

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, 2009

Surveillance Report: December, 2011

Surveillance Report: August, 2012

Surveillance Report: July, 2015

Summary of Key Findings from Surveillance Reports:

- Key Question 1: Conclusions are possibly not be current to findings that ARB may be more beneficial than placebo for reducing the risk of stroke (reported in 12/2011 surveillance report)
- Key Question 2: Report conclusions are still valid.
- Key Question 3: Report conclusions are still valid.
- Key Question 4: Report conclusions are still valid.
- Key Question 5: Report conclusions are still valid
- Key Question 6: Report conclusions are still valid.
- Key Question 7: Conclusions are probably not current due to findings indicating that ARB may relate to an increase in CV deaths, hypotension, headaches and dizziness, as compared to placebo, and that the use of ARB compared to placebo demonstrated benefit for composite endpoint, and increased risk of hospitalization for AF in ACEI users but not in non-ACEI users (reported in 12/2011 surveillance report).

Signal Assessment: The signals examined in this surveillance assessment suggest that the original CER may not be current.

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Conflict of Interest:

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Introduction

The purpose of the surveillance process for the EPC Program is to decide if the findings of a systematic review are current. Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #18 titled “Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease” was originally released in October, 2009¹

The key questions for the original CER are 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)?

Our surveillance assessment began in July 2015. We conducted an electronic search for literature published since the end date of the most recent surveillance report search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this CER, we contacted experts involved in the original CER to request their opinions as to whether the conclusions had changed.

Methods

Prior Surveillance

A surveillance report for the original CER was released in August 2012, and included a search for relevant literature published between May 2011 and July 2012, expert opinion, and a search of U.S. 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). The findings from this report are included in our assessment.

Literature Searches

We conducted a literature search of PubMed covering January 2012 to July 2015, using the identical search strategy used for the original report¹ and searching for studies published since the end date of the most recent surveillance search².

The search was conducted to assess the currency of conclusions using journals from among the top 10 journals from relevant specialty subject areas and among those most highly represented among the references for the original report. We included the journals searched in the previous surveillance assessment. The included journals were five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and New England Journal of Medicine) and five specialty journals (American Heart Journal, American Journal of Cardiology, Circulation, European Heart Journal, and Journal of American College of Cardiology). The search strategy is reported in Appendix A.

Study Selection

Using the same inclusion and exclusion criteria as the original CER (see Appendix B), one investigator reviewed the titles and abstracts of the 10 high-impact journal search results (Appendix C).

Expert Opinion

We shared the conclusions of the original report and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with 12 experts in the field (original peer reviewers, technical expert panel members [TEP], and a local experts) to request their assessment of the

currency of report conclusions and their recommendations of any relevant new studies. Two subject matter experts responded to our request. Appendix D shows the form experts were asked to complete.

Horizon Scanning

The AHRQ Healthcare Horizon Scanning System identifies emerging health care technologies and innovations with the potential to impact health care for AHRQ's 14 priority conditions.⁴ We reviewed the Cardiovascular Disease section to identify new potentially high-impact interventions related to the key questions in this CER. Potentially high impact interventions were considered in the final assessment of currency of the report and its conclusions.

FDA Black Box Warnings

We searched the FDA MedWatch online database website for black box warnings relevant to the key questions in this CER.

Check for Qualitative Signals

The authors of the original CER conducted qualitative and quantitative synthesis of data on the comparative effectiveness and associated harms of ACEIs or ARBs, or the combination of ACEIs and ARBs. We compared the conclusions of the included abstracts to the conclusions of the original CER and surveillance reports, and assessed expert opinions to identify qualitative signals about the currency of conclusions.

Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix E) that includes the key questions and conclusions from the original CER, findings of the new literature search, and the expert assessments that pertained to each key question. Because we did not find any FDA black box warnings or Horizon Scan interventions relevant to the key questions in this CER, we did not include a column for this in the summary table. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the CER is likely current
- Original conclusion is possibly out of date and this portion of the CER may not be current
- Original conclusion is out of date.

We considered 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 likely current.
- 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 not current.
- 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.

Signal Assessment for Currency of the CER

We used the following considerations in our assessment of currency of the CER:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original report out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original report. This may occur when abstract review and expert assessment indicates that some conclusions from the original report may not be current, or when it is unclear from abstract review how new evidence may impact the findings from the original report. In this case, full-text review and data abstraction may be needed to more clearly classify a signal.
- **Weak signal:** A report is considered to have a weak signal if little or no new evidence is identified that would change the conclusions from the original report. This may occur when little to no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original report.

