Comparative Effectiveness Review

Number 18

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

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This report is based on research conducted by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10067-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Craig I. Coleman, Pharm.D., has been a primary investigator on projects sponsored by Boehringer-Ingelheim Pharmaceuticals, the makers of the angiotensin receptor blocker telmisartan, but none of the projects were related to ischemic heart disease, angiotensin receptor blockers, or telmisartan. Dr. Coleman was not involved in the data extraction, analysis, or synthesis of the two key questions involving trials including telmisartan. None of the other investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

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

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

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

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

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

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Background

Nearly 2,400 Americans die of cardiovascular disease each day, an average of one death every 36 seconds. Cardiovascular disease claims more lives each year than cancer, chronic lower respiratory diseases, accidents, and diabetes mellitus combined. An estimated 79,400,000 American adults (one in three), of whom 37,500,000 are estimated to be age 65 or older, have one or more types of cardiovascular disease. Approximately 8,900,000 adults suffer from angina. Since 1900, cardiovascular disease has accounted for more deaths than any other single cause or group of causes of death in the United States in every year except one.

Based on clinical trial evidence, American College of Cardiology and American Heart Association guidelines support the use of angiotensin converting enzyme (ACE) inhibitors in patients who have chronic heart failure or those with myocardial infarction and left ventricular dysfunction, while angiotensin receptor blockers (ARBs) are reserved for those who cannot tolerate ACE inhibitors. Combined ACE inhibitor and ARB therapy has been shown to provide additional benefits over therapy with an ACE inhibitor alone among patients with heart failure. However, the combined use of an ACE inhibitor and ARB in post-myocardial-infarction patients with left ventricular dysfunction or heart failure was no better than the use of captopril alone and carried an increased risk of harms.

Studies have been conducted that evaluate the use of ACE inhibitors and ARBs, either alone or in combination, in patients who have ischemic heart disease or an ischemic heart disease risk equivalent but without heart failure or left ventricular dysfunction. From this body of evidence, the benefits and harms associated with use of these therapies in this population of patients may be discerned.

This report summarizes the available evidence comparing the efficacy and safety of using ACE inhibitors, ARBs, or their combination vs. standard medical therapy in a population with stable ischemic heart disease, or an ischemic heart disease risk equivalent, and preserved left ventricular function. This report addresses the following questions:

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)?

Conclusions

Table A provides an aggregated view of the strength of evidence and brief conclusions from this review of the comparative long-term benefits and harms of ACE inhibitors, ARBs, or their combination vs. standard medical therapy in a population with stable ischemic heart disease and preserved left ventricular function.

Key Question 1

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 (evaluated in Key Question 2) should be considered.

Key Question 2

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.

Key Question 3

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.

Key Question 4

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.

Key Question 5

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.

Key Question 6

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.

Key Question 7

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.

Table A. Summary of conclusions from evidence on the use of ACE inhibitors and ARBs in addition to standard medical therapy for stable ischemic heart disease

Key Question	Strength of evidence	Conclusions
KQ1. 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?		
KQ1a. Total mortality	High High Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor therapy is similar to calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, imidapril, lisinopril[1]) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Low Low Insufficient	▪ ACE inhibitor therapy is similar to placebo in patients with stable ischemic heart disease risk equivalents. (ARB therapy not evaluated.) ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.
KQ1b. Cardiovascular mortality	Moderate Moderate Moderate	▪ ACE inhibitor or ARB therapy is similar to placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.

	Moderate Moderate Insufficient	▪ ACE inhibitor therapy is similar to calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, imidapril, lisinopril[1]) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor therapy is similar to placebo in patients with ischemic heart disease risk equivalents. (ARB therapy not evaluated.) ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.
KQ1c. Nonfatal myocardial infarction	High High Insufficient	▪ ACE inhibitor therapy is better than placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor therapy is similar to calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril) are similar to calcium channel blockers (amlodipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Low Low Insufficient	▪ ACE inhibitor therapy is similar to placebo in patients with ischemic heart disease risk equivalents. (ARB therapy not evaluated.) ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.

KQ1d. Stroke	Moderate Moderate Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor therapy is similar to calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, imidapril, lisinopril[1]) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Low Low Insufficient	▪ ACE inhibitor therapy is similar to placebo in patients with ischemic heart disease risk equivalents. (ARB therapy not evaluated.) ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.
KQ1e. Composite of cardiovascular mortality, nonfatal myocardial infarction, or stroke	High Moderate Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (ramipril, trandolapril) are similar to placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is better than placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to calcium channel blockers in patients with stable ischemic heart disease.
	Low Low Insufficient	▪ ACE inhibitor therapy is similar to placebo in patients with ischemic heart disease risk equivalents. (ARB therapy not evaluated.) ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.
KQ1f. Atrial fibrillation	High	▪ ACE inhibitor (ramipril) or ARB (telmisartan) therapy is similar to placebo in patients with stable ischemic heart disease.

