is insufficient evidence regarding the adjunctive use of intravascular diagnostic techniques immediately post-procedure, to evaluate the success of stent placement.
- Two studies, both evaluating IVUS were rated as being at a high risk of bias.
- No studies evaluated FFR or any other intravascular diagnostic technique on the success of stenting immediately after the procedure.

Overall strength of evidence

There is insufficient evidence regarding the comparisons of interest in this Key Question, as data were drawn from two studies, both evaluating IVUS and rated as being at a high risk of bias, with each reporting on two different types of outcomes at different time points. There is insufficient evidence for any intravascular diagnostic technique, as none of the reviewed studies evaluated the effect of FFR or any other intravascular diagnostic technique on the success of stent placement immediately post- procedure.

Available evidence

Two retrospective studies rated as being at a high risk of bias addressed this Key Question.[51,52] Neither of these studies adjusted for potential confounders.

Nasu 2004 compared the use of IVUS with angiography in patients with either *de novo* or restenotic lesions who had a stand-alone directional coronary atherectomy (DCA) without angioplasty.[51] The study did not provide baseline characteristics for the two groups separately. IVUS assessments were obtained for 38 patients with 38 lesions. This was compared with 53 patients (inferred from paper, not explicitly reported) with 63 lesions without IVUS assessments. No significant differences in postprocedure angiographic results were observed between the two groups: reference diameter (mm) (3.31 ± 0.17 [SD] vs. 3.36 ± 0.56 [SD], P = 0.69); minimal luminal diameter (mm) (2.91 ± 0.35 [SD] vs. 2.79 ± 0.50 [SD], P = 0.23); diameter stenosis (%) (12.6 ± 8.3 [SD] vs. 16.5 ± 10.5 [SD], P = 0.07)). In addition, no significant differences in these parameters were observed at short- (4 to 10 months) or long-term (5 to 9 years) followup. No clinical outcomes were reported.

Seo 1996 evaluated the use of IVUS after stent placement in 83 patients with angina and classified them into sufficient and insufficient dilatation groups defined as luminal area <5 mm^2 or luminal stenosis >60 percent by IVUS, respectively. Patients in the insufficient dilatation group consequently received additional treatments, including larger balloon, longer dilatation time, DCA, or stenting (35 of 83 patients; 42 percent). The IVUS after stenting (83 patients) was compared with no IVUS after stenting (192 patients). The observed incidence of restenosis at 3 to 6 months of followup was 17 percent in the IVUS versus 42 percent in the no IVUS after stent placement, respectively (statistical significance not reported).[52]

Key Question 4

How do different intravascular diagnostic techniques compare to each other in their effects on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Points

- There is insufficient evidence comparing different intravascular diagnostic techniques and their effects on outcomes
- Only one study rated as being at a high risk of bias provided relevant data for the comparison of FFR versus IVUS.

Overall strength of evidence

There is insufficient evidence regarding the comparison of FFR versus IVUS, as only one study rated as being at a high risk of bias provided relevant data. There is insufficient evidence for all other comparisons, as none of the studies reviewed examining other intravascular diagnostic techniques addressed this Key Question.

Available evidence

One retrospective study rated as being at a high risk of bias due to the potential for selection bias and lack of adjusted analyses addressed this Key Question.[53] Nam 2010 compared the use of FFR-guided with IVUS-guided stent placement in patients with intermediate coronary lesions (40 percent to 70 percent diameter stenosis by visual assessment).[53] The study included 167 consecutive patients (83 in the FFR group and 94 in the IVUS group). The use of FFR or IVUS was based on operator preference. The cutoff value for the use of PCI in the FFR group was 0.80, and 4 mm^2 derived minimal lumen area in the IVUS group. Twenty-eight of 83 patients in the FFR group received stenting, while 86 of 94 patients in the IVUS group received stenting (33.7 percent vs. 91.5 percent, respectively; $P < 0.001$). The one-year composite outcome of death/myocardial infarction/ischemia-driven target vessel revascularization was not significantly different between FFR and IVUS (3.6 percent vs. 3.2 percent, respectively; $P = 1.00$). There were no significant differences between groups in postintervention MLD and percent diameter stenosis.