Results

Prior Surveillance

The most recent prior surveillance of the topic included 3 studies and consultation with two subject matter experts, and concluded that for Key Question 1 may possibly not be current to findings that ARB may be more beneficial than placebo for reducing the risk of stroke. In addition, Key Question 7 may probably not be current due to findings indicating that ARB may relate to an increase in CV deaths, hypotension, headaches and dizziness, as compared to placebo, and that the use of ARB compared to placebo demonstrated benefit for composite endpoint, and increased risk of hospitalization for AF in ACEI users but not in non-ACEI users. All other original CER conclusions were determined to be up to date.²

Literature Search

The literature search identified 31 unique titles from the 10 selected high profile general medical and specialty journals (Appendix C). Upon abstract review, 28 studies were excluded because they did not meet the original CER inclusion criteria (see Appendix B), and an additional 2 were excluded because they were included in the August 2012 surveillance report. The remaining 1 study³ was sent to peer reviewers and examined for potential to change the results of the original review. However, one peer reviewer noted that the study population did not meet inclusion criteria, thus the study was excluded.

Horizon Scanning

Our review of the most recent Horizon Scan did not identify interventions relevant to the key questions in this report. Thus, we did not identify new interventions with high-impact potential for this topic.

FDA Black Box Warnings

We did not find any FDA black box warnings relevant to the key questions in this CER.

Expert Opinion

We shared the conclusions of the original report with 12 in the field (original peer reviewers, TEP members and a local expert) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Two subject matter experts responded.

The two reviewers agreed that the conclusions for Key Questions 1, 2, 4, 6, and 7 were still current or did not know. One expert identified three studies⁴⁻⁶ related to Key Question 5, of which one was potentially relevant⁶ (see Appendix E).

Identifying Qualitative Signals

Appendix E shows the original key questions, the conclusions of the original report and the most recent surveillance report, the results of the literature search, the experts' assessments, and the conclusions regarding the currency of the CER. We did not identify relevant information from AHRQ's Horizon Scanning Report and FDA black box warnings.

No studies identified by the search of the literature or the experts had the potential to change the conclusions of the original CER or previous surveillance reports for Key Questions 1-7. We identified no studies relevant to the key question. For Key Question 5, one⁶ study identified by an expert found a nominal increase in cancer risk associated with combination therapy vs. ACEI alone. We did not identify relevant information from AHRQ's Horizon Scanning Report and FDA black box warnings.

Signal Assessment

The conclusions based on the results of the prior surveillance assessment, literature published since the original report, FDA boxed warnings, horizon scanning, and expert assessment is that:

- Key Question 1: Conclusions are possibly not be current to findings that ARB may be more beneficial than placebo for reducing the risk of stroke (reported in 12/2011 surveillance report)
- Key Question 2: Report conclusions are still valid.
- Key Question 3: Report conclusions are still valid.
- Key Question 4: Report conclusions are still valid.
- Key Question 5: Report conclusions are still valid
- Key Question 6: Report conclusions are still valid.
- Key Question 7: Conclusions are probably not be current due to findings indicating that ARB may relate to an increase in CV deaths, hypotension, headaches and dizziness, as compared to placebo, and that the use of ARB compared to placebo demonstrated benefit for composite endpoint, and increased risk of hospitalization for AF in ACEI users but not in non-ACEI users (reported in 12/2011 surveillance report).

The signal for this report is medium, suggesting that the conclusions in the original CER are probably not current.

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Appendices

Appendix A: Search Strategy

Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix C: Literature Search Results

Appendix D: Questionnaire Sent to Expert Reviewers

Appendix E: Summary Table

Appendix A. Search Strategy

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to June Week 4 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 06, 2015>	
Search Strategy:	
	Original Search Strategy
1 Coronary Artery Disease/ or Coronary Disease/ (166531)	
2 Myocardial Ischemia/ (33412)	
3 Angina Pectoris/ or Angina, Unstable/ (37638)	
4 Arterial Occlusive Diseases/ (25088)	
5 Peripheral Vascular Diseases/ (11282)	
6 Vascular Diseases/ (27218)	
7 Atherosclerosis/ (22731)	
8 Cardiovascular Diseases/ (106963)	
9 Carotid Artery Diseases/ (18735)	
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. (9967)	
11 or/1-10 (421308)	
12 randomized controlled trial.pt. (398697)	
13 controlled clinical trial.pt. (89792)	
14 randomized.ab. (325272)	
15 placebo.ab. (164018)	
16 clinical trials as topic.sh. (173525)	
17 randomly.ab. (233760)	
18 trial.ti. (140852)	
19 or/12-18 (971039)	
20 humans.sh. (14043436)	
21 19 and 20 (814856)	
22 (alacepril or be nazepril 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 t randolapril or zofenopril).mp. (26641)	
23 (losartan or olmesartan or telmisartan or valsartan or eprosartan or candesartan or tasosartan or irbesartan).mp. (16420)	
24 Angiotensin - Converting Enzyme Inhibitors/ (28975)	
25 Angiotensin II Type 1 Receptor	