	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1g. Symptom reporting	Moderate	▪ ACE inhibitor (zofenopril) therapy increases the time to onset of ischemic symptoms via treadmill exercise test vs. placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1h. Total hospitalization	Moderate	▪ ACE inhibitor (ramipril) or ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1i. Hospitalization for angina	High	▪ ACE inhibitor (enalapril, ramipril) or ARB (telmisartan) therapy is similar to placebo in patients with stable ischemic heart disease.
	Moderate	▪ ACE inhibitor therapy is similar to calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, imidapril, lisinopril[1]) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1j. Hospitalization for heart failure	High High Moderate	▪ ACE inhibitor therapy is better than placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.

	Moderate Moderate Insufficient	▪ ACE inhibitor therapy is similar to calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, imidapril, lisinopril[1]) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1k. Revascularization	High High Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor therapy is similar to calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, imidapril, lisinopril[1]) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1l.Quality of life	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to either placebo or calcium channel blockers in patients with ischemic heart disease or ischemic heart disease risk equivalents.
KQ2. 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 adding ACE inhibitors and ARBs vs. either an ACE inhibitor or ARB alone in terms of total mortality, cardiovascular death, 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?		
KQ2a. Total mortality	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.

KQ2b. Cardiovascular mortality	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2c. Fatal + nonfatal myocardial infarction	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2d. Fatal + nonfatal stroke	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2e. Composite of cardiovascular mortality, fatal + nonfatal myocardial infarction, and fatal + nonfatal stroke	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2f. New atrial fibrillation	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2g. Worsening or new angina	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2h. Total hospitalization	Insufficient	▪ No data are available comparing the combination of ACE inhibitor + ARB therapy vs. ACE inhibitor therapy alone in patients with stable ischemic heart disease.
KQ2i. Hospitalization for angina	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2j. Hospitalization for heart failure	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2k. Revascularization	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2l. Quality of life	Insufficient	▪ No data are available comparing the combination of ACE inhibitor + ARB therapy vs. ACE inhibitor therapy alone in patients with stable ischemic heart disease.
KQ3. 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?		
KQ3a. Total mortality	Moderate	▪ ACE inhibitor (cilazapril, quinapril, ramipril) or ARB (candesartan) therapy is similar to placebo.
KQ3b. Cardiovascular mortality	Low	▪ ACE inhibitor (quinapril, ramipril) or ARB (candesartan) therapy is similar to placebo.

KQ3c. Nonfatal myocardial infarction	Low	▪ ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy is similar to placebo.
KQ3d. Stroke	Low	▪ ACE inhibitor therapy is similar to placebo. (ARB therapy not evaluated.) ▪ ACE inhibitors (quinapril, ramipril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3e. Composite of cardiovascular mortality, nonfatal myocardial infarction, and stroke	Moderate	▪ ACE inhibitor therapy is similar to placebo. (ARB therapy not evaluated.) ▪ ACE inhibitors (quinapril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3f. Atrial fibrillation	Moderate	▪ ACE inhibitor therapy is similar to placebo. (ARB therapy not evaluated.) ▪ ACE inhibitors (quinapril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3g. Symptom reporting	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo.
KQ3h. Total hospitalization	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo.
KQ3i. Hospitalization for angina	Moderate	▪ ACE inhibitor therapy is similar to placebo. (ARB therapy not evaluated.) ▪ ACE inhibitors (quinapril, ramipril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3j. Hospitalization for heart failure	Low	▪ ACE inhibitor therapy is similar to placebo. (ARB therapy not evaluated.) ▪ ACE inhibitors (quinapril, ramipril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3k. Revascularization	High	▪ ACE inhibitor or ARB therapy is worse than placebo. ▪ ACE inhibitors (cilazapril, quinapril) are worse than placebo. ▪ ARB (candesartan) therapy is similar to placebo.
KQ3l.Quality of life	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo.

KQ4. 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?		
KQ4a. Withdrawals due to adverse events	Low	▪ The risk of withdrawing from a trial is greater with ACE inhibitor therapy than with placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, ramipril, trandolapril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Low	▪ ACE inhibitor therapy is similar to calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, imidapril, lisinopril[1]) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4b. Hypotension	Low	▪ The risk of hypotension is similar with ACE inhibitor therapy vs. placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, ramipril, zofenopril) are similar to placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Low	▪ The risk of hypotension with ACE inhibitor therapy is greater than with calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril) are worse than calcium channel blockers (amlodipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.

KQ4c. Syncope	Low	▪ The risk of syncope with ACE inhibitor therapy is greater than with placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (ramipril, trandolapril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4d. Cough	Low	▪ The risk of cough with ACE inhibitor therapy is greater than with placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril, ramipril, trandolapril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Low	▪ The risk of cough with ACE inhibitor therapy is greater than with calcium channel blockers in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (enalapril) are worse than calcium channel blockers (amlodipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4e. Angioedema	Low	▪ The risk of angioedema is similar with ACE inhibitor therapy vs. placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (ramipril, trandolapril) are similar to placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.

	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4f. Hyperkalemia	Low	▪ The risk of hyperkalemia is greater with ACE inhibitor (ramipril) or ARB (telmisartan) therapy than with placebo therapy in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4g. Rash	Insufficient	▪ No data are available comparing ACE inhibitors or ARBs to placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4h. Blood dyscrasias	Insufficient	▪ No data are available comparing ACE inhibitors or ARBs to placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data are available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ5. 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?		
KQ5a. Study withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) has more discontinuations than ACE inhibitor (ramipril) alone.
KQ5b. Hypotension withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) has more discontinuations due to hypotension than ACE inhibitor (ramipril) alone.
KQ5c. Syncope withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) has more discontinuations due to syncope than ACE inhibitor (ramipril) alone.
KQ5d. Cough withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) has a similar number of discontinuations due to cough as ACE inhibitor (ramipril) alone.
KQ5e. Angioedema withdrawal	Low	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) has a similar number of discontinuations due to angioedema as ACE inhibitor (ramipril) alone.

KQ5f. Renal impairment withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) has more discontinuations due to renal impairment than ACE inhibitor (ramipril) alone.
KQ5g. Rash	Insufficient	▪ No data are available comparing the combination of ACE inhibitor + ARB therapy vs. ACE inhibitor therapy alone in patients with stable ischemic heart disease.
KQ5h. Blood dyscrasias	Insufficient	▪ No data are available comparing the combination of ACE inhibitor + ARB therapy vs. ACE inhibitor therapy alone in patients with stable ischemic heart disease.
KQ6. 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?		
KQ6a. Study withdrawal	Low	▪ The risk of withdrawals is greater with ACE inhibitor therapy than with placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (quinapril, ramipril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
KQ6b. Hypotension	Moderate	▪ The risk of hypotension is greater with ACE inhibitor therapy than with placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (quinapril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
KQ6c. Syncope	Insufficient	▪ No data are available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ6d. Cough	Low	▪ The risk of cough with ACE inhibitor therapy is similar to placebo in patients with stable ischemic heart disease. (ARB therapy not evaluated.) ▪ ACE inhibitors (quinapril) are similar to placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
KQ6e. Angioedema	Insufficient	▪ No data are available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ6f. Renal impairment or hyperkalemia	Insufficient	▪ No data are available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.

KQ6g. Rash	Insufficient	▪ No data are available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ6h. Blood dyscrasias	Insufficient	▪ No data are available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ7. 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).		
KQ7a. Sex	Moderate	▪ ACE inhibitors (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or one of the following depending on the trial: stroke or nonfatal cardiac arrest) similarly in males and females.
	Low	▪ ARB therapy (telmisartan) may not reduce the composite efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure in females as much as in males (p-value for interaction = 0.08).
	Low	▪ When ACE inhibitor (ramipril) and ARB (telmisartan) therapy are directly compared, there is a nonsignificant indication that ACE inhibitor therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in females than ARB therapy, with similar efficacy between treatments in males.
	Low	▪ When ACE inhibitor therapy (ramipril) is compared to combination therapy with ACE inhibitors and ARBs (ramipril + telmisartan), there is a nonsignificant indication that combination therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in females than ACE inhibitor therapy, with similar efficacy between treatments in males.
	Low	▪ ACE inhibitors (enalapril, imidapril, lisinopril) appear to be similar to calcium channel blockers (nifedipine) in efficacy in either males or females with stable ischemic heart disease and preserved left ventricular function.
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in males and females cannot be determined at this time.
KQ7b. Age	Low	▪ ACE inhibitors (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or one of the following depending on the trial: stroke or nonfatal cardiac arrest) to a greater degree than placebo in both younger and older subjects.

	Low	▪ ARB therapy (telmisartan) impacts the composite efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure similarly to placebo in those under 65 years, 65-74 years, and greater than 74 years of age (p-value for interaction = 0.895). No significant benefits are seen with ARB therapy vs. placebo in any of the age subgroups.
	Low	▪ When ACE inhibitor therapy (ramipril) is compared to ARB therapy (telmisartan) or to the combination of ACE inhibitor plus an ARB (ramipril + telmisartan), results are similar in the different age subgroups for the composite efficacy endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure).
	Low	▪ ACE inhibitors (enalapril, imidapril, lisinopril[1]) appear to be similar in efficacy to calcium channel blockers (nifedipine) in either younger or older subjects with stable ischemic heart disease and preserved left ventricular function.
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in subjects of differing ages cannot be determined at this time.
KQ7c. Ethnicity/genetic polymorphisms	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination in subjects of differing ethnicity or genetic polymorphisms cannot be determined at this time.
KQ7d. Left ventricular ejection fraction	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination in subjects with varying degrees of preserved left ventricular function cannot be determined at this time.
KQ7e. Degree and location of lesion	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination in subjects with differing extents and locations of atherosclerotic lesions cannot be determined at this time.
KQ7f. Presence and pattern of symptoms	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination in subjects with different presence and pattern of angina symptoms cannot be determined at this time.
KQ7g. Dose of ACE inhibitor or ARB used	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on efficacy or harms depending on the dose employed cannot be determined at this time.
KQ7h. Diabetes mellitus	Moderate	▪ ACE inhibitