

AHRQ Comparative Effectiveness Review

Surveillance Program

CER # 18:

Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease

Original release date:

October 16, 2009

Surveillance Report (1st Assessment/cycle 1):

December, 2011

Surveillance Report (2nd Assessment/cycle 2)

August, 2012

Key Findings (1st assessment/cycle 1)

- KQ1 possibly out of date
- KQ2, KQ3, KQ4, KQ5, and KQ6 up to date
- KQ7 probably out of date
- There are no new significant safety concerns

Key Findings – (cumulative: 1st and 2nd assessments/cycle 1-2)

- KQ1 possibly out of date
- KQ2, KQ3, KQ4, KQ5, and KQ6 up to date
- KQ7 probably out of date
- There are no new significant safety concerns

Summary Decision:

This CER's priority for updating is **Low** (unchanged from the 1st assessment)

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1. Introduction

The purpose of this mini-report was to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether or not the CER No. 18 (Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease),¹ is in need of updating. This CER was originally released in October, 2009. It was therefore due for a surveillance assessment in April, 2010. When the Surveillance program began in the summer of 2011, this CER was selected to be in the first wave of reports to go through the assessment. The first surveillance assessment report of this CER was submitted to AHRQ in December, 2011. This second assessment was completed in October 2012.

This CER included 54 studies and 6 systematic reviews identified by using searches through February, 2009 and addressed seven key questions to evaluate effectiveness and safety of Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Blockers (ARB) for ischemic heart disease (IHD).

The key questions of the original CER were as follows:

Key Question 1: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?

Key Question 2: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function and are receiving standard medical therapy, what is the comparative effectiveness of combining ACE inhibitors and ARBs vs. either an ACE inhibitor or ARB alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?

Key Question 3: In patients with ischemic heart disease and preserved left ventricular function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?

Key Question 4: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function, what are the comparative

harms of adding ACE inhibitors or ARBs to standard medical therapy when compared to standard medical therapy alone?

Key Question 5: In patients with stable ischemic heart disease who have preserved left ventricular systolic function and are receiving standard medical therapy, what is the evidence of comparative harms of combination ACE inhibitor and ARB therapy vs. use with either an ACE inhibitor or ARB alone?

Key Question 6: In patients with ischemic heart disease and preserved left ventricular systolic function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what are the comparative harms of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone?

Key Question 7: What is the evidence that benefits or harms differ by subpopulations, including: demographics [sex, age, ethnicity, left ventricular ejection fraction (LVEF)], clinical course (previous treatment with a stent or coronary artery bypass surgery, degree and location of lesion, presence and pattern of symptoms), dose of the ACE inhibitor or ARB used, comorbidities (diabetes, renal dysfunction, hypertension), and other medications (vitamins, lipid lowering drugs, beta-blockers, anti-platelet agents)?

The conclusion(s) for each key question are found in the executive summary of the CER report.¹

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The Food and Drug Administration (FDA), Health Canada, and Medicines and Healthcare Products Regulatory Agency (MHRA) surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, safety surveillance alerts), a consensus-based conclusion was drawn whether or not any given conclusion warrants any updating (up to date, possibly out of date, or out of date). Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere.²⁻⁴

2.1 Literature Searches

Cycle 2 (2nd assessment)

The same search strategy was used as in the 1st assessment (cycle 1) but using different search dates for Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <17 May 2011 to 5 July 2012>, Embase <2011 to 2012 Week 27>, the Cochrane Central Register of Controlled Trials (CCRCT; search date 4 JULY 2012), and Cochrane Database of Systematic Reviews (CDSR; search date – 28 June 2012) as per the original search strategies appearing in the CER's Appendix A.¹

Cycle 1 (1st assessment)

The CER search strategies were reconstructed in MEDLINE (January 1, 2009-November 16, 2011), Embase (2008 Week 1 to 2011 Week 45), the Cochrane Central Register of Controlled Trials (CENTRAL; search date - November 16, 2011), and Cochrane Database of Systematic Reviews (CDSR; search date - November 16, 2011) as per the original search strategies appearing in the CER's Appendix A.¹ The Embase RCT search was run using the OVID platform because the platform used by CER was not available through our institutional subscription. For the same reason we used the Wiley platform for the Cochrane search. The syntax and vocabulary, which include both controlled subject headings (e.g., MeSH) and keywords, were applied according to the databases indicated in the appendix and in the search strategy section of the CER report. The MEDLINE search was limited to five general medical journals (Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine) and several specialty journals (the Journal of American College of Cardiology, Circulation, American Heart Journal, American Journal of Cardiology, and European Heart Journal). Restricting by journal title was not possible in the Cochrane search and pertinent citations were instead selected from the results. Study design filters were not applied to the Cochrane search since the Cochrane Central Register only contains randomized or controlled clinical trials. Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

All identified bibliographic records were screened using the same inclusion/exclusion criteria as one described in the original CER.

2.3 Expert Opinion

Cycle 2 (2nd assessment)

We contacted 2 experts (1 CER-specific and 1 local expert) that had responded to the first assessment and 1 external additional expert.

Cycle 1 (1st assessment)

In total, 2 CER-specific (e.g., lead author, clinical content experts, and technical expert panel members) and 5 additional clinical content experts (2 ‘local’ and 3 ‘others’) were requested to provide their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER were examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only. For any given CER that included a meta-analysis, the assessment started with the identification of qualitative signal(s), and if no qualitative signal was found, this assessment extended to identify any quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The definition and categories of updating signals are presented in Appendix B and publications.^{2,3}

2.5 Compilation of Findings and Conclusions

All the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and safety surveillance alerts) was collated and summarized. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, and safety surveillance alerts) presented in a tabular form, a conclusion was drawn whether or not any conclusion(s) of the CER warrant(s) updating.

Conclusions were drawn based on four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating
- Original conclusion is **possibly out of date** and this portion of CER may need updating
- Original conclusion is **probably out of date** and this portion of CER may need updating

- Original conclusion is **out of date** and this portion of CER is in need of updating

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still up to date.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

Determination of priority groups (i.e., Low, Medium, and High) for updating any given CER was based on two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?
- How out of date are conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

Cycle 2 (2nd assessment)

A total of 115 bibliographic records were identified (MEDLINE=26, CCRCT =10, CDSR=8, Embase=71). After ~~eliminating duplicates~~ ~~de-duping~~, 101 records remained (MEDLINE=22 and CCRCT=5, CDSR=8, Embase=66), from which 22 potentially eligible records were assessed for full text. Of these, 3 publications were included in the update.⁵⁻⁷

Cycle 1 (1st assessment)

A total of 272 bibliographic records were identified (MEDLINE=77, Embase=135, CENTRAL=52, and CDSR=8). After de-duping, 203 records were remained (MEDLINE=58, Embase=124, CENTRAL=13, and CDSR=8). Of the 203 records, 155 were excluded at abstract screening level, leaving 48 potentially eligible records for full text screening. The full text screening of 48 records resulted in 11 included publications.⁸⁻¹⁸ One additional publication was identified through an FDA alert.¹⁹ Thus, a total of 12 publications were included in this surveillance report.⁸⁻¹⁹

3.2 Signals for Updating in Newly Identified Studies [Cycle 2]

3.2.1 Study overview

The study, population, treatment characteristics, and results for the 3 included studies⁵⁻⁷ are presented in Appendix C (Evidence Table).

One of the 3 included studies was a randomized trial⁶ and two were systematic reviews/meta-analyses.^{5,7}

The randomized trial compared harms of ARB (candesartan) vs. standard therapy (ACEI, diuretics, calcium channel blockers) in 2,049 hypertensive patients with coronary artery disease (risk equivalent of stable ischemic heart disease) who were followed up for 4.2 years.⁶ The measured outcomes were the incidence of total adverse events and cancer.

Two systematic reviews/meta-analyses compared the efficacy of ACEIs (or ARBs) to placebo in patients with non-diabetic chronic kidney disease (risk equivalent of stable ischemic disease)⁷ and atherosclerotic vascular disease (stable ischemic heart disease)⁵ in terms of total mortality and the composite outcome rate (cardiovascular death, nonfatal myocardial infarction, or stroke). The meta-analyses were based on 2 randomized trials (1,906 patients)⁷ and 10 randomized trials (21,226 patients).⁵ The dose of ACE and ARB across the reviews ranged from 1.25mg to 20mg and 80mg to 300mg, respectively.

3.2.2 Qualitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

Key question #1

ACEI or ARB vs. Placebo (or standard treatment)-Efficacy

| In agreement with CER, ~~according to one~~ the newly published meta-analysis,⁵ reported that in patients with stable ischemic heart disease, ACEI or ARB compared to placebo was beneficial in reducing the risk of composite endpoint (OR=0.81, 95% CI: 0.75, 0.88). **No Signal**

| In agreement with CER, ~~according to one~~ another meta-analysis,⁷ observed that in patients with stable ischemic heart disease risk equivalents, ACEI compared to placebo influenced neither total mortality rate (RR=1.80, 95% CI 0.17, 19.27) nor the risk of composite endpoint (RR=0.87, 95% CI : 0.66, 1.14). **No Signal**

ACEI or ARB vs. CCB (or standard treatment) – Efficacy

No new evidence. **No Signal**

Key question #4

ACEI or ARB vs. Placebo (or standard treatment) - Harms

In agreement with CER, 1 randomized trial⁶ in patients with risk equivalent of stable ischemic heart disease, demonstrated no difference between ARB vs. standard treatment in the risk of total adverse events (78% vs. 78.8%, p=NR) or cancer (HR=0.95, 95% CI: 0.65, 1.38). **No Signal**

ACEI (or ARB) vs. CCB (or standard treatment) – Harms

No new evidence. **No Signal**

Key questions #2, 3, 5, 6, and 7

None of the included studies provided any evidence to answer these key questions. **No Signal**

3.2.3 Quantitative signals

No meta-analysis was performed.

3.3 Safety surveillance alerts [Cycle 2]

None of the received safety surveillance alerts was relevant to the key questions of the given CER.

3.4 Expert opinion [Cycle 2]

Of the 2 ~~contacted~~-experts who had provided feedback for the 1st cycle, only one responded for the 2nd cycle. ~~The external expert contacted for the 2nd-cycle only has also responded.~~ In total, 2 experts provided their feedback.

4. Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from studies identified through the update search, safety surveillance alerts, and expert opinion) are provided in Table 1 (Summary Table). Based on the two assessments (cycles 1-2), this CER is categorized in the Low (unchanged from the 1st assessment) priority group for updating.

Key Question # 1

Signals from studies identified through update search (Cycle 2)

In agreement with the conclusions of the original CER, 1 meta-analysis,⁵ showed that patients with stable ischemic heart disease benefited from ACEI or ARB more than from placebo in terms of reduced risk of the composite outcome (CV mortality, MI, or stroke) . **No Signal.** In agreement with the conclusions of the original CER, 1 meta-analysis,⁷ showed that patients with stable ischemic heart disease risk equivalent receiving ACEI, experienced similar mortality and the composite outcome rates compared to placebo. **No Signal.**

Experts (Cycle 2): Both experts stated that conclusions in the key question # 1 are still valid.

Safety surveillance alerts (Cycle 2): No relevant safety alerts.

1st assessment conclusion (Cycle 1): **Possibly out of date**

Total (cumulative) conclusion (Cycles 1-2): **Possibly out of date**

Key Questions # 2, 3, 5, and 6

Signals from studies identified through update search (Cycle 2)

No new evidence. **No Signal.**

Experts (Cycle 2): Both experts stated that conclusions in the key questions # 2-3, 5-6 are still valid.

Safety surveillance alerts (Cycle 2): No relevant safety alerts.

1st assessment conclusion (Cycle 1): **Up to date**

Total (cumulative) conclusion (Cycles 1-2): **Up to date**

Key Question # 4

Signals from studies identified through update search (Cycle 2)

In agreement with the original CER findings, 1 RCT⁶ showed similar rates of total adverse events between ARB and standard treatment in patients with risk equivalent of stable ischemic heart disease. **No Signal.**

Experts (Cycle 2): Both experts stated that conclusions in the key question # 4 are still valid.

Safety surveillance alerts (Cycle 2): No relevant safety alerts.

1st assessment conclusion (Cycle 1): **Up to date**

Total (cumulative) conclusion (Cycles 1-2): **Up to date**

Key Question # 7

Signals from studies identified through update search (Cycle 2)

No new evidence. **No Signal.**

Experts (Cycle 2): Both experts stated that conclusions in the key question # 7 are still valid.

Safety surveillance alerts (Cycle 2): No relevant safety alerts.

1st assessment conclusion (Cycle 1): **Probably out of date**

Total (cumulative) conclusion (Cycles 1-2): **Probably out of date**

Table 1. Summary Table

Conclusions from CER's Executive Summary	Update literature search results	Signals for updating		Safety surveillance alerts	Expert opinion	Validity of CER conclusions	
		Qualitative	Quantitative			Cycle 1 assessment	Cycles 1-2 (total cumulative) assessment
<p>Key Question 1: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?</p>							
<p>Patients with stable ischemic heart disease and preserved left ventricular function benefit from receiving ACE inhibitors, and perhaps ARBs as well, in addition to standard medical therapy, but may not benefit more than from using calcium channel blockers in addition to standard medical therapy. Future research is needed to determine if ACE inhibitors or ARBs offer additional benefits over other vasoactive drugs. The TRANSCEND (Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular Disease) trial was the only placebo-controlled trial available to evaluate major efficacy outcomes for ARB therapy. ARB therapy was associated with reductions in the composite endpoint of cardiovascular mortality, nonfatal myocardial infarction, and stroke similar to the pooled results from the HOPE (Heart Outcomes Prevention Evaluation) and PEACE (Prevention of Events with Angiotensin Converting Enzyme inhibition) trials comparing ACE inhibitors to placebo. While major ACE inhibitor trials utilized a run-in period to ensure that subjects tolerated ACE inhibitor therapy, subjects in TRANSCEND were intolerant of ACE inhibitors and may represent a distinct population. This reduces the confidence of indirect comparisons, and direct evidence comparing ACE inhibitors and ARBs should be considered.</p>	Cycle 2 (August 2012)				Possibly out of date	Possibly out of date	
	2 SR/MA ^{5,7}	<p>No Signal In agreement with CER, according to one MA,⁵ in patients with stable ischemic heart disease, ACEI or ARB compared to placebo was beneficial in reducing the risk of composite endpoint (OR=0.81, 95% CI: 0.75, 0.88)</p> <p>No Signal In agreement with CER, according to one MA,⁷ in patients with IHD risk equivalents, compared to placebo, ACEI influenced neither total mortality risk (RR=1.80, 95% CI 0.17, 19.27) nor the risk of composite endpoint (RR=0.87,</p>	<p>No Signal Given the newly identified MAs, no MA in the original CER was <u>not</u> updated</p>	None	Still valid (2 experts)		

		95% CI: 0.66, 1.14)				
Cycle 1 (December 2011)						
4 RCTs 12,13,15,18	No Signal Findings of all three SRs/MA are in agreement with those of CER indicating that patients receiving ACEI compared to placebo experienced significantly reduced rates of total mortality, ^{14,16} CV mortality, ^{14,16} non-fatal MI, ^{14,16} stroke, ¹⁴ composite endpoint, ^{14,16} revascularization ¹⁶ or hospitalization for HF. ^{16,17}	No Signal The MA for ACEI in CER were not updated, since the newly identified 3 evidence reports included multiple MA. ^{14,16,17}	None	All 3 experts stated that there is absence or only confirmatory evidence rendering this conclusion still valid		
1 Non-RCT ¹¹		No Signal To check if the pooling of ARB RCTs would overturn the observed non-significant findings of individual trials between ARB and placebo, results of the only ARB trial ²⁰ included in CER were pooled with those from newly identified ARB trials. ^{12,13,18}				
3 SR/MA ^{14,16,17}	Corroborating results of CER, in 3 newly identified RCTs, of which one was pivotal, ¹² there were no significant differences between ARB (valsartan, olmesartan, irbesartan) and placebo/standard treatment for reduction in total mortality, ^{12,18} CV mortality, ^{12,13,18} non-fatal MI, ^{12,13} stroke, ^{12,13} composite endpoint, ^{12,13,18} revascularization ^{12,13} or hospitalization for CV reason. ^{12,13}	For none of the outcomes except stroke the pooled RR estimates was overturned, thereby indicating no difference between ARB vs. placebo, corroborating the CER findings:				
	No Signal There was no new					

		evidence comparing ACEI or ARB with CCB.	total mortality (RR=0.99, 95% CI: 0.92, 1.08) ^{12,18,20} CV mortality (RR=1.04, 95% CI: 0.93, 1.15) ^{12,13,18,20} MI (RR=0.92, 95% CI: 0.79, 1.08), ^{12,18,20} any hospitalization (RR=0.99, 95% CI: 0.95, 1.02), ^{18,20} and revascularization (RR=0.93, 95% CI: 0.84, 1.03). ^{12,13,20}				
			1 Signal (B1) The pooled estimate for stroke indicated ARB to be more beneficial than placebo in reducing the risk of stroke (RR=0.82, 95% CI: 0.70, 0.96). ^{12,18,20}				

Key question 2: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function and are receiving standard medical therapy, what is the comparative effectiveness of combining ACE inhibitors and ARBs versus either an ACE inhibitor or ARB alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?

There is direct comparative evidence from ONTARGET (Ongoing Telmisartan Alone in combination with Ramipril Global Endpoint Trial) that ACE inhibitors and ARBs provide similar benefits in major outcomes of interest in this population. Since ONTARGET directly compared the same drugs as were evaluated in the placebo-controlled HOPE and TRANSCEND trials (ramipril and telmisartan), the direct evidence of similar	Cycle 2 (August 2012)					Up to date	Up to date
	No new evidence	NA	NA	None	Still valid (2 experts)		
	Cycle 1 (December 2011)						
	No new evidence	NA	NA	None	Still valid (3 experts)		

benefit is more compelling than indirect evidence of possible differences from Key Question 1.							
Key question 3: In patients with ischemic heart disease and preserved left ventricular function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?							
Trials compared the addition of ACE inhibitors or ARBs to standard medical therapy vs. standard medical therapy alone (with or without a placebo). For our base case analysis, we limited the trials to randomized, double-blinded comparisons of ACE inhibitors or ARBs to placebo. ACE inhibitors or ARBs did not significantly impact any of the endpoints evaluated. However, except for the endpoint “need for subsequent revascularization,” the incidence rates for the endpoints were low. Overall, the evidence from Key Question 3 suggests that initiation of ACE inhibitors or ARBs in close proximity to a revascularization procedure does not confer significant clinical benefit. However, findings for Key Question 1 suggested that patients with established ischemic heart disease do derive significant clinical benefits from ACE inhibitor or ARB therapy in addition to standard medical therapy. Thus the question becomes, At what point following a cardiac revascularization procedure does a patient with ischemic heart disease derive benefits from these agents? A majority of the trials included in Key Question 1, including HOPE, PEACE, and EUROPA (EUropean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease), included patients who were at least 3 to 6 months removed from undergoing a coronary procedure. Thus it seems plausible that this period of time should be given following a revascularization procedure before ACE inhibitors or ARBs are initiated in these populations. However, no studies have prospectively investigated the optimal time to begin therapy, and more concrete interpretations cannot be made until this evidence becomes available.	Cycle 2 (August 2012)					Up to date	Up to date
	No new evidence	NA	NA	None	Still valid (2 experts)		
	Cycle 1 (December 2011)						
No new evidence	NA	NA	None	Still valid (3 experts)			
Key question 4: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function, what are the comparative harms of adding ACE inhibitors or ARBs to standard medical therapy when compared to standard medical therapy alone?							
ACE inhibitors or ARBs significantly increase the risk of	Cycle 2 (August 2012)					Up to date	Up to date

<p>withdrawing due to adverse events, syncope, cough, and hyperkalemia compared with placebo. ACE inhibitors or ARBs significantly increase the risk of cough and hypotension compared with calcium channel blockers. A number of the included trials had run-in periods in their study design. Thus, the true incidence of harms with these therapies in environments outside of clinical trials may be higher than that reported here. The unique design of the TRANSCEND trial, which compared telmisartan to placebo, deserves special discussion. All of the patients included in TRANSCEND were intolerant to ACE inhibitors at baseline. Following a median followup of 56 months, the ARB telmisartan was relatively well tolerated, with only a statistically higher risk of hypotension symptoms compared with placebo (p=0.049). Thus it appears that ARBs may be a relatively safe alternative for patients with stable ischemic heart disease who cannot tolerate ACE inhibitors or are at an increased risk for harms. Given the benefits seen in Key Question 1, the balance of benefits to harms for the use of ACE inhibitors or ARBs in patients with stable ischemic heart disease seems favorable.</p>	<p>1 SR/MA⁷</p> <p>1 RCT⁶</p>	<p>No Signal 1 RCT⁶ in pts with risk equivalent of stable IHD, demonstrated no difference between ARB vs. standard treatment in the risk of total AEs (78% vs. 78.8%, p=NR) or cancer (HR=0.95, 95% CI: 0.65, 1.38)</p>	<p>No Signal No MA in CER</p>	<p>None</p>	<p>Still valid (2 experts)</p>		
	Cycle 1 (December 2011)						
	<p>2 RCTs^{12,18}</p> <p>1 SR/MA¹⁴</p>	<p>No Signal In agreement with CER, findings of one SR/MA¹⁴ indicated significantly greater risk for WDAEs (pooled RR=2.30, 95% CI: 1.34, 3.95), syncope (pooled RR=1.24, 95% CI: 1.02, 1.52), or cough (pooled RR=1.67, 95% CI: 1.22, 2.29) in patients randomized to ACEI (enalapril, ramipril, trandolapril) vs. placebo.</p> <p>In agreement with CER, there was no significant difference in hypotension rates between ACEI and placebo (pooled RR=1.79, 95% CI: 0.68, 4.71).¹⁴</p> <p>No Signal There was no new evidence comparing ACEI or ARB with CCB.</p> <p>No Signal Two newly identified RCTs^{12,18} compared and</p>	<p>No Signal The MA for ACEI in CER were not updated, since the newly identified evidence report included MA.¹⁴</p> <p>No Signal To check if the pooling of ARB RCTs would overturn the observed non-significant findings of individual trials between ARB and placebo, results of the only ARB trial²⁰ included in CER were pooled with those from newly identified ARB trials for WDAE</p>	<p>2 FDA alerts (April-June 2011) were received indicating potential safety issues. No causality has been established and FDA decided no action was necessary at this time:</p> <p>ARB (olmesartan and valsartan) use:</p> <p>1. anaphylactic reactions^μ</p> <p>2. hemolytic anemia^Ω</p>	<p>Still valid (3 experts)</p>		

		<p>reported adverse events between patients randomized to ARB and placebo. One pivotal trial¹² reported similar results to those of CER, indicating similar risk of WDAE (12.0% vs. 11.4%, p=0.33) and excess risk for only hypotension (42.4% vs. 35.9%, p<0.001) and back pain (16.7% vs. 14.6%, p<0.01) in ARB- vs. placebo-treated patients. Similarly, the other trial¹⁸ showed no differences between ARB and placebo in risk of WDAE (16.0% vs. 14.0%, p=0.07), hypotension (3.0% vs. 3.0%, p=0.84), renal failure (3.0% vs. 3.0%, p=0.29), or hyperkalemia (0.6% vs. 0.4%, p=0.84).</p>	<p>(pooled RR=1.0, 95% CI: 0.95, 1.06),^{12,18,20} renal dysfunction (pooled RR=1.00, 95% CI: 0.81, 1.25)^{12,20} and cough (pooled RR=0.99, 95% CI: 0.88, 1.12).^{12,20}</p> <p>None of the pooled RR estimates became statistically significant.</p>				
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Key question 5: In patients with stable ischemic heart disease who have preserved left ventricular systolic function and are receiving standard medical therapy, what is the evidence of comparative harms of combination ACE inhibitor and ARB therapy versus use with either an ACE inhibitor or ARB alone?

<p>The results of Key Questions 2 and 5 are evaluated together to discern the comparative balance of benefits and harms. ACE inhibitor therapy, represented by ramipril, provides efficacy similar to the combination of an ACE inhibitor plus an ARB, represented by ramipril and telmisartan, with a lower risk of patient harm. As such, current evidence does not support the use of combination therapy at this time. The ACE inhibitor ramipril and the ARB telmisartan have similar efficacy, similar risks of harms, and therefore a similar balance of benefits to harms.</p>	Cycle 2 (August 2012)					Up to date	Up to date
	No new evidence	NA	NA	None	Still valid (2 experts)		
	Cycle 1 (December 2011)						
	No new evidence	NA	NA	None	Still valid (3 experts)		

Key question 6: In patients with ischemic heart disease and preserved left ventricular systolic function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what are the comparative harms of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone?

<p>The constituent trials did not utilize a lengthy run-in period. Only the APRES (Angiotensin-converting Enzyme inhibition Post Revascularization Study) trial</p>	Cycle 2 (August 2012)					Up to date	Up to date
	No new evidence	NA	NA	None	Still valid (2 experts)		

used a run-in period, and this was a single test dose. Since the only trial evaluating an ARB did not report adverse event results, our results cannot be applied to ARBs. The use of ACE inhibitors was associated with hypotension. While ACE inhibitors nonsignificantly increased the risk of cough, only three trials provided information on this. They all agreed on the direction of effect, and two of the three trials individually found ACE inhibitors to increase cough vs. placebo. Given the lack of significant benefits found in Key Question 3, the balance of benefits to harms for the initiation of an ACE inhibitor or ARB in close proximity to a revascularization procedure is not favorable.	Cycle 1 (December 2011)						
	No new evidence	NA	NA	None	Still valid (3 experts)		
Key question 7: What is the evidence that benefits or harms differ by subpopulations, including: demographics [sex, age, ethnicity, left ventricular ejection fraction], clinical course (previous treatment with a stent or coronary artery bypass surgery, degree and location of lesion, presence and pattern of symptoms), dose of the ACE inhibitor or ARB used, co-morbidities (diabetes, renal dysfunction, hypertension), and other medications (vitamins, lipid lowering drugs, beta-blockers, anti-platelet agents)?							
This Key Question provides important information regarding the applicability of the benefits data. Since there were no subgroup comparisons based on harms, the balance of benefits to harms in these subgroups is not known. While we cannot state with certainty that ARBs do not work as well in females as in males, the subgroup analyses of the TRANSCEND and ONTARGET trials support the need for more research in this area. Patients with renal dysfunction have at least as robust relative reductions in the risk of cardiovascular events as those without dysfunction when ACE inhibitors are given. Even in the PEACE trial, where the overall benefits associated with ACE inhibitor therapy was not as robust, a strong trend toward benefits was seen in the subgroup with renal dysfunction receiving ACE inhibitors vs. those receiving placebo. When we evaluated the impact of baseline risk on efficacy, there was a suggestion that ARBs might work better in lower risk patients while ACE inhibitors work better in higher risk patients. Perhaps the lowest risk group was least likely to receive aspirin therapy. The aspirin therapy itself may attenuate the benefits of ACE inhibitors. Lipid lowering therapy does not seem to negatively impact the benefits of ACE inhibitor or ARB therapy. This is important, since patients with stable ischemic heart disease are receiving higher intensity lipid lowering therapy than they did previously. Patients without a prior revascularization procedure may benefit more from ACE inhibitors than those with	Cycle 2 (August 2012)					Probably out of date	Probably out of date
	No new evidence	NA	NA	None	Still valid (2 experts) One expert cited subgroup analyses results from ONTARGET which indicated no subgroup beneficial effects of dual therapy with ARB and ACE vs. monotherapy In TRANSCEND trial, ARB vs. placebo was associated with higher rate of renal events for patients with normo albuminuria (HR= 2.35, 95% CI: 1.33, 4.15)		

<p>revascularization. More work is needed to evaluate the impact of different modalities of revascularization (bare metal stents, drug-eluting stents, coronary artery bypass grafting, atherectomy) on the benefits associated with ACE inhibitors and ARBs. The balance of benefits to harms derived from initiating ACE inhibitor or ARB therapy along with a revascularization procedure is not favorable.</p>				<p>However, in patients with microalbuminuria the rate of renal events was not significantly different between ARB vs. placebo (HR=0.60, 95% CI: 0.25, 1.46)</p>	
Cycle 1 (December 2011)					
	<p>3 RCTs^{10,12,18} 2 non-RCTs^{8,9} 1 SR/MA¹⁶</p>	<p>1 Signal (A1) The data reported in an ARB pivotal trial of pts with type 2 diabetes¹⁰ indicated increased rate of CV deaths (HR=4.94, 95% CI: 1.43, 17.06), hypotension, headache, and dizziness for ARB vs. placebo.</p> <p>No Signal In two other RCTs,^{12,18} the similar effects of ARB vs. placebo on composite endpoint (definition differed across studies) did not change across subgroups defined by gender, age, race, BMI, hypertension, and history of CVD.</p> <p>1 Signal (A5) In one pivotal trial,¹² the use of ARB compared to placebo demonstrated benefit for composite endpoint in ACEI users (HR=0.70, 95% CI: 0.49, 0.99), but not in non-users of ACEI (HR=1.05,</p>	<p>Pooling was not attempted because of the presence of qualitative signals</p>	<p>One FDA alert (June 2011)^β reported higher CV death rate for diabetic patients after receiving ARB (olmesartan) vs. placebo in ROADMAP¹⁰ and ORIENT^ε trials¹⁹</p> <p>FDA review is ongoing and the agency has not concluded that olmesartan increases the risk of death. According to FDA, results from other trials have not suggested an increased risk</p>	<p>Still valid (3 experts)</p> <p>One expert mentioned two trials ROADMAP¹⁰ and ORIENT¹⁹ in which diabetic patients had increased risk of CV death after receiving ARB - olmesartan (vs. placebo)</p>

		<p>95% CI: 0.89, 1.23).</p> <p>No Signal In agreement with CER, one SR/MA¹⁶ showed that the benefit in composite endpoint associated with ACEI vs. placebo was not modified across age, gender, diabetes, hypertension, history of MI, use of lipid lowering agents, revascularization, or systolic blood pressure.</p> <p>1 Signal (A7) One study of ESRD pts⁸ suggested an increased risk of hospitalization for AF in ACEI users compared to non-users (HR=1.41, 95% CI: 1.11, 1.80).</p> <p>1 Signal (Other) One study⁹ showed that the benefit in composite endpoint conferred by ACEI relative to placebo was modified by genetic polymorphism, specifically patients with smaller pharmacogenetic score (<3) experienced fewer events (HR=0.67, 95% CI: 0.56, 0.79), whereas patients with greater score (≥ 3) did not (HR=1.26, 95% CI: 0.97, 1.67).</p>		<p>of CV death associated with olmesartan and other ARBs</p>			
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pts=patients; d=day(s); yr(s)=years; mo=month(s); HR=hazard ratio; KMA=Kaplan-Meier analysis MVA=multivariable analysis; NR=not reported; CER=comparative effectiveness review; ACEI=angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blockers; RCT=randomized controlled trial; AF=atrial fibrillation; EF=ejection fraction; CAD= coronary artery disease; AE=adverse event; FU=follow-up; SR=systematic review; MA=meta-analysis; IPD=individual patient data; CV=cardiovascular; CVD=cardiovascular disease; MI=myocardial infarction; PL=placebo; WDAE=withdrawals due to adverse events; HF=heart failure; IHD=ischemic heart disease; CCB=calcium channel blocker; PCI= percutaneous coronary intervention; ST=standard treatment; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; EF=ejection fraction; CHD=coronary heart disease; RR=relative risk; CAD=coronary artery disease; ESRD=end-stage renal disease; FDA=food and drug administration

[‡] The **ORIENT** trial¹⁹ which has been published electronically on October 13, 2011 was initially identified through FDA alert (see above). The update search did not capture this study because it was not published in one of the 10 journals the update search was restricted to.

[‡] <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258781.htm>

^Ω <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm085916.htm>

^β <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm215249.htm>

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Appendix A: Search Methodology

All MEDLINE searches were limited to the following journals:

General biomedical – Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine

Specialty journals – the Journal of American College of Cardiology, Circulation, American Heart Journal, American Journal of Cardiology, and European Heart Journal

Cycle 2 (2nd assessment)

Database: Ovid MEDLINE(R)

Time period covered: 17 May 2011 to 5 July, 2012

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

-
- 1 Coronary Artery Disease/ or Coronary Disease/ (152928)
 - 2 Myocardial Ischemia/ (29829)
 - 3 Angina Pectoris/ or Angina, Unstable/ (36261)
 - 4 Arterial Occlusive Diseases/ (23821)
 - 5 Peripheral Vascular Diseases/ (10457)
 - 6 Vascular Diseases/ (25236)
 - 7 Atherosclerosis/ (15994)
 - 8 Cardiovascular Diseases/ (86513)
 - 9 Carotid Artery Diseases/ (16883)
 - 10 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (7296)
 - 11 or/1-10 (370897)
 - 12 randomized controlled trial.pt. (330350)
 - 13 controlled clinical trial.pt. (84367)
 - 14 randomized.ab. (245837)
 - 15 placebo.ab. (137086)
 - 16 clinical trials as topic.sh. (160766)
 - 17 randomly.ab. (180149)
 - 18 trial.ti. (105778)
 - 19 or/12-18 (792103)
 - 20 humans.sh. (12353420)

- 21 19 and 20 (688885)
- 22 (alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide or trandolapril or zofenopril).mp. (25861)
- 23 (losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (13737)
- 24 Angiotensin-Converting Enzyme Inhibitors/ (26684)
- 25 Angiotensin II Type 1 Receptor Blockers/ (6101)
- 26 (ACEI or ARB).mp. (3963)
- 27 or/22-26 (52072)
- 28 11 and 21 and 27 (1562)
- 29 lancet.jn. (122331)
- 30 jama.jn. (62388)
- 31 "annals of internal medicine".jn. (27403)
- 32 bmj.jn. (73546)
- 33 "new england journal of medicine".jn. (65472)
- 34 american journal of cardiology.jn. (32009)
- 35 circulation.jn. (37036)
- 36 "journal of the american college of cardiology".jn. (18580)
- 37 american heart journal.jn. (21599)
- 38 european heart journal.jn. (12379)
- 39 or/29-38 (472743)
- 40 28 and 39 (390)
- 41 limit 40 to yr="2012-current" (7)
- 42 ("20110517" or "20110518" or "20110519" or "20110520" or "20110521" or "20110522" or "20110523" or "20110524" or "20110525" or "20110526" or "20110527" or "20110528" or "20110529" or "20110530" or "20110531" or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112*).ed. (637897)
- 43 40 and 42 (13)
- 44 41 or 43 (20)

MEDLINE – Observational

Search for: 35 or 37

-
- 1 epidemiologic studies/ (5410)
 - 2 exp case control studies/ (557107)
 - 3 exp Cohort Studies/ (1183054)
 - 4 case control.tw. (63770)
 - 5 (cohort adj (study or studies)).tw. (65164)
 - 6 cohort analy\$.tw. (2892)

- 7 (follow up adj (study or studies)).tw. (34030)
- 8 (observational adj (study or studies)).tw. (33696)
- 9 longitudinal.tw. (117682)
- 10 retrospective.tw. (225412)
- 11 cross sectional.tw. (132446)
- 12 Cross-Sectional Studies/ (141891)
- 13 or/1-12 (1619204)
- 14 (alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril).mp. (20996)
- 15 (moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide ortrandolapril or zofenopril).mp. (6018)
- 16 (losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (13737)
- 17 Angiotensin-Converting Enzyme Inhibitors/ (26684)
- 18 Angiotensin II Type 1 Receptor Blockers/ (6101)
- 19 (ACEI or ARB).mp. (3963)
- 20 or/14-19 (52072)
- 21 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (7296)
- 22 13 and 20 and 21 (117)
- 23 lancet.jn. (122331)
- 24 jama.jn. (62388)
- 25 "annals of internal medicine".jn. (27403)
- 26 bmj.jn. (73546)
- 27 "new england journal of medicine".jn. (65472)
- 28 american journal of cardiology.jn. (32009)
- 29 circulation.jn. (37036)
- 30 "journal of the american college of cardiology".jn. (18580)
- 31 american heart journal.jn. (21599)
- 32 european heart journal.jn. (12379)
- 33 or/23-32 (472743)
- 34 22 and 33 (43)
- 35 limit 34 to yr="2012-current" (1)
- 36 ("20110517" or "20110518" or "20110519" or "20110520" or "20110521" or "20110522" or "20110523" or "20110524" or "20110525" or "20110526" or "2010527" or "20110528" or "20110529" or "20110530" or "20110531" or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112*).ed. (637897)
- 37 34 and 36 (2)
- 38 35 or 37 (3)

MEDLINE – Systematic Reviews (SRs)

- 1 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (7296)
- 2 (alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril).mp. (20996)
- 3 (moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide ortrandolapril or zofenopril).mp. (6018)
- 4 (losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (13737)
- 5 or/2-4 (36976)
- 6 (angiotensin-converting enzyme inhibitors or angiotensin II type 2 receptor blockers or ACEI or ARB).mp. (32543)
- 7 5 or 6 (54674)
- 8 (coronary artery disease or coronary disease or myocardial ischemia or angina pectoris or unstable angina or arterial occlusive diseases or peripheral vascular disease or vascular disease or atherosclerosis or cardiovascular diseases or carotid artery diseases).mp. (427806)
- 9 1 or 8 (432045)
- 10 7 and 9 (6921)
- 11 meta-analysis.pt. (34360)
- 12 search.tw. (141542)
- 13 cochrane database of systematic reviews.jn. (8650)
- 14 (medline or systematic review).tw. (65687)
- 15 or/11-14 (193880)
- 16 10 and 15 (190)
- 17 lancet.jn. (122331)
- 18 jama.jn. (62388)
- 19 "annals of internal medicine".jn. (27403)
- 20 bmj.jn. (73546)
- 21 "new england journal of medicine".jn. (65472)
- 22 american journal of cardiology.jn. (32009)
- 23 circulation.jn. (37036)
- 24 "journal of the american college of cardiology".jn. (18580)
- 25 american heart journal.jn. (21599)
- 26 european heart journal.jn. (12379)
- 27 or/17-26 (472743)
- 28 16 and 27 (38)
- 29 limit 28 to yr="2012-current" (1)
- 30 ("20110517" or "20110518" or "20110519" or "20110520" or "20110521" or "20110522" or

"20110523" or "20110524" or "20110525" or "20110526" or "2010527" or "20110528" or "20110529"
or "20110530" or "20110531" or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or
201112*).ed. (637897)

31 28 and 30 (2)

32 29 or 31 (3)

EMBASE – Randomized Controlled Trials (RCT)

<1980 to 2012 Week 25>

-
- 1 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (10745)
 - 2 (angiotensin converting enzyme inhibitor or ACE inhibitor or ACEI or arb or angiotensin receptor blocker or angiotensin ii type 1 receptor blocker).mp. (21452)
 - 3 (alacapril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril or moveltipril or pentopril or perinodopril or quinapril or ramipril or spirapril or temocapril or teprotide ortrandolapril or zofenopril or losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (86167)
 - 4 random.ab. (154974)
 - 5 (double-blind or placebo or random).ti. (57430)
 - 6 4 or 5 (204491)
 - 7 1 and (2 or 3) and 6 (12)
 - 8 lancet.jn. (117453)
 - 9 ("jama journal of the american medical association" or "jama the journal of the american medical association").jn. (42338)
 - 10 "annals of internal medicine".jn. (29288)
 - 11 (bmj or bmj clinical research ed).jn. (34966)
 - 12 "new england journal of medicine".jn. (37386)
 - 13 american journal of cardiology.jn. (27495)
 - 14 circulation.jn. (45409)
 - 15 "journal of the american college of cardiology".jn. (29243)
 - 16 american heart journal.jn. (20403)
 - 17 european heart journal.jn. (25816)
 - 18 or/8-17 (409797)
 - 19 7 and 18 (4)
 - 20 (2011* or 2012*).em. (1657326)
 - 21 19 and 20 (2)

EMBASE – Observational studies

<1980 to 2012 Week 25>

- 1 Clinical study/ (39716)
- 2 case control study/ (67754)
- 3 Family study/ (9577)
- 4 Longitudinal study/ (53366)
- 5 Retrospective study/ (282319)
- 6 Prospective study/ (206317)
- 7 "randomized controlled trial (topic)"/ (17196)
- 8 6 not 7 (205902)
- 9 Cohort analysis/ (124503)
- 10 (Cohort adj (study or studies)).mp. (83889)
- 11 (Case control adj (study or studies)).tw. (61460)
- 12 (followup adj (study or studies)).tw. (819)
- 13 (observational adj (study or studies)).tw. (45068)
- 14 (epidemiologic\$ adj (study or studies)).tw. (64810)
- 15 (cross sectional adj (study or studies)).tw. (61424)
- 16 1 or 2 or 3 or 4 or 5 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (902864)
- 17 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (10745)
- 18 16 and 17 (1219)
- 19 lancet.jn. (117453)
- 20 ("jama journal of the american medical association" or "jama the journal of the american medical association").jn. (42338)
- 21 "annals of internal medicine".jn. (29288)
- 22 (bmj or bmj clinical research ed).jn. (34966)
- 23 "new england journal of medicine".jn. (37386)
- 24 american journal of cardiology.jn. (27495)
- 25 circulation.jn. (45409)
- 26 "journal of the american college of cardiology".jn. (29243)
- 27 european heart journal.jn. (25816)
- 28 or/19-27 (389394)
- 29 18 and 28 (232)
- 30 (2011* or 2012*).em. (1657326)
- 31 29 and 30 (69)

Cochrane Database of Systematic Reviews (CDSR)

search date: 2012 Jun 28

ID	Search	Hits
#1	<u>(preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef):ti,ab,kw</u>	305
#2	<u>(alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril):ti,ab,kw</u>	5428
#3	<u>(moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide ortrandolapril or zofenopril):ti,ab,kw</u>	1870
#4	<u>(losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan):ti,ab,kw</u>	3000
#5	<u>(#2 OR #3 OR #4)</u>	9215
#6	<u>(angiotensin-converting enzyme inhibitors or angiotensin II type 2 receptor blockers or ACEI or ARB):ti,ab,kw</u>	5564
#7	<u>(#5 OR #6)</u>	10618
#8	<u>(coronary artery disease or coronary disease or myocardial ischemia or angina pectoris or unstable angina or arterial occlusive diseases or peripheral vascular disease or vascular disease or atherosclerosis or cardiovascular diseases or carotid artery diseases):ti,ab,kw</u>	33228
#9	<u>(#1 OR #8)</u>	33469
#10	<u>(#7 AND #9)</u>	1645
#11	<u>(#10), from 2011 to 2012</u>	76

CDSR – 8 records

Cochrane CENTRAL Register of Controlled Trials (CCRT)

Search date: 2012 Jun 28

ID	Search	Hits
#1	<u>(alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril):ti,ab,kw</u>	5428
#2	<u>(moveltipril or pentopril or perindopril or quinapril or ramipril or</u>	1870

	<u>spirapril or temocapril or teprotide ortrandolapril or zofenopril):ti,ab,kw</u>	
#3	<u>(losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan):ti,ab,kw</u>	3000
#4	<u>MeSH descriptor Angiotensin-Converting Enzyme Inhibitors, this term only</u>	3496
#5	<u>MeSH descriptor Angiotensin II Type 1 Receptor Blockers, this term only</u>	931
#6	<u>(ACEI or ARB):ti,ab,kw</u>	650
#7	<u>(#1 OR #2 OR #3 OR #4 OR #5 OR #6)</u>	10110
#8	<u>MeSH descriptor Coronary Artery Disease, this term only</u>	2254
#9	<u>MeSH descriptor Coronary Disease, this term only</u>	5908
#10	<u>MeSH descriptor Myocardial Ischemia, this term only</u>	1748
#11	<u>MeSH descriptor Angina Pectoris, this term only</u>	3034
#12	<u>MeSH descriptor Angina, Unstable, this term only</u>	869
#13	<u>MeSH descriptor Arterial Occlusive Diseases, this term only</u>	750
#14	<u>MeSH descriptor Peripheral Vascular Diseases, this term only</u>	543
#15	<u>MeSH descriptor Vascular Diseases, this term only</u>	376
#16	<u>MeSH descriptor Atherosclerosis, this term only</u>	373
#17	<u>MeSH descriptor Cardiovascular Diseases, this term only</u>	3736
#18	<u>MeSH descriptor Carotid Artery Diseases, this term only</u>	352
#19	<u>(preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef):ti,ab,kw</u>	305
#20	<u>(#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)</u>	18191
#21	<u>(#7 AND #20)</u>	752
#22	<u>(#21), from 2011 to 2012</u>	39

CENTRAL – 32 records; 10 fitting jnl selection criteria

Cycle 1 (1st assessment)

Database: Ovid MEDLINE(R)