Blockers/ (0) 26 (ACEI or ARB).mp. (5155) 27 or/22-26 (57508) 28 11 and 21 and 27 (1695)	
29 lancet.jn. (130265) 30 jama.jn. (66896) 31 "annals of internal medicine".jn. (30458) 32 bmj.jn. (62902) 33 "new england journal of me dicine".jn. (0)	Journal Limits : General Medicine
34 american journal of cardiology.jn. (34388) 35 circulation.jn. (40464) 36 "journal of the american college of cardiology".jn. (21814) 37 american heart journal.jn. (23372) 38 european heart journal.jn. (14386) 39 or/29-38 (424945) 40 28 and 39 (377)	Journal Limits : Specialty Medicine
41 limit 40 to yr="2012 -Current" (33)	Date Limits

Appendix B. Inclusion and Exclusion Criteria from Original Systematic Review

Citations at the abstract review stage could be excluded, in a hierarchical order, for the following reasons: not a study of human subjects, not a randomized controlled or observational trial, not a comparison of ACE inhibitor, ARB or their combination versus control therapy (studies directly comparing two different ACE inhibitors, or two ARBs were not included), not conducted in patients with stable ischemic heart disease or a risk equivalent [including diabetes mellitus or chronic kidney disease, or mixed vascular atherosclerotic disorders (coronary disease, peripheral artery disease, carotid atherosclerosis)], did not enroll at least 75 patients for a randomized controlled trial (RCT) or 1000 (observational study) patients, or was not at least 6 months duration..

Full text articles for all citations progressed through the title/abstract review phase were assessed, in parallel, by two independent reviewers. Articles could be excluded at this stage, in hierarchical order, for the following reasons: not a study of human subjects, not a randomized controlled or observational trial, not a comparison of ACE inhibitor, ARB or their combination versus control therapy, not conducted in patients with stable ischemic heart disease or a risk equivalent, did not include patients with preserved ventricular function, did not enroll at least 75 patients (RCT) or 1000 patients (observational study), was not at least 6 months duration, or did not provide potentially usable efficacy data on the pre-specified clinical/humanistic outcomes. For an article to be eliminated, both reviewers had to indicate that it was ineligible for the same reason. A query report was generated identifying articles where discrepancies in the determinations of the two reviewers occurred and were reconciled via consensus adjudication or upon a subsequent determination by a third reviewer if consensus could not be reached.

Articles making it through the full text article review were included in the ‘clinical outcomes’ search evaluation if they were 1) randomized, controlled trials of ACE inhibitor or ARB therapy versus control therapy (placebo, open label, active control) or combination ACE inhibitor and ARB therapy versus either agent alone, 2) conducted in patients with stable ischemic heart disease, diabetes mellitus or chronic kidney disease, or mixed vascular atherosclerotic disorders (coronary disease, peripheral artery disease, carotid atherosclerosis), 3) enrolled patients who had preserved left ventricular function (an average LVEF in experimental groups >40 percent or no systematic evaluation of LVEF but exclusion of patients with signs or symptoms of heart failure), 4) included at least 75 patients, 5) studies that followed patients for a minimum of 6 months, and 6) reported efficacy data on pre-specified clinical or humanistic outcomes (Figure 2.1).

Articles making it through the full text article review were included in the ‘harms’ evaluation if they were 1) randomized, controlled or observational trials of ACE inhibitor or ARB therapy versus control therapy or combination ACE inhibitor and ARB therapy versus either agent alone, 2) conducted in patients with stable ischemic heart disease, diabetes mellitus or chronic kidney disease, or mixed vascular atherosclerotic disorders (coronary disease, peripheral artery disease, carotid atherosclerosis), 3) enrolled patients who had preserved ventricular function (an average LVEF in experimental groups >40 percent or no systematic evaluation of LVEF but exclusion of patients with signs or symptoms of heart failure), 4) included at least 75 patients for RCTs or observational studies of at least 1000 patients, and 5) reported data on pre-specified harms (hyperkalemia, cough, angioedema, hypo

Appendix C. Literature Search Results

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Appendix D. Questionnaire Sent to Expert Reviewers

AHRQ Comparative Effectiveness Review Surveillance Program

Reviewer Form

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

[Link to Report](#)

[Surveillance Report](#)

Name of Reviewer: _____

Instructions:

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ reviews to assist with prioritization of reports for updating. One part of this process includes soliciting expert review of our synthesis of recently published literature and any identified FDA black box warnings.