Key Question 5

What factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) influence the effect of intravascular diagnostic techniques and angiography—when compared to angiography alone (or among different intravascular diagnostic techniques)—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Points

- There is a moderate strength of evidence from one large sample size (9070 patients) prospective study with a medium risk of bias that fails to support an association between IVUS and modifying factors, and its effect on outcomes.
- No studies addressed this Key Question for any technique other than IVUS.

Overall strength of evidence

There is a moderate strength of evidence that fails to support an association between IVUS and factors such as LMD, sex, diabetes mellitus status, lesion length and reference diameter, and its effect on outcomes. There were no studies to address this Key Question for any technique other than IVUS.

Available evidence

Two studies, one multicenter prospective study (a post hoc RCT),[40] and one single center retrospective study[46] evaluated various factors that influenced the effect of IVUS-guided stenting on outcomes, compared with stent placement guided by angiography alone. The multicenter prospective study (a post hoc RCT), Orford 2004 was rated as being at a medium risk of bias due to potential for selection bias by excluding of subjects who refused to undergo followup angiography. The single center retrospective study, Agostoni 2005 was rated as being at a high risk of bias due to the potential for selection bias and lack of adjusted analyses. Both studies enrolled CAD patients with angina, silent ischemia or patients with left main coronary artery disease who were undergoing a PCI procedure with or without stenting.

The multicenter prospective study (post hoc RCT) included 9070 patients with an average age of 60 years.[40] The proportions of men included were 79 percent. The proportion of patients with diabetes was 24 percent, hypertension was 59 percent, and dyslipidemia was 67 percent. Smokers accounted for 24 percent, and the average ejection fraction was not reported in this study.[46] The average followup period was 9 months.[40]

The single center retrospective study included 58 patients with an average age 63 years.[46] The proportions of men included 68 percent. The proportions of patients with diabetes were 33 percent, hypertension was 59 percent, and dyslipidemia was 65 percent. Smokers accounted for 19 percent, and the average ejection fraction was 47 percent. The followup period for this study was 1 year.[46]

The multicenter prospective study (post hoc RCT), Orford 2004 evaluated various patient- and lesion-related factors—such as sex, diabetes mellitus status, lesion length, and reference vessel diameter—for their influence on the effect of IVUS-guided stent placement versus

stenting guided by angiography alone, through interaction tests. These tests for interaction did not reach statistical significance for the composite clinical end point (any event), or any of their three individual components (death, myocardial infarction, or target-vessel revascularization; P >05).[40]

The retrospective study, Agostoni 2005 stratified patients on the basis of LMD (nondistal versus distal LMD) and evaluated the effect of IVUS-guided PCI among patients with different anatomic LMD.[46] In multivariate analysis, patients with distal LMD were significantly more likely to experience more adverse outcomes compared to those with nondistal LMD (HR 7.7; 95 percent CI 1, 62.6, p=0.05).The stratification on the basis of LMD (nondistal versus distal LMD) revealed that IVUS-guided PCI was performed less often in distal LMD patients (31%, 10 of 32) than in patients with nondistal LMD (54%, 14 of 26) However, regardless of the differences in anatomic LMD, the rate of events was not significantly different between the IVUS-guided PCI group and the non-IVUS-guided PCI group.

Other than these two studies of IVUS, we found no studies of other intravascular diagnostic techniques that evaluated factors influencing the effect of intravascular diagnostic techniques compared to angiography alone or different intravascular diagnostic techniques on outcomes.

We found no studies evaluating additional subgroups of interest, including patients with and without diabetes, patients with chronic inflammation (e.g., systemic lupus erythematosus), and patients with atherosclerosis following heart transplantation.

Discussion

Key Findings and Strength of Evidence

We found comparative studies for only two techniques (IVUS and FFR). Our review of the evidence found the bulk of the available data addressed Key Questions 1 (FFR to decide which coronary lesions need intervention) and 2 (IVUS to guide PCI and optimize stent deployment). There were insufficient data available to answer the remaining Key Questions 3 and 4. For Key Question 5, there is a moderate strength of evidence that fails to support an association between IVUS use and factors such as LMD, sex, diabetes mellitus status, lesion length and reference diameter, and its effect on the diagnostic thinking and therapeutic decisionmaking, or other outcomes. For all other intravascular diagnostic techniques as compared with angiography there were insufficient data to address this Key Question 5.