Time period covered: 01 January 2009 to November 16, 2011

- 1 Coronary Artery Disease/ or Coronary Disease/ (152786)
- 2 Myocardial Ischemia/ (29730)
- 3 Angina Pectoris/ or Angina, Unstable/ (36416)
- 4 Arterial Occlusive Diseases/ (23714)
- 5 Peripheral Vascular Diseases/ (10474)
- 6 Vascular Diseases/ (25080)
- 7 Atherosclerosis/ (15230)
- 8 Cardiovascular Diseases/ (84262)
- 9 Carotid Artery Diseases/ (16700)
- 10 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (7177)
- 11 or/1-10 (367491)
- 12 randomized controlled trial.pt. (321988)
- 13 controlled clinical trial.pt. (83978)
- 14 randomized.ab. (237160)
- 15 placebo.ab. (134283)
- 16 clinical trials as topic.sh. (159305)
- 17 randomly.ab. (173839)
- 18 trial.ti. (101816)
- 19 or/12-18 (771753)
- 20 humans.sh. (12219765)
- 21 19 and 20 (674040)
- 22 (alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide or trandolapril or zofenopril).mp. (25938)
- 23 (losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (13537)
- 24 Angiotensin-Converting Enzyme Inhibitors/ (27050)
- 25 Angiotensin II Type 1 Receptor Blockers/ (6144)
- 26 (ACEI or ARB).mp. (3921)
- 27 or/22-26 (52225)
- 28 11 and 21 and 27 (1556)
- 29 lancet.jn. (121642)
- 30 jama.jn. (62217)
- 31 "annals of internal medicine".jn. (27064)
- 32 bmj.jn. (51798)
- 33 "new england journal of medicine".jn. (64943)
- 34 american journal of cardiology.jn. (31705)
- 35 circulation.jn. (36874)
- 36 "journal of the american college of cardiology".jn. (18237)
- 37 american heart journal.jn. (21493)
- 38 european heart journal.jn. (12125)

- 39 or/29-38 (448098)
- 40 28 and 39 (379)
- 41 limit 40 to yr="2009-current" (53)
- 42 (200808* or 200809* or 200810* or 200811* or 200812*).ed. (365006)
- 43 40 and 42 (14)
- 44 41 or 43 (67)

MEDLINE – Observational studies

- 1 epidemiologic studies/ (5237)
- 2 exp case control studies/ (535838)
- 3 exp Cohort Studies/ (1149521)
- 4 case control.tw. (61410)
- 5 (cohort adj (study or studies)).tw. (60961)
- 6 cohort analy\$.tw. (2742)
- 7 (follow up adj (study or studies)).tw. (33823)
- 8 (observational adj (study or studies)).tw. (31173)
- 9 longitudinal.tw. (114893)
- 10 retrospective.tw. (214921)
- 11 cross sectional.tw. (125438)
- 12 Cross-Sectional Studies/ (134657)
- 13 or/1-12 (1566158)
- 14 (alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril).mp. (21101)
- 15 (moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide or trandolapril or zofenopril).mp. (5994)
- 16 (losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (13537)
- 17 Angiotensin-Converting Enzyme Inhibitors/ (27050)
- 18 Angiotensin II Type 1 Receptor Blockers/ (6144)
- 19 (ACEI or ARB).mp. (3921)
- 20 or/14-19 (52225)
- 21 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (7177)
- 22 13 and 20 and 21 (122)
- 23 lancet.jn. (121642)
- 24 jama.jn. (62217)
- 25 "annals of internal medicine".jn. (27064)
- 26 bmj.jn. (51798)
- 27 "new england journal of medicine".jn. (64943)
- 28 american journal of cardiology.jn. (31705)
- 29 circulation.jn. (36874)
- 30 "journal of the american college of cardiology".jn. (18237)
- 31 american heart journal.jn. (21493)
- 32 european heart journal.jn. (12125)
- 33 or/23-32 (448098)
- 34 22 and 33 (39)

- 35 limit 34 to yr="2009-current" (5)
- 36 (200808* or 200809* or 200810* or 200811* or 200812*).ed. (365006)
- 37 34 and 36 (1)
- 38 35 or 37 (6)

MEDLINE – Systematic Reviews (SR)

- 1 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (7177)
- 2 (alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril).mp. (21101)
- 3 (moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide ortrandolapril or zofenopril).mp. (5994)
- 4 (losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (13537)
- 5 or/2-4 (36846)
- 6 (angiotensin-converting enzyme inhibitors or angiotensin II type 2 receptor blockers or ACEI or ARB).mp. (32764)
- 7 5 or 6 (54744)
- 8 (coronary artery disease or coronary disease or myocardial ischemia or angina pectoris or unstable angina or arterial occlusive diseases or peripheral vascular disease or vascular disease or atherosclerosis or cardiovascular diseases or carotid artery diseases).mp. (422445)
- 9 1 or 8 (426623)
- 10 7 and 9 (6913)
- 11 meta-analysis.pt. (31743)
- 12 search.tw. (135512)
- 13 cochrane database of systematic reviews.jn. (8210)
- 14 (medline or systematic review).tw. (60653)
- 15 or/11-14 (183727)
- 16 10 and 15 (187)
- 17 lancet.jn. (121642)
- 18 jama.jn. (62217)
- 19 "annals of internal medicine".jn. (27064)
- 20 bmj.jn. (51798)
- 21 "new england journal of medicine".jn. (64943)
- 22 american journal of cardiology.jn. (31705)
- 23 circulation.jn. (36874)
- 24 "journal of the american college of cardiology".jn. (18237)
- 25 american heart journal.jn. (21493)
- 26 european heart journal.jn. (12125)
- 27 or/17-26 (448098)
- 28 16 and 27 (34)
- 29 limit 28 to yr="2009-current" (3)
- 30 (200808* or 200809* or 200810* or 200811* or 200812*).ed. (365006)
- 31 28 and 30 (1)
- 32 29 or 31 (4)

Embase – Observational studies

Time period covered: 2008 Week 1 to 2011 Week 45

- 1 Clinical study/ (34734)
- 2 case control study/ (55454)
- 3 Family study/ (9305)
- 4 Longitudinal study/ (46783)
- 5 Retrospective study/ (242056)
- 6 Prospective study/ (176077)
- 7 "randomized controlled trial (topic)"/ (9854)
- 8 6 not 7 (175842)
- 9 Cohort analysis/ (104416)
- 10 (Cohort adj (study or studies)).mp. (69697)
- 11 (Case control adj (study or studies)).tw. (54879)
- 12 (followup adj (study or studies)).tw. (754)
- 13 (observational adj (study or studies)).tw. (38093)
- 14 (epidemiologic\$ adj (study or studies)).tw. (59603)
- 15 (cross sectional adj (study or studies)).tw. (53235)
- 16 1 or 2 or 3 or 4 or 5 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (781099)
- 17 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef)).mp. (9361)
- 18 16 and 17 (999)
- 19 limit 18 to yr="2008 -current" (602)
- 20 lancet.jn. (112589)
- 21 ("jama journal of the american medical association" or "jama the journal of the american medical association").jn. (36333)
- 22 "annals of internal medicine".jn. (26291)
- 23 (bmj or bmj clinical research ed).jn. (27651)
- 24 "new england journal of medicine".jn. (36402)
- 25 american journal of cardiology.jn. (27012)
- 26 circulation.jn. (38492)
- 27 "journal of the american college of cardiology".jn. (25842)
- 28 european heart journal.jn. (25281)
- 29 or/20-28 (355893)
- 30 19 and 29 (134)

Embase – Randomized Controlled Trials (RCT)

Time period covered: 2008 Week 1 to 2011 Week 45

- 1 ((preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or

- (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef).mp. (9361)
- 2 (angiotensin converting enzyme inhibitor or ACE inhibitor or ACEI or arb or angiotensin receptor blocker or angiotensin ii type 1 receptor blocker).mp. (18999)
- 3 (alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide ortrandolapril or zofenopril or losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (81677)
- 4 random.ab. (142659)
- 5 (double-blind or placebo or random).ti. (53694)
- 6 4 or 5 (188923)
- 7 1 and (2 or 3) and 6 (9)
- 8 limit 7 to yr="2008 -Current" (4)
- 9 lancet.jn. (112589)
- 10 ("jama journal of the american medical association" or "jama the journal of the american medical association").jn. (36333)
- 11 "annals of internal medicine".jn. (26291)
- 12 (bmj or bmj clinical research ed).jn. (27651)
- 13 "new england journal of medicine".jn. (36402)
- 14 american journal of cardiology.jn. (27012)
- 15 circulation.jn. (38492)
- 16 "journal of the american college of cardiology".jn. (25842)
- 17 american heart journal.jn. (19945)
- 18 european heart journal.jn. (25281)
- 19 or/9-18 (375838)
- 20 8 and 19 (1)

Cochrane CENTRAL Register of Controlled Trials (CCRT)

Search date - November 16, 2011

ID	Search	Hits
#1	(alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril):ti,ab,kw	5381
#2	(moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide ortrandolapril or zofenopril):ti,ab,kw	1833
#3	(losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan):ti,ab,kw	2873
#4	MeSH descriptor Angiotensin-Converting Enzyme Inhibitors, this term only	3436
#5	MeSH descriptor Angiotensin II Type 1 Receptor Blockers, this term only	879
#6	(ACEI or ARB):ti,ab,kw	614
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	9886

#8	MeSH descriptor Coronary Artery Disease, this term only	2103
#9	MeSH descriptor Coronary Disease, this term only	5850
#10	MeSH descriptor Myocardial Ischemia, this term only	1703
#11	MeSH descriptor Angina Pectoris, this term only	3006
#12	MeSH descriptor Angina, Unstable, this term only	864
#13	MeSH descriptor Arterial Occlusive Diseases, this term only	735
#14	MeSH descriptor Peripheral Vascular Diseases, this term only	538
#15	MeSH descriptor Vascular Diseases, this term only	364
#16	MeSH descriptor Atherosclerosis, this term only	341
#17	MeSH descriptor Cardiovascular Diseases, this term only	3514
#18	MeSH descriptor Carotid Artery Diseases, this term only	337
#19	(preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef):ti,ab,kw	186
#20	(#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)	17532
#21	(#7 AND #20)	725
#22	(#21), from 2008 to 2011	172

CENTRAL – 149 (52 from selected journals)

Cochrane Database of Systematic Reviews (CDSR)

Search date - November 16, 2011

ID	Search	Hits
#1	(preserved adj left) or (stable adj cad) or (stable adj chd) or (stable adj coronary) or (preserved adj coronary) or (preserved adj systolic) or (preserved adj ventricular) or (preserved adj lvef) or (preserved adj ef) or (preserved adj ejection) or (intact adj left) or (intact adj systolic) or (intact adj ventricular) or (intact adj lvef) or (intact adj ef) or (normal adj systolic) or (normal adj ventricular) or (normal adj lvef) or (normal adj ef):ti,ab,kw	186
#2	(alacepril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or imidapril or libenzapril or lisinopril or moexipril):ti,ab,kw	5381
#3	(moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or teprotide or trandolapril or zofenopril):ti,ab,kw	1833
#4	(losartan or olmesartan or telmisartan or valsartan or eprosartan or	2873

	candesartan or tasosartan or irbesartan):ti,ab,kw	
#5	(#2 OR #3 OR #4)	9028
#6	(angiotensin-converting enzyme inhibitors or angiotensin II type 2 receptor blockers or ACEI or ARB):ti,ab,kw	5443
#7	(#5 OR #6)	10386
#8	(coronary artery disease or coronary disease or myocardial ischemia or angina pectoris or unstable angina or arterial occlusive diseases or peripheral vascular disease or vascular disease or atherosclerosis or cardiovascular diseases or carotid artery diseases):ti,ab,kw	32185
#9	(#1 OR #8)	32331
#10	(#7 AND #9)	1589
#11	(#10), from 2008 to 2011	345

CDSR – 13 (8 fitting time period)

Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) specifies findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of “opposing findings” – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007² for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B: Updating Signals (Continued)

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the ‘borderline’ changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old ≤ 0.5 or RRR new / RRR old ≥ 1.5 . Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old ≤ 0.5 or RD new / RD old ≥ 1.5).