The attached document includes a table highlighting the conclusions from the original report, conclusions from a surveillance review conducted in 2012, and our synthesis of the recently published literature. Abstracts from relevant literature are included at the end of the attached document. If you would like a list of our full search results, please let us know.

Please review the table in the attached document and provide responses to the questions for each key question below. The primary goal of this review is to identify any missing studies, drugs, interventions, or devices; and ensure the accuracy of our synthesis of the recently published literature.

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?

Prior Surveillance Assessment (August 2012):

- Conclusions were possibly out-of-date, although no signals were detected
- Quantitative signals:
 - In agreement with CER, according to one MA,⁵ in patients with stable ischemic heart disease, ACEI or ARB compared to placebo beneficial in reducing risk of composite endpoint (OR=0.81, 95% CI: 0.75, 0.88)
 - 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 95% CI: 0.66, 1.14)
- Qualitative signals:
 - Given the newly identified MAs, MA in the original CER was not updated

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

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?

Prior Surveillance Assessment (August 2012):

- All conclusions were up to date

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

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 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?

Prior Surveillance Assessment (August 2012):

- All conclusions were up to date

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

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?

Prior Surveillance Assessment (August 2012):

- All conclusions were up to date
- Quantitative signals:
 - 1 RCT in patients 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)
- Qualitative signals:
 - No MA in CER

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

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?

Prior Surveillance Assessment (August 2012):

- All conclusions were up to date

SRC Literature Analysis:

- One RCT examined LCZ696, a first in class angiotensin receptor neprilysin inhibitor compared to valsartan and found that LCZ696 was well tolerated with adverse effects similar to valsartan.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

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?

Prior Surveillance Assessment (August 2012):

- All conclusions were up to date

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

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)?

Prior Surveillance Assessment (August 2012):

- Conclusions are probably out of date
- Expert opinion:
 - 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 a higher rate of renal events for patients with normo albuminuria (HR=2.35, 95% CI: 1.33, 4.15). 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).

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Original Review Conclusions and Literature Analysis

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

[Link to Report](#)

[Surveillance Report](#)

The conclusions from the original report, conclusions from a prior surveillance assessment and an analysis of recent literature identified by the Scientific Resource Center (SRC) are summarized below. Abstracts are provided for included literature at the end of the document.

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Aug 2012)	SRC Literature Analysis (Jul 2015)
<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.</p> <p>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</p>	<p>Possibly out-of-date</p>	<p>No new research was found</p>

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Aug 2012)	SRC Literature Analysis (Jul 2015)
<p>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>		
<p>Key Question (KQ 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?</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>Up-to-date</p>	<p>No new research was found</p>
<p>Key Question (KQ 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</p>		

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Aug 2012)	SRC Literature Analysis (Jul 2015)
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>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</p>	Up-to-date	No new research was found

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Aug 2012)	SRC Literature Analysis (Jul 2015)
optimal time to begin therapy, and more concrete interpretations cannot be made until this evidence becomes available.		
Key Question (KQ 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>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 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>	Up-to-date	No new research was found
Key Question (KQ 5): In patients with stable ischemic heart disease who have preserved left ventricular systolic function and are receiving standard medical		

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Aug 2012)	SRC Literature Analysis (Jul 2015)
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>	Up-to-date	<p>One RCT examined LCZ696, a first in class angiotensin receptor neprilysin inhibitor compared to valsartan and found that LCZ696 was well tolerated with adverse effects similar to valsartan.</p>
<p>Key Question (KQ 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>	Up-to-date	No new research was found

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Aug 2012)	SRC Literature Analysis (Jul 2015)
Key Question (KQ 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)?		
<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</p>	Probably out-of-date	No new research was found

Conclusions From Original Review	Conclusions from Prior Surveillance Assessment (Aug 2012)	SRC Literature Analysis (Jul 2015)
<p>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>		

Legend: 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

ε 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.

μ <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>

Abstracts from Relevant Literature

Solomon, S. D., Zile, M., Pieske, B., Voors, A., Shah, A., Kraigher-Krainer, E., Shi, V., Bransford, T., Takeuchi, M., Gong, J., Lefkowitz, M., Packer, M., McMurray, J. J. and Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectionN fracTion (PARAMOUNT) Investigators. (2012). The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*, 380: 9851: 1387-95.