Our review suggests that the use of FFR in patients with intermediate coronary stenosis in order to decide which coronary lesions require intervention would confer a lower risk of the combined endpoint of death or MI, as compared with stenting guided by angiography alone. Additionally, our review indicates that FFR-guided stenting would decrease total cost and length of stay, and would lead to fewer stents implanted, without sacrificing freedom from angina or without the need for further revascularization as compared with angiography-guided PCI.

The study upon which these findings are primarily based, the FAME trial, found benefit in stent deployment in physiologically or functionally stenosed lesions, and we concluded that, in view of this RCT (rated as being at a low risk of bias) and one additional nonrandomized study (rated as being at a medium risk of bias), there is moderate evidence favoring FFR-guided stenting over stent placement guided by angiography alone in patients with intermediate coronary lesions, excluding left main disease and acute MI.

Our review also indicates that the use of IVUS compared with angiography alone to guide PCI and stent deployment achieved some measureable, though inconsistent, gains in QCA outcomes, such as lumen diameter in the short- and medium-term. The inconsistency can be mostly attributed to heterogeneity in outcome assessment (data reporting by lesion or by patient). It should be noted that the gains achieved in intermediate outcomes with IVUS-guided stenting did not translate into significant differences in mortality or MI. Nevertheless, there were significant reductions in TVR and restenosis rates during medium-term followup (>30 days to 1 year) with IVUS-guided stenting versus angiography-guided stenting, with a reduction in TVR of about 30 percent (mostly observed in RCTs of modest sample size).

The lower TVR and restenosis rates reported with IVUS-guided stenting should be interpreted cautiously; as these studies were conducted using a previous generation of bare-metal stents, and their results may no longer be applicable to current clinical practice with a widespread use of drug-eluting stents.

In the reviewed studies, IVUS-guided stenting appears to be associated with longer procedural times, greater radiation exposure, and greater contrast use than angiography-guided stenting, all factors that may be associated with short- and long-term risks of complications. **Table 2** summarizes the main findings with regards to the five Key Questions of this systematic review. Discussion regarding the report and recommendations for future research follow.

Table 2. Summary of evidence addressing key questions

Key Question	Strength of Evidence	Summary/Conclusions/Comments
Key Question 1 (deciding which coronary lesions need intervention): ***Overall***	FFR: moderate (favors FFR during medium- and long-term) Other intravascular diagnostic techniques: insufficient	• Favorable effect for FFR-guided stenting over stent placement guided by angiography alone, in intermediate coronary lesions (≥50 percent stenosis) for improved patient-centered outcomes, in studies that focused on men with intermediate coronary disease and lower grade angina, and excluded patients with left main disease. • None reported on IVUS and other investigational intravascular diagnostic techniques in studies with low or medium risk of bias
Key Question 2 (guiding PCI and deployment of stent and optimization): ***Overall***	IVUS: moderate (favors IVUS with reduction in TVR and restenosis, but none for mortality and MI) Other intravascular diagnostic techniques: insufficient	• Favorable effect for IVUS-guided stent deployment over stenting guided by angiography alone, for reduction in TVR and restenosis, in studies conducted before 2000 that focused on men, excluded patients with LMD and acute MI, and used a previous generation of bare-metal stents. • None reported on FFR-guided stent deployment and other investigational intravascular diagnostic techniques in studies with low or medium risk of bias
Key Question 3: ***Overall***	All intravascular diagnostic techniques: insufficient	• Two small retrospective studies addressed this question. One compared the use of IVUS with angiography in patients who had a stand-alone DCA. No significant differences in angiographic results were observed up to a mean of 5.7 years of followup. The other study compared the use of IVUS after PTCA with PTCA without IVUS. Some differences in incidence of restenosis were observed at 3 to 6 months. However, no statistical comparison was reported, making the results difficult to interpret
Key Question 4: ***Overall***	All intravascular diagnostic techniques: insufficient	• One small retrospective study compared FFR-guided PCI with IVUS-guided PCI in patients with intermediate coronary lesions. The one-year composite outcome of death/myocardial infarction/ischemia-driven target vessel revascularization was not significantly different between FFR and IVUS
Key Question 5: ***Overall***	IVUS: moderate (no association) Other intravascular diagnostic techniques: insufficient	• Two studies evaluating by subgroups of IVUS- or angiography-guided PCI reported no association between factors including sex, diabetes mellitus status, lesion length and reference diameter and LMD with individual components or composite outcome of MACE