* Please, see Shojania et al. 2007² for further definitions and details

Appendix C: Evidence Table

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
Key Question # 1: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?					
Cycle 2					
Sharma 2011 ⁷	SR/MA	2,177 pts with early non-diabetic chronic kidney disease (stage 1-3) who received ACEI or ARB (4 RCTs) Pts with risk equivalent of stable IHD Mean age range: 18-70 yrs; % male range: 72-80	ACEI [benazepril,trandolapril; dose range: 4mg-10mg] vs. PL	36-63 mo	<u>ACEI vs. PL (FU= 3-5 yrs)</u> Total mortality RR=1.80, 95% CI 0.17, 19.27 MA based on 2 RCTs (ACEI: n=1,001 PL: n=905) The composite outcome (CV death/nonfatal MI/stroke) RR=0.87, 95% CI : 0.66, 1.14 MA based on 2 RCTs (ACEI: n=1,001 PL: n=905)
McAlister 2012 ⁵	SR/MA	80,594 pts with or increased risk for atherosclerotic vascular disease who received ACEI or ARB for at least 12 mo (13 RCTs) Pts with stable IHD Mean age range: 55-67 yrs; % male range: 41-91	ACEI [enalapril, ramipril, perindopril; dose range: 1.25mg-20mg] or ARB [losartan, telmisartan, irbesartan; dose range: 80mg-300mg] vs. PL	≥ 12 mo	<u>ACEI or ARB vs. PL (FU=24-56 mo)</u> Total mortality For pts without heart failure (LVEF ≥ 40%): NR The composite outcome (CV death/nonfatal MI/stroke) OR=0.81, 95% CI: 0.75, 0.88 MA based on 10 studies (ACEI/ARB: n=10,695 PL: n=10,531)
Cycle 1					
McMurray 2010 ¹² The NAVIGATOR study	RCT pivotal	9,306 pts with impaired glucose tolerance and CVD or CV risk factors; mean age: 64 yrs; male:	ARB [valsartan] (n=4,631; 80-160 mg/d) vs. PL (n=4,675)	5 yrs	<u>ARB vs. PL (FU=6.5 yrs)</u> Total mortality 295/4,631 (6.4%) vs. 327/4,675 (7.0%) HR=0.90, 95% CI: 0.77, 1.05

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
		50%			<p>CV mortality 128/4,631 (2.8%) vs. 116/4,675 (2.5%) HR=1.09, 95% CI: 0.85, 1.40</p> <p>MI (nonfatal or fatal) 138/4,631 (3.0%) vs. 140/4,675 (3.0%) HR=0.97, 95% CI: 0.77, 1.23</p> <p>Stroke (nonfatal or fatal) 105/4,631 (2.3%) vs. 132/4,675 (2.8%) HR=0.79, 95% CI: 0.61, 1.02</p> <p>Composite endpoint (CV death/nonfatal MI/stroke/hospitalization) 375/4,631 (8.1%) vs. 377/4,675 (8.1%) HR=0.99, 95% CI: 0.86, 1.14</p> <p>Hospitalization for CV reason 886/4,631 (19.1%) vs. 879/4,675 (18.8%) HR=1.00, 95% CI: 0.91, 1.10</p> <p>Revascularization 316/4,631 (6.8%) vs. 331/4,675 (7.1%) HR=0.94, 95% CI: 0.80, 1.10</p>
Bertrand 2010 ¹¹ The EUROPA study	Non-RCT (secondary analysis)	2,122 pts with stable CAD (previous MI, revascularization, narrowing of major coronary arteries); mean age: 62 yrs; male: 83%	<p>ACEI [perindopril] (n=3,326; 8 mg/d) vs. PL (n=3,095)</p> <p>ACEI [perindopril] + CCB (n=1,022; ACEI dose: 8 mg/d; CCB dose: NR) vs. CCB + PL (n=1,100; CCB dose: NR)</p>	≥ 3 yrs	<p><u>ACEI vs. PL (FU=4 yrs)</u> Total mortality: HR=0.91, 95% CI: 0.75, 1.11, p=0.35 CV mortality: HR=0.81, 95% CI: 0.63, 1.04, p=0.10 Composite endpoint (CV death, non-fatal MI, or resuscitated cardiac arrest): HR=0.82, 95% CI: 0.68, 0.98, p<0.05 Fatal/non-fatal MI: HR=0.78, 95% CI: 0.61, 0.98, p<0.05 Hospitalization for HF: HR=0.69, 95% CI: 0.45, 1.07, p=0.09</p> <p><u>ACEI + CCB vs. CCB + PL (FU=4 yrs)</u> Total mortality: HR=0.54, 95% CI: 0.34, 0.86, p<0.01 CV mortality: HR=0.59, 95% CI: 0.32, 1.08, p=0.09</p>

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
					Composite endpoint (CV death, non-fatal MI, or resuscitated cardiac arrest): HR=0.65, 95% CI: 0.45, 0.92, p<0.05 Fatal/non-fatal MI: HR=0.72, 95% CI: 0.48, 1.07, p=0.10 Hospitalization for HF: HR=0.46, 95% CI: 0.12, 1.76, p=0.25
Baker 2009 ¹⁴	SR/MA	32,210 pts with stable IHD and preserved ventricular function (6 ACEI RCTs); mean age range: 57-67 yrs; % male range: 57-89	ACEI [enalapril, ramipril, perindopril, trandolapril, zofenopril] (n=16,123 for total mortality; dose range: 4 – 80 mg/d) vs. PL (n=16,087 for total mortality)	6-56 mo	<u>ACEI vs. PL (FU= from 6 to 56 mo)</u> Total mortality: pooled RR (6 RCTs)=0.87, 95% CI: 0.81, 0.94 CV mortality: pooled RR (5 RCTs)=0.83, 95% CI: 0.70, 0.98 Non-fatal MI: pooled RR (6 RCTs)=0.83, 95% CI: 0.73, 0.94 Stroke: pooled RR (6 RCTs)=0.78, 95% CI: 0.63, 0.97 Composite endpoint (CV death, non-fatal MI or stroke): pooled RR (2 RCTs)=0.85, 95% CI: 0.72, 1.01
Hirohata 2010 ¹³ The OLIVUS study	RCT	247 stable angina pectoris pts with CAD and hypertension scheduled for PCI; mean age: 68 yrs; male: 58%	ARB [olmesartan] + ST [beta-blockers, CCB, diuretics, nitrates, glycemic control agents] (n=126; ARB dose: 10-40 mg/d) vs. ST [beta-blockers, CCB, diuretics, nitrates, glycemic control agents] (n=121)	14 mo	<u>ARB + ST vs. ST (FU=14 mo)</u> CV mortality: 0% vs. 1.7%, p=0.31 Composite endpoint (CV death, non-fatal MI, or non-fatal stroke): 1.6% vs. 2.5%, p>0.05 Non-fatal MI: 1.6% vs. 0%, p=0.17 Non-fatal stroke: 0% vs. 0.8%, p>0.05 Coronary revascularization: 7.9% vs. 10.0%, p=0.61 Hospitalization for unstable angina: 0% vs. 0.8%, p>0.05 Hospitalization for congestive heart failure: 1.6% vs. 0.8%, p>0.05
Massie 2008 ¹⁸ The I-Preserve study	RCT	4,128 pts 60 yrs or older with HF (NYHA class II-IV) and EF ≥ 45%; mean age: 72 yrs; male: 40%	ARB [irbesartan] (n=2,067; 75-300 mg/d) vs. PL (n=2,061)	NR	<u>ARB vs. PL (FU=49.5 mo)</u> Total mortality: HR=1.00, 95% CI: 0.88, 1.14, p=0.98 CV death: HR=1.01, 95% CI: 0.86, 1.18, p=0.92 Composite endpoint (all-cause death or CV hospitalization): HR=0.95, 95% CI: 0.86, 1.05, p=0.35 Hospitalization all causes: HR=1.02, 95% CI: 0.94, 1.11, p=0.64 Composite vascular event endpoint (CV death, non-fatal MI or stroke): HR=0.99, 95% CI: 0.86, 1.13, p=0.84
Nicolosi 2009 ¹⁵ The PREAMI echo study	RCT	1,252 pts 65 yrs or older after acute MI with preserved LVEF	ACEI [perindopril] (n=631; 8 mg/d) vs. PL (n=621)	12 mo	<u>ACEI vs. PL (FU=12 mo)</u> Total mortality: 39/631 (6.1%) vs. 38/621 (6.1%), p=NR Hospitalization for HF: 16/631 (2.5%) vs. 27/621 (4.3%),

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
		(≥40%); mean age: 73 yrs; male: 65%			p=NR
Brugts 2009 ¹⁶	IPD combined analysis (data from 3 RCTs)	29,463 pts (from ADVANCE , EUROPA , and PROGRESS trials) with CAD, diabetes, and cerebrovascular disease; mean age: 63 yrs; male: 72%	ACEI [perindopril] (n=14,730; 4-8 mg/d) vs. PL (n=14,733)	4 yrs	<u>ACEI vs. PL (FU=4 yrs)</u> Total mortality: pooled HR (3 RCTs)=0.89, 95% CI: 0.82, 0.96 CV mortality: pooled HR (3 RCTs)=0.85, 95% CI: 0.76, 0.95 Composite endpoint (CV death, non-fatal MI, stroke): pooled HR (3 RCTs)=0.82, 95% CI: 0.76, 0.87 Non-fatal MI: pooled HR (3 RCTs)=0.80, 95% CI: 0.71, 0.90 Hospitalization for HF: pooled HR (3 RCTs)=0.84, 95% CI: 0.72, 0.96 Revascularization: pooled HR (3 RCTs)=0.92, 95% CI: 0.84, 1.01
Law 2009 ¹⁷	SR/MA	Hypertensive pts at increased risk of CVD; mean age: NR; male%: NR	2 pooled estimates of 21 ACEI vs. PL and 4 ARB vs. PL trials (for CHD events); n=NR 1 pooled estimate of 13 ACEI vs. PL trials (for stroke); n=NR	NR	<u>ACEI vs. PL (FU=NR)</u> CHD events (fatal/non-fatal MI or sudden cardiac death, excluding silent infarcts): pooled RR (21 trials)=0.83, 95% CI: 0.78, 0.89 Stroke: pooled RR (13 trials)=0.78, 95% CI: 0.66, 0.92 <u>ARB vs. PL (FU=NR)</u> CHD events (fatal/non-fatal MI or sudden cardiac death, excluding silent infarcts): pooled RR (4 trials)=0.86, 95% CI: 0.53, 1.40
Key question # 2: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function and are receiving standard medical therapy, what is the comparative effectiveness of combining ACE inhibitors and ARBs versus either an ACE inhibitor or ARB alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?					
Cycle 2					
No new evidence	NA	NA	NA	NA	NA
Cycle 1					
No new evidence	NA	NA	NA	NA	NA
Key question # 3: In patients with ischemic heart disease and preserved left ventricular function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?					