BACKGROUND: Heart failure with preserved ejection fraction is associated with substantial morbidity and mortality, but effective treatments are lacking. We assessed the efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), in patients with this

disorder.;METHODS: PARAMOUNT was a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association (NYHA) class II-III heart failure, left ventricular ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1) by central interactive voice response system to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. Investigators and participants were masked to treatment assignment. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks; analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment. This trial is registered at Clinicaltrials.gov, number NCT00887588.;FINDINGS: 149 patients were randomly assigned to LCZ696 and 152 to valsartan; 134 in the LCZ696 group and 132 in the valsartan group were included in analysis of the primary endpoint. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group (LCZ696: baseline, 783 pg/mL [95% CI 670-914], 12 weeks, 605 pg/mL [512-714]; valsartan: baseline, 862 pg/mL [733-1012], 12 weeks, 835 [710-981]; ratio LCZ696/valsartan, 0.77, 95% CI 0.64-0.92, p=0.005). LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan had one or more serious adverse event.;INTERPRETATION: In patients with heart failure with preserved ejection fraction, LCZ696 reduced NT-proBNP to a greater extent than did valsartan at 12 weeks and was well tolerated. Whether these effects would translate into improved outcomes needs to be tested prospectively.;FUNDING: Novartis. Copyright © 2012 Elsevier Ltd. All rights reserved

Appendix E. Summary Table*

Conclusions From CER Executive Summary	Literature Analysis and Assessment from Most Recent Surveillance Assessment (Aug 2012 – Link to Paper)	Current Literature Search (July 2015)	Expert Opinion	Surveillance 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.</p> <p>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</p>	<p>Qualitative: 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, 95% CI : 0.66, 1.14)</p> <p>Possibly out of date based on 12/11 surveillance</p>	<p>No new research was identified</p>	<p>Both reviewers felt there was no new evidence that would change conclusions.</p>	<p>May not be current based on 12/2011 surveillance report.</p>

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<p>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>				
<p>Key Question (KQ) 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?</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</p>	<p>No new research was identified</p>	<p>No new research was identified</p>	<p>One reviewer felt there was no new evidence that would change the conclusions of the original report. The second reviewer was not sure.</p>	<p>Likely current</p>

Conclusions From CER Executive Summary	Literature Analysis and Assessment from Most Recent Surveillance Assessment (Aug 2012 – Link to Paper)	Current Literature Search (July 2015)	Expert Opinion	Surveillance Assessment
evidence of possible differences from Key Question 1.				
Key Question (KQ 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>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</p>	No new research was identified	No new research was identified	Both reviewers felt there was no new evidence that would change conclusions.	Likely current

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<p>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 (KQ 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</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 new research was identified</p>	<p>Both reviewers felt there was no new evidence that would change conclusions.</p>	<p>Likely current</p>

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<p>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>Key Question (KQ 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	No new research was identified	No new research was identified	One reviewer felt there was no new evidence that would	Likely current

Conclusions From CER Executive Summary	Literature Analysis and Assessment from Most Recent Surveillance Assessment (Aug 2012 – Link to Paper)	Current Literature Search (July 2015)	Expert Opinion	Surveillance Assessment
<p>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>change the conclusions of the original report. The same reviewer noted that the study we had identified as potentially relevant should be excluded due to the participant sample having signs/symptoms of heart failure.</p> <p>The second reviewer identified three meta-analyses comparing combination therapy to ACEIs alone; however, one combined patient populations⁴, and the second examined patients with AMI⁵ or HF. The third⁶ was an IPD meta-analysis including one trial meeting inclusion criteria and comparing combination therapy to an ACEI or ARB alone (ONTARGET). There was a nominally significant increase in cancer risk associated with combination therapy vs. ACEI alone (OR = 1.12, 95% CI 1.00-1.26).</p>	
<p>Key Question (KQ 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</p>	<p>No new research was identified</p>	<p>No new research was found</p>	<p>Both reviewers felt there was no new evidence that would change conclusions.</p>	<p>Likely current</p>

Conclusions From CER Executive Summary	Literature Analysis and Assessment from Most Recent Surveillance Assessment (Aug 2012 – Link to Paper)	Current Literature Search (July 2015)	Expert Opinion	Surveillance Assessment
<p>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 (KQ 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)?</p>				
<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</p>	<p>No new research was identified Probably out of date based on 12/11 surveillance</p>	<p>No new research was identified</p>	<p>Both reviewers felt there was no new evidence that would change conclusions.</p>	<p>May not be current based on 12/2011 surveillance report.</p>

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<p>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</p>				

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<p>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>				

*No relevant FDA warnings or Horizon Scanning interventions were identified.