CAD = coronary artery disease, DCA = directional coronary atherectomy, FFR = fractional flow reserve, IVUS = intravascular ultrasound, LMD = left main coronary artery disease, MACE = major adverse cardiac event, MI = myocardial infarction, PCI = percutaneous coronary intervention, PTCA = percutaneous transluminal coronary angioplasty, RCT = randomized controlled trial, TVR = target vessel revascularization

Context of Findings (Comparison with Other Reviews)

Our search identified three recently published systematic reviews comparing the effect of IVUS-guided PCI and non-IVUS-guided PCI.[14,54,55] These reviews included a total of 21 nonoverlapping studies (9 trials in Casella 2003,[14] 15 in Berry 2000,[54] and 7studies in Parise 2011[55]), with followup durations that ranged from 5 months to 2.5 years. Both randomized and nonrandomized trials, as well as registries, were included in these reviews. The clinical endpoints evaluated were TLR, TVR, MACE, mortality, MI, CABG, and restenosis. Angiographic outcomes including restenosis rate, MLD, percent diameter stenosis, acute gain, late lumen loss,

net gain, and resource utilization were also evaluated. The definition of MACE varied across the reviews.

All three reviews consistently reported a significant reduction in 6-month angiographic restenosis rate and TVR with IVUS-guided PCI versus non–IVUS-guided PCI. Two of these reviews also found a significant decrease in MACE with the use of IVUS for guiding PCI over non–IVUS-guided PCI.[14,55] No significant differences were observed between groups for the clinical outcomes of mortality or MI.

We reviewed 27 studies for comparisons of IVUS- and angiography-guided stent deployment, including two trials that were conducted in the era of drug-eluting stents. Our analyses revealed that only TVR was significantly lower in the IVUS-guided PCI group, as compared with the angiography-guided PCI group, during intermediate-term and long-term followup. Nonetheless, only six[23,25,28,30-32] and three[22,24,26,29] of the nine eligible RCTs had medium-term and long-term followup, respectively. Our review including recent literature did not find a significant decrease in MACE in the IVUS group compared with the angiography alone group. The disparity in our findings could be explained by the differences in eligibility criteria, in the number of included studies, or the methods of analyses. The first review searched until 1999 but found only two RCTs overlapping with our review, because of differences in eligibility criteria;[14] the second review searched until 2001 and identified only five of the total nine RCTs included in our review;[54] and the third review combined medium- and long-term data, which resulted in a statistical significant results for MACE.[55]

In this review, we examined both older studies (examining PCI with bare-metal stents) and more recent studies (examining PCI with drug-eluting stents). Our review also comprehensively evaluated nonrandomized comparative studies of intravascular diagnostic techniques. Our analyses evaluated both intermediate and clinical outcomes at various time points. Such extensive evaluations have not been carried out by prior reviews, which most often evaluated only the last reported time point. In addition, we conducted subgroup analyses, stratifying older versus newer studies (studies conducted before 2000 versus those conducted since 2000). Also in contrast to prior reviews, our review examined the impact of FFR in both RCTs and nonrandomized studies on short-, intermediate-, and long-term outcomes. In addition, our review synthesized data and analyzed gaps in the literature on the use of intravascular diagnostic techniques at various stages of the stenting (before, during, and after), and evaluated the role of these techniques in therapeutic decisionmaking. In summary, our review comprehensively examined both IVUS and FFR data, and has identified a lack of comparative studies for all other emerging novel and hybrid techniques.

Applicability

Reviewed studies were all conducted in tertiary care centers (with only one exception[32]), and were carried out mostly in Western Europe and North America. Studies included patients with various eligibility criteria for CAD undergoing PCI and stent placement at entry. Some studies included patients who had to be willing and be able to undergo followup angiography. The majority of the included patients were men. The majority of the studies specifically stated exclusion of individuals with LMD or acute MI. Minorities were underrepresented, although a few studies reported baseline data by race or ethnicity. These eligibility criteria likely selected groups of patients with intermediate coronary stenosis, better functional status, and higher socio-economic status, thus limiting applicability in patients with severe CAD. Thus, overall, there are

several important groups of patients who have not been adequately represented in the available studies.

Two studies reported the effect of various patient or lesion characteristics on outcomes among those who had an IVUS-guided stent placement versus stenting guided by angiography alone. These included controls of age, sex, and LMD. These subgroup analyses were limited by a lack of reporting for all subgroups, or statistical analyses for other intravascular diagnostic techniques. Thus, no overall conclusion could be drawn regarding the effect of patient characteristics on outcomes for FFR-guided stent placement versus stenting guided by angiography alone.

Drug-eluting stent deployment came into clinical use since the year 2000. Most IVUS trials (seven of nine RCTs) reviewed were performed before the year 2000. Interventional techniques and technology have evolved considerably since then, not only in terms of high-pressure balloon inflation, but also in stent design, composition, delivery systems, balloon technology, adjunctive pharmacotherapy, and other features. Current bare-metal stents are radically different than those used before 2000, and only two RCTs (both conducted in Eastern Europe) evaluated IVUS-guided stent placement in patients with a drug-eluting stent, and none evaluated second-generation drug-eluting stents. Thus, overall, there are several important groups of patients who have not been adequately represented in the available literature.

Implications for Clinical and Policy Decisionmaking

There is moderate strength of evidence favoring FFR-guided PCI over angiography-guided PCI in patients with intermediate coronary lesions; these findings are supported by only one large trial (FAME) and one nonrandomized study. Although the evidence was rated to be of moderate strength, there is the possibility that future studies will not support the favorable effect of FFR-guided PCI; this phenomenon, an initial effect that eventually dissipates through subsequent studies, has been well documented.[56]. (Although some data exist for the role of FFR after intervention in side branches or after stent deployment, no randomized or direct comparative studies have evaluated FFR in these circumstances.[57-59]) It is also worth noting that the FAME trial included patients with intermediate stenosis and lower grades of angina, patients who may otherwise not undergo stent implantation. The intrinsic risk of a non-ischemic stenosis may be lower than the risk of stent implantation itself. Treating low-risk lesions could lead to additional invasive tests or treatments that could adversely impact long-term clinical outcomes. Therefore, the use of stents in treating low-risk lesions should be weighed against this consideration. These decisions are, of course, not always straightforward in clinical practice. A further gap revolves around the role of FFR post-intervention or stent deployment, as FFR use has been primarily evaluated only in deciding whether revascularization is indicated.

Currently, IVUS is extensively applied in certain clinical situations and specific lesion subsets (e.g., LMD), without the backing of sufficient comparative data. Additionally IVUS is used to assess stent apposition and adequate stent expansion, lesion coverage, and edge dissections when the operator is in doubt and cannot angiographically determine with certainty whether a potentially life-threatening technical complication exists (i.e., one that could lead to stent thrombosis and potentially death). However, IVUS cannot fully assess the physiological significance of lesions (in deciding if a coronary lesion needs intervention), which depends not only on minimal lumen area (MLA), but also on numerous other factors including lesion length, reference vessel dimensions, and the amount of myocardium jeopardized by the lesion.

Our review did not find comparative data correlating findings of OCT, IVUS-VH, and NIRS with subsequent outcomes and events, or on their relative impacts and resource utilization profiles. Intravascular diagnostic techniques are quickly evolving, and differences in their learning curves and the skill with which they are employed can potentially influence outcomes. Additional study is necessary to figure out the implications of these factors on clinical and policy decisionmaking.

Limitations of this CER

Intravascular diagnostic techniques are quickly evolving, which likely explains why we found few comparative studies except for two techniques, IVUS and FFR. There was insufficient evidence to answer all but the first two of the review's Key Questions. Our review included only direct comparisons and only studies that had two distinct comparison groups (intravascular diagnostic technique and angiography versus angiography alone). We excluded studies that lacked a distinct angiography-guided PCI group both at intervention and at followup.

Other restrictions included the focus of Key Questions on the short time-frame around PCI, thereby excluding studies evaluating the intravascular diagnostic techniques during followup only (but not during PCI). The reporting of timing of intravascular diagnostic technique application in reviewed studies was often unclear (e.g., during PCI or immediately after).

Limitations of the Evidence Base

Outcome reporting (primarily with respect to patient-centered outcomes) were not completely available in the included studies. There is also substantial heterogeneity in composite outcome definitions of MACE. Less than one-quarter of the included populations were women, and studies often did not evaluate the use of intravascular diagnostic techniques in patients with acute MI and LMD. Most of the IVUS studies enrolled and followed patients before the year 2000. None of the studies included in our review was itself sufficiently powered to address the effectiveness of IVUS to improve long-term outcomes, and few studies reported long-term outcome data.

Few studies evaluated the comparative effectiveness of these intravascular diagnostic techniques in patients undergoing drug-eluting stent implantation, specifically the latest generation of stents. And studies often did not evaluate the effect of training of operators and their variability in the application of these techniques on clinical outcomes. Studies did not report on the effect of evolution intravascular diagnostic technique during study period.

Ongoing Research

A search in the ClinicalTrials.gov registry yielded two active (recent, ongoing) studies and one recently terminated study examining intravascular diagnostic techniques that are potentially relevant to the Key Questions in our report. None of the entries provided results. Two were RCTs evaluating the effect of FFR-guided PCI. The comparator in one RCT was angiography-guided PCI, and IVUS-guided PCI in the other. The first RCT (DEFER-DES), conducted in South Korea, compared FFR-guided stenting with stent placement guided by angiography alone for the treatment of intermediate coronary lesions using drug-eluting stents, and has since been terminated owing to the slow enrollment.

The second RCT (FAVOR) is an ongoing trial conducted in South Korea comparing the effectiveness of FFR-guided PCI with IVUS-guided PCI for the treatment of intermediate

coronary lesions. The primary outcome of this trial is MACE; secondary outcomes are the individual components of MACE. Patients will be followed clinically for up to 2 years. This trial is expected to enroll 1400 patients and will be completed by January 2014 (ClinicalTrials.gov number NCT01175863).

In addition to these two RCTs, the role of optimal medical therapy and FFR is also being further assessed in the ongoing FAME II study (ClinicalTrials.gov number NCT01132495). Recent unpublished data confirm that the trial has been halted after an interim analysis revealing significant benefit in the FFR arm.

Evidence Gaps

Table 3 summarizes the evidence gaps with regards to the five Key Questions of this systematic review.

Table 3. Evidence gaps

Key Question	PICO Categories	Evidence Gap
Key Question 1	Population	For the comparison between FFR-guided stenting or other intravascular diagnostic techniques and stenting guided by angiography alone: Because the vast majority of included studies enrolled a large proportion (>75%) of male patients with lower grades of angina, there is an evidence gap comparing the use of FFR-guided PCI with angiography-guided PCI in female patients and in patients with more serious diseases like LMD or acute MI.
	Intervention	There is an overall evidence gap for this comparison because there were only 3 comparative studies on FFR.
	Comparator	There is an evidence gap comparing patients with low angina score who could be potentially eligible to receive aggressive medical therapy instead of PCI to patients who will receive stenting guided by FFR, angiography alone, or other intravascular diagnostic techniques.
	Outcome	There is an evidence gap for within 30 days outcomes because the single RCT only reported periprocedural MI, but did not provide data for in-hospital death, TVR, or MACE.
	General evidence gap	There is an evidence gap because only one RCT with low risk of bias compared FFR with angiography.* There is an overall evidence gap for this comparison because no studies compared the use of other intravascular diagnostic techniques besides FFR with angiography.
Key Question 2	Population	For the comparison between IVUS guided stent placement and stenting guided by angiography alone: The vast majority of included studies enrolled a large proportion (>75%) of male patients and all but one RCT specifically excluded patients with left main coronary artery disease or acute MI. Therefore, there is an evidence gap comparing the use of IVUS-guided PCI with angiography-guided PCI in female patients and in patients with more serious diseases like left main coronary artery disease or acute MI.
	Intervention	There is lack of description of evolution of technology. Lack of IVUS trial data on the influence of operator's choice of balloon size and inflation pressures and their impact on clinical outcomes.
	Comparator	Because only two studies (both RCTs) conducted after year 2000 used the newer and current DESs, there is an evidence gap concerning the use of newer types of stents.
	Outcome	There is an evidence gap concerning long-term outcomes since neither RCT reported data on cardiac mortality and few studies reported outcomes greater than 1 year.

Key Question	PICO Categories	Evidence Gap
Key Question 3	General evidence gap	There is an evidence gap because only two observational studies and with high risk of bias reported on this comparison.
Key Question 4	General evidence gap	There is an evidence gap because only one observational study and with high risk of bias reported on this comparison.
Key Question 5	General evidence gap	No studies evaluated additional subgroups of interest, including patients with and without diabetes, patients with chronic inflammation (e.g., systemic lupus erythematosus), and patients with atherosclerosis following heart transplantation. There is an evidence gap in terms of lack of reporting of subgroup analyses of patients who underwent intravascular diagnostic-guided PCI compared with angiography-guided PCI and their impact on outcomes. .

CABG = coronary artery bypass grafting, IVUS = intravascular ultrasound, LMD = left main disease, MACE = major adverse cardiac event, MI = myocardial infarction, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, and TVR = target vessel revascularization.

*Despite moderate evidence from one RCT and one nonrandomized study favoring FFR-guided PCI over angiography-guided PCI, further trials are needed to corroborate the evidence.

Future Research

This review has identified substantial gaps in the intravascular diagnostic literature. Chief among them are the contemporary role of IVUS guidance in the placement of drug-eluting stents; the prognostic role of FFR, which should be confirmed in further trials; and evaluation of hybrid and novel techniques for comparative efficacy and safety. While early studies evaluating drug-eluting stents have used IVUS during stent placement, comparative studies, particularly RCTs of drug eluting stent placement guided by IVUS or angiography alone, are lacking. Drug-eluting stents prevent neointimal hyperplasia, and profoundly reduce the rate of restenosis and TVR, as compared with bare-metal stents. The potential advantage of IVUS guidance in stent placement to reduce restenosis and TVR has become less significant with the widespread use of drug-eluting stents. However, IVUS continues to be used in small vessels, complex lesions, and long lesions. It is important, then, that additional studies in these populations are conducted to assess the comparative effectiveness of IVUS in the drug-eluting stent era.

The role of FFR after intervention or stent deployment, in side branches and other clinical situations, and the roles of FFR and IVUS in other vascular territories, outside of the coronary circulation, should also be better defined in future trials. Data correlating findings of OCT, IVUS-VH, and NIRS with subsequent outcomes and events are not yet available. Although OCT is a very useful technology, particularly in stent research, its clinical role remains to be determined and will depend upon data demonstrating that OCT improves patient care and outcomes. The same applies for NIRS. Although the PROSPECT trial suggests that the addition of radiofrequency backscatter analysis to grayscale IVUS (IVUS-VH) might provide incremental information in predicting the site of future coronary events, further studies are warranted to investigate this hypothesis, and at present, PCI of nonsignificant lesions on the basis of plaque composition alone is not justified.[60,61] Catheters are currently deployed in combination with multiple imaging modalities for more comprehensive assessment, and variations or combinations of OCT or IVUS systems may further assist in the management of certain lesions. The future use of hybrid and novel intravascular diagnostic techniques may impact effectiveness and resource utilization. With an increase in availability, there will be increased utilization of hybrid and novel intravascular diagnostic techniques in the near future. The total cost and resources used for a

combination of techniques may be less than those for any technique alone. Furthermore, the use of combined intravascular diagnostic devices may decrease the total time required for imaging while also providing data from multiple intravascular diagnostic techniques. At present, the lack of available comparative data for hybrid and novel devices (as opposed to individual devices) limits evaluations of their effectiveness in routine clinical practice.

Future research is also needed to enrich our understanding of the comparative effectiveness of angiography and intravascular diagnostic techniques (both older and novel) in diverse ethnic populations, in women, and in patients with LMD and acute MI, as published studies often excluded these populations. Furthermore, more studies with followup duration greater than 1 year may enhance our understanding of the long-term impact of the use of intravascular diagnostic techniques as compared with angiography.

Consensus is needed among investigators in harmonizing outcomes assessment. Studies either reported data by patients or by lesions, thereby making synthesis difficult across studies. Future research is also needed to assess the usefulness of how these procedural data are presented, for example, if data by patients is preferable over data by lesions. Until consensus is achieved, investigators should be encouraged to present data both by patients and by lesions.

Conclusions

In summary, there is moderate evidence that the use of FFR-guided stenting to decide whether stenting for intermediate coronary lesions can confer a lower risk of death or MI, decrease total costs and length of stay, and lead to fewer stents being implanted, without sacrificing freedom from angina or the need for further revascularizations, as compared with angiography-guided PCI. These findings are limited, somewhat, by the fact that the FAME trial is the only large trial supporting them; further trials are needed to confirm and expand on these results.

There is a moderate strength of evidence that supports a significant difference in TVR and restenosis, but no significant difference in the clinical outcomes of mortality and MI, between IVUS-guided and angiography-guided stent placement, during medium- and long-term followup. However, most of the IVUS trials reviewed were performed before the year 2000. Further, there were only two RCTs (both conducted in Eastern Europe) evaluating IVUS-guided drug-eluting stent placement, and none of second-generation drug-eluting stents. These factors could affect the present-day applicability of the data, and the impact of current IVUS devices on TVR and restenosis must be reassessed in future studies of PCI with drug-eluting stent implantation.

Intravascular diagnostic techniques are quickly evolving, and further research is needed to evaluate the future use of novel and hybrid intravascular diagnostic techniques, as well as their relative impacts and resource utilization profiles. Furthermore, the majority of the eligible studies focused on men with lower grade disease and excluded patients with LMD; future studies (regardless of technology or the current intervention of interest) will also need to include women and patients with more serious CAD. Future work will also need to evaluate longer-term (on the order of years) patient outcomes to better appreciate real-world effectiveness and to better account for harms that may take years to manifest.

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Abbreviations

AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AVID	Angiography Versus Intravascular Ultrasound-Directed Stent Placement (study)
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CER	Comparative Effectiveness Review
CFR	Coronary flow reserve
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CRUISE	Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin (study)
DCA	Directional coronary atherectomy
DIPOL	Direct Stenting vs. Optimal Angioplasty Trial
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration (U.S.)
FFR	Fractional flow reserve
IMRI	Intravascular magnetic resonance imaging
IVUS	Intravascular ultrasound
KQ	Key Question
LAD	Left anterior descending
LMD	Left main (coronary artery) disease
MACE	Major adverse cardiac event
MRI	Magnetic resonance imaging
MI	Myocardial infarction
NIRS	Near-infrared spectroscopy
NS	Not significant
OCT	Optical coherence tomography
OFDI	Optical frequency domain imaging
OPTICUS	OPTimization with ICUS to reduce stent restenosis (study)
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary angiography
RCT	Randomized controlled trial
RESIST	REStenosis after IVUS-guided Stenting (study)
RR	Relative risk
SD	Standard deviation
SE	Standard error
SIPS	Strategy for Intracoronary Ultrasound-Guided PTCA and Stenting (trial)
STEMI	ST-segment elevation myocardial infarction
TCTMD	Transcatheter Cardiovascular Therapeutics
TEP	Technical Expert Panel
TLR	Target lesion revascularization
TOO	Task Order Officer

TULIP	Thrombocyte activity evaluation and effects of Ultrasound guidance in Long Intracoronary stent Placement (trial)
TVR	Target vessel revascularization