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
Cycle 2					
No new evidence	NA	NA	NA	NA	NA
Cycle 1					
No new evidence	NA	NA	NA	NA	NA
Key question 4: In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function, what are the comparative harms of adding ACE inhibitors or ARBs to standard medical therapy when compared to standard medical therapy alone?					
Cycle 2					
Sharma 2011 ⁷	SR/MA	2,177 pts with early non-diabetic chronic kidney disease (stage 1-3) who received ACEI or ARB (4 RCTs) Pts with risk equivalent of stable IHD Mean age range: 18-70 yrs; % male range: 72-80	ACEI [benazepril, trandolapril] (dose range: 4mg-10mg) vs. PL	36-63 mo	<u>ACEI vs. PL (FU= 3-5 yrs)</u> AEs or WDAE: RR=1.09, 95% CI: 0.70, 1.68 (AIPRI study 1996)
Sugiura 2012 ⁶ HIJ-CREATE sub-study	RCT	2,049 hypertensive pts with CAD Pts with risk equivalent of stable IHD Mean age: 65 yrs; % male: 80	ARB [candesartan] (n=1,024; dose NR) vs. Standard therapy [ACEI, diuretics, calcium channel blockers, dose NR] (n=1,025)	4.2 years	<u>ARB vs. Standard treatment (FU= 4.2 yrs)</u> Total AEs: 798/1,024 (77.9%) vs. 808/1,025 (78.8%), p=NR Cancer: HR=0.95, 95% CI: 0.65, 1.38 [Cox regression] Cancer death: HR=0.74, 95% CI: 0.39, 1.39 [Cox regression]
Cycle 1					
McMurray 2010 ¹² The NAVIGATOR study	RCT pivotal	9,306 pts with impaired glucose tolerance and CVD or CV risk factors; mean age: 64 yrs; male: 50%	ARB [valsartan] (n=4,631; 80-160 mg/d) vs. PL (n=4,675)	5 yrs	<u>ARB vs. PL (FU=6.5 yrs)</u> WDAE: 556/4,631 (12.0%) vs. 531/4,675 (11.4%), p=0.33 Hypotension: 1,964/4,631 (42.4%) vs. 1,680/4,675 (35.9%), p<0.001 Hypertension: 693/4,631 (15.0%) vs. 950/4,675 (20.3%), p<0.001

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
					Renal dysfunction: 136/4,631 (2.9%) vs. 146/4,675 (3.1%), p=0.55 Hypokalemia: 45/4,631 (1.0%) vs. 84/4,675 (1.8%), p<0.001 Angioedema: 89/4,631 (1.9%) vs. 123/4,675 (2.6%), p=0.02 Back pain: 775/4,631 (16.7%) vs. 682/4,675 (14.6%), p<0.01 Headache: 537/4,631 (11.6%) vs. 626/4,675 (13.4%), p=0.01 Peripheral edema: 431/4,631 (9.3%) vs. 555/4,675 (11.9%), p<0.001 The occurrence of cough, bronchitis, upper respiratory tract infection, osteoarthritis, pain in extremity, nasopharyngitis, and hyperkalemia was not significantly different between the two study groups
Baker 2009 ¹⁴	SR/MA	10,235 pts with stable IHD and preserved ventricular function (3 ACEI RCTs); mean age range: 60-64 yrs; % male range: 72-83	ACEI [enalapril, ramipril, trandolapril] (n=5,139 for WDAE; dose range: 4 – 20 mg/d) vs. PL (n=5,096 for WDAE)	2-4.8 yrs	<u>ACEI vs. PL (FU=2 to 4.8 yrs)</u> WDAE: pooled RR (3 RCTs)=2.30, 95% CI: 1.34, 3.95 Hypotension: pooled RR (3 RCTs)=1.79, 95% CI: 0.68, 4.71 Syncope: pooled RR (2 RCTs)=1.24, 95% CI: 1.02, 1.52 Cough: pooled RR (3 RCTs)=1.67, 95% CI: 1.22, 2.29
Massie 2008 ¹⁸ The I-Preserve study	RCT	4,128 pts 60 yrs or older with HF (NYHA class II-IV) and EF ≥ 45%; mean age: 72 yrs; male: 40%	ARB [irbesartan] (n=2,067; 75-300 mg/d) vs. PL (n=2,061)	NR	<u>ARB vs. PL (FU=49.5 mo)</u> WDAE: 331/2,067 (16%) vs. 288/2,061 (14%), p=0.07 Hypotension: 60/2,067 (3%) vs. 62/2,061 (3%), p=0.84 Renal failure: 69/2,067 (3%) vs. 57/2,061 (3%), p=0.29 Hyperkalemia: 12/2,067 (0.6%) vs. 9/2,061 (0.4%), p=0.84
Key question 5: In patients with stable ischemic heart disease who have preserved left ventricular systolic function and are receiving standard medical therapy, what is the evidence of comparative harms of combination ACE inhibitor and ARB therapy versus use with either an ACE inhibitor or ARB alone?					
Cycle 2					
No new evidence	NA	NA	NA	NA	NA
Cycle 1					
No new evidence	NA	NA	NA	NA	NA
Key question 6: In patients with ischemic heart disease and preserved left ventricular systolic function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what are the comparative harms of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone?					
Cycle 2					

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
No new evidence	NA	NA	NA	NA	NA
Cycle 1					
No new evidence	NA	NA	NA	NA	NA
Key question 7: What is the evidence that benefits or harms differ by subpopulations, including: demographics [sex, age, ethnicity, left ventricular ejection fraction], clinical course (previous treatment with a stent or coronary artery bypass surgery, degree and location of lesion, presence and pattern of symptoms), dose of the ACE inhibitor or ARB used, co-morbidities (diabetes, renal dysfunction, hypertension), and other medications (vitamins, lipid lowering drugs, beta-blockers, anti-platelet agents)?					
Cycle 2					
No new evidence	NA	NA	NA	NA	NA
Cycle 1					
McMurray 2010 ¹² The NAVIGATOR study	RCT pivotal	9,306 pts with impaired glucose tolerance and CVD or CV risk factors; mean age: 64 yrs; male: 50%	ARB [valsartan] (n=4,631; 80-160 mg/d) vs. PL (n=4,675)	5 yrs	<p>Composite endpoint (CV death/nonfatal MI/stroke/hospitalization) Subgroup analyses revealed no significant differences between ARB and placebo by age (heterogeneity p=0.36), gender (heterogeneity p=0.78), race (heterogeneity p=0.54), fasting plasma glucose (heterogeneity p=0.50), body mass index (heterogeneity p=0.95), waist circumference (heterogeneity p=0.97), hypertension (heterogeneity p=0.15), and history of CVD (heterogeneity p=0.25).</p> <p>There was a statistically significant heterogeneity of the effect of ARB with regards to ACEI use (heterogeneity p=0.04), suggesting benefits of ARB use amongst ACEI users (HR=0.70, 95% CI: 0.49, 0.99) as opposed to no benefit amongst non-users of ACEIs (HR=1.05, 95% CI: 0.89, 1.23)</p>
Haller 2011 ¹⁰ The ROADMAP trial	RCT pivotal	4,447 pts with type 2 diabetes with at least two CV risk factors	ARB [olmesartan] (n=2,232; 40 mg/d) vs. PL (n=2,215)	3.2 yrs	<p>ARB vs. PL (FU=4 yrs)</p> <p>Total mortality 26/2,232 (1.2%) vs. 15/2,215 (0.7%), p=0.10 HR=1.70, 95% CI: 0.90, 3.22</p> <p>CV mortality 15/2,232 (0.7%) vs. 3/2,215 (0.1%), p=0.01 HR=4.94, 95% CI: 1.43, 17.06</p> <p>Adverse events</p>

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
					<p>Hypotension: 58/2,232 (2.6%) vs. 6/2,215 (0.3%), p<0.001 Headache: 100/2,232 (4.5%) vs. 153/2,215 (6.9%), p<0.001 Dizziness: 103/2,232 (4.6%) vs. 61/2,215 (2.8%), p=0.001 Peripheral edema: 60/2,232 (2.7%) vs. 86/2,215 (3.9%), p=0.03 Hyperkalemia: 11/2,232 (0.5%) vs. 8/2,215 (0.4%), p=0.50 SAEs: 335/2,232 (15.0%) vs. 337/2,215 (15.2%), p=0.85 Hypertension: 164/2,232 (7.3%) vs. 178/2,215 (8.0%), p=0.39</p> <p>The occurrence of bronchitis, nasopharyngitis, influenza, and back pain was not significantly different between the two study groups.</p>
Chang 2011 ⁸ The HEMO study	Non-RCT (secondary analysis)	1,820 pts with end-stage renal disease (ESRD) on hemodialysis; mean age: 57 yrs; male: 45%	ACEI use (n=458; dose NR) vs. no ACEI use (n=1,362; dose NR)	NR (only baseline use of ACEI was reported)	<p><u>ACEI users vs. ACEI non-users (FU=2.5 yrs)</u> All-cause mortality: HR=0.97, 95% CI: 0.82, 1.14 Hospitalization due to CV: HR=1.02, 95% CI: 0.87, 1.19 Hospitalization due to AF: HR=1.41, 95% CI: 1.11, 1.80 Composite endpoint (death or first CV hospitalization): HR=0.99, 95% CI: 0.86, 1.14 Composite endpoint (death or first HF hospitalization): HR=1.09, 95% CI: 0.94, 1.27</p> <p>The observed treatment effect on the above-mentioned outcomes was not modified by age, race, prior history of HF, diabetes, or IHD (heterogeneity p value > 0.05).</p>
Brugts 2010 ⁹ The EUROPA study	Non-RCT (secondary analysis)	8,726 pts with stable CAD (previous MI, revascularization, narrowing of major coronary arteries); age: 60 yrs; male: 85.7%	ACEI [perindopril] (n=4,275; 8 mg/d) vs. PL (n=4,451)	≥ 3 yrs	<p><u>ACEI vs. PL (FU=4 yrs)</u> Composite endpoint (CV death, non-fatal MI, or resuscitated cardiac arrest) Pharmacogenetic score < 3: HR=0.67, 95% CI: 0.56, 0.79 Pharmacogenetic score ≥ 3: HR=1.26, 95% CI: 0.97, 1.67</p> <p>The treatment benefit of ACEI was modified by gene polymorphism (p value for interaction < 0.00001).</p>
Brugts 2009 ¹⁶	IPD combined analysis (data from 3 RCTs)	29,463 pts (from ADVANCE , EUROPA , and PROGRESS trials) with CAD, diabetes, and cerebrovascular disease; mean age: 63 yrs; male:	ACEI [perindopril] (n=14,730; 4-8 mg/d) vs. PL (n=14,733)	4 yrs	<p><u>ACEI vs. PL (FU=4 yrs)</u> Composite endpoint (CV death, non-fatal MI, stroke): The observed treatment benefit for the composite endpoint favoring perindopril was not modified by age (heterogeneity p=0.07), gender (heterogeneity p=0.66), hypertension (heterogeneity p=0.48), diabetes (heterogeneity p=0.06), history</p>

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
		72%			of MI (heterogeneity p=0.81), cerebrovascular accident (heterogeneity p=0.39), use of antihypertensive agents (heterogeneity p=0.49), lipid-lowering agents (heterogeneity p=0.38), baseline systolic blood pressure (heterogeneity p=0.17), or revascularization (heterogeneity p=0.18).
Massie 2008 ¹⁸ The I-Preserve study	RCT	4,128 pts 60 yrs or older with HF (NYHA class II-IV) and EF ≥ 45%; mean age: 72 yrs; male: 40%	ARB [irbesartan] (n=2,067; 75-300 mg/d) vs. PL (n=2,061)	NR	Composite endpoint (all-cause death or hospitalization for CV cause) Subgroup analyses revealed no significant differences between ARB and placebo by age (heterogeneity p=0.60), gender (heterogeneity p=0.78), race (heterogeneity p=0.54), EF (heterogeneity p=0.28), diabetes (heterogeneity p=0.28), hospitalization for HF (heterogeneity p=0.81)
Imai 2011 ¹⁹ The ORIENT study	RCT	577 pts with type 2 diabetes with one or two CAD risk factor	ARB [olmesartan] (n=288; 10-40 mg/d) vs. PL (n=289)	3.2 yrs	<u>ARB vs. PL (FU=5 yrs)</u> Total mortality 19/288 (6.7%) vs. 20/289 (7.0%) HR=0.99, 95% CI: 0.53, 1.86 Composite endpoint (CV death, non-fatal stroke/MI, hospitalization) 40/288 (14.2%) vs. 53/289 (18.7%) HR=0.73, 95% CI: 0.48, 1.09 CV death 10/288 (3.5%) vs. 3/289 (1.1%) HR=2.81, 95% CI: 0.76, 10.38 Non-fatal MI 3/288 (1.1%) vs. 7/289 (2.5%) HR=0.45, 95% CI: 0.11, 1.75 Hospitalization for HF 18/288 (6.4%) vs. 25/289 (8.8%) HR=0.59, 95% CI: 0.32, 1.10

pts=patients; d=day(s); yr(s)=years; mo=month(s); HR=hazard ratio; KMA=Kaplan-Meier analysis MVA=multivariable analysis; NR=not reported; CER=comparative effectiveness review; ACEI= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blockers; RCT=randomized controlled trial; AF=atrial fibrillation; EF=ejection fraction; CAD= coronary artery disease; AE=adverse event; FU=follow-up; SR=systematic review; MA=meta-analysis; IPD=individual patient data; CV=cardiovascular; CVD=cardiovascular disease; MI=myocardial infarction; PL=placebo; WDAE=withdrawals due to adverse events; HF=heart failure; IHD=ischemic heart

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcomes and findings
disease; CCB=calcium channel blocker; PCI= percutaneous coronary intervention; ST=standard treatment; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; EF=ejection fraction; CHD=coronary heart disease; RR=relative risk; CAD=coronary artery disease; ESRD=end-stage renal disease; CHF=coronary heart failure					

Appendix D: Questionnaire Matrix

Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease

AHRQ Publication No. 10-EHC002-EF October 2009

Access to full report: <http://www.ncbi.nlm.nih.gov/books/NBK36476/>

Clinical expert name:

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question 1. In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?			
Patients with stable ischemic heart disease and preserved left ventricular function benefit from receiving ACE inhibitors, and perhaps ARBs as well, in addition to standard medical therapy, but may not benefit more than from using calcium channel blockers in addition to standard medical therapy. Future research is needed to determine if ACE inhibitors or ARBs offer additional benefits over other vasoactive drugs. The TRANSCEND (Telmisartan Randomized Assessment Study in ACE iNtolerant subjects with cardiovascular Disease) trial was the only placebo-controlled trial available to evaluate major efficacy outcomes for ARB therapy. ARB therapy was associated with reductions in the composite endpoint of cardiovascular mortality, nonfatal myocardial infarction, and stroke similar to the pooled results from the HOPE (Heart Outcomes Prevention Evaluation) and PEACE (Prevention of Events			

<p>with Angiotensin Converting Enzyme inhibition) trials comparing ACE inhibitors to placebo. While major ACE inhibitor trials utilized a run-in period to ensure that subjects tolerated ACE inhibitor therapy, subjects in TRANSCEND were intolerant of ACE inhibitors and may represent a distinct population. This reduces the confidence of indirect comparisons, and direct evidence comparing ACE inhibitors and ARBs (evaluated in Key Question 2) should be considered.</p>			
<p>Key Question 2. In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function and are receiving standard medical therapy, what is the comparative effectiveness of combining ACE inhibitors and ARBs vs. either an ACE inhibitor or ARB alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?</p>			
<p>There is direct comparative evidence from ONTARGET (Ongoing Telmisartan Alone in combination with Ramipril Global Endpoint Trial) that ACE inhibitors and ARBs provide similar benefits in major outcomes of interest in this population. Since ONTARGET directly compared the same drugs as were evaluated in the placebo-controlled HOPE and TRANSCEND trials (ramipril and telmisartan), the direct evidence of similar benefit is more compelling than indirect evidence of possible differences from Key Question 1.</p>			
<p>Key Question 3. In patients with ischemic heart disease and preserved left ventricular function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what is the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone in terms of total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, the composite endpoint of the latter three items, and atrial fibrillation? What is the evidence of benefit on other outcomes such as symptom reporting, hospitalization, revascularization, and quality of life measures?</p>			
<p>Trials compared the addition of ACE inhibitors or ARBs to standard medical therapy vs. standard medical therapy alone (with or without a placebo). For our base case analysis, we limited the trials to randomized, double-blinded comparisons of ACE inhibitors or ARBs to placebo. ACE inhibitors or ARBs did not significantly impact any of the endpoints evaluated. However, except for the endpoint “need for subsequent revascularization,” the incidence rates for the endpoints were low. Overall, the evidence from Key Question 3 suggests that initiation of ACE inhibitors or ARBs in close proximity to a revascularization procedure does not confer significant clinical benefit.</p>			

<p>However, findings for Key Question 1 suggested that patients with established ischemic heart disease do derive significant clinical benefits from ACE inhibitor or ARB therapy in addition to standard medical therapy. Thus the question becomes, At what point following a cardiac revascularization procedure does a patient with ischemic heart disease derive benefits from these agents? A majority of the trials included in Key Question 1, including HOPE, PEACE, and EUROPA (EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease), included patients who were at least 3 to 6 months removed from undergoing a coronary procedure. Thus it seems plausible that this period of time should be given following a revascularization procedure before ACE inhibitors or ARBs are initiated in these populations. However, no studies have prospectively investigated the optimal time to begin therapy, and more concrete interpretations cannot be made until this evidence becomes available.</p>			
<p>Key Question 4. In patients with stable ischemic heart disease or ischemic heart disease risk equivalents who have preserved left ventricular systolic function, what are the comparative harms of adding ACE inhibitors or ARBs to standard medical therapy when compared to standard medical therapy alone?</p>			
<p>ACE inhibitors or ARBs significantly increase the risk of withdrawing due to adverse events, syncope, cough, and hyperkalemia compared with placebo. ACE inhibitors or ARBs significantly increase the risk of cough and hypotension compared with calcium channel blockers. A number of the included trials had run-in periods in their study design. Thus, the true incidence of harms with these therapies in environments outside of clinical trials may be higher than that reported here. The unique design of the TRANSCEND trial, which compared telmisartan to placebo, deserves special discussion. All of the patients included in TRANSCEND were intolerant to ACE inhibitors at baseline. Following a median followup of 56 months, the ARB telmisartan was relatively well tolerated, with only a statistically higher risk of hypotension symptoms compared with placebo ($p=0.049$). Thus it appears that ARBs may be a relatively safe alternative for patients with stable ischemic</p>			

<p>heart disease who cannot tolerate ACE inhibitors or are at an increased risk for harms. Given the benefits seen in Key Question 1, the balance of benefits to harms for the use of ACE inhibitors or ARBs in patients with stable ischemic heart disease seems favorable.</p>			
<p>Key Question 5. In patients with stable ischemic heart disease who have preserved left ventricular systolic function and are receiving standard medical therapy, what is the evidence of comparative harms of combination ACE inhibitor and ARB therapy vs. use with either an ACE inhibitor or ARB alone?</p>			
<p>The results of Key Questions 2 and 5 are evaluated together to discern the comparative balance of benefits and harms. ACE inhibitor therapy, represented by ramipril, provides efficacy similar to the combination of an ACE inhibitor plus an ARB, represented by ramipril and telmisartan, with a lower risk of patient harm. As such, current evidence does not support the use of combination therapy at this time. The ACE inhibitor ramipril and the ARB telmisartan have similar efficacy, similar risks of harms, and therefore a similar balance of benefits to harms.</p>			
<p>Key Question 6. In patients with ischemic heart disease and preserved left ventricular systolic function who had to have recently undergone, or are set to undergo, a coronary revascularization procedure, what are the comparative harms of ACE inhibitors or ARBs added to standard medical therapy when compared to standard medical therapy alone?</p>			
<p>The constituent trials did not utilize a lengthy run-in period. Only the APRES (Angiotensin-converting Enzyme inhibition Post Revascularization Study) trial used a run-in period, and this was a single test dose. Since the only trial evaluating an ARB did not report adverse event results, our results cannot be applied to ARBs. The use of ACE inhibitors was associated with hypotension. While ACE inhibitors nonsignificantly increased the risk of cough, only three trials provided information on this. They all agreed on the direction of effect, and two of the three trials individually found ACE inhibitors to increase cough vs. placebo. Given the lack of significant benefits found in Key Question 3, the balance of benefits to harms for the initiation of an ACE inhibitor or ARB in close proximity to a revascularization procedure is not favorable.</p>			
<p>Key Question 7. What is the evidence that benefits or harms differ by subpopulations, including: demographics [sex, age, ethnicity, left ventricular ejection fraction (LVEF)], clinical course (previous treatment with a stent or coronary artery bypass surgery, degree and location of lesion, presence and pattern of symptoms), dose of the ACE inhibitor or ARB used, comorbidities (diabetes, renal dysfunction, hypertension), and other medications (vitamins, lipid lowering drugs, beta-blockers, anti-</p>			

platelet agents)?			
<p>This Key Question provides important information regarding the applicability of the benefits data. Since there were no subgroup comparisons based on harms, the balance of benefits to harms in these subgroups is not known. While we cannot state with certainty that ARBs do not work as well in females as in males, the subgroup analyses of the TRANSCEND and ONTARGET trials support the need for more research in this area. Patients with renal dysfunction have at least as robust relative reductions in the risk of cardiovascular events as those without dysfunction when ACE inhibitors are given. Even in the PEACE trial, where the overall benefits associated with ACE inhibitor therapy was not as robust, a strong trend toward benefits was seen in the subgroup with renal dysfunction receiving ACE inhibitors vs. those receiving placebo. When we evaluated the impact of baseline risk on efficacy, there was a suggestion that ARBs might work better in lower risk patients while ACE inhibitors work better in higher risk patients. Perhaps the lowest risk group was least likely to receive aspirin therapy. The aspirin therapy itself may attenuate the benefits of ACE inhibitors. Lipid lowering therapy does not seem to negatively impact the benefits of ACE inhibitor or ARB therapy. This is important, since patients with stable ischemic heart disease are receiving higher intensity lipid lowering therapy than they did previously. Patients without a prior revascularization procedure may benefit more from ACE inhibitors than those with revascularization. More work is needed to evaluate the impact of different modalities of revascularization (bare metal stents, drug-eluting stents, coronary artery bypass grafting, atherectomy) on the benefits associated with ACE inhibitors and ARBs. The balance of benefits to harms derived from initiating ACE inhibitor or ARB therapy along with a revascularization procedure is not favorable.</p>			
<p>CER=comparative effectiveness review; RCT=randomized controlled trial; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blockers</p>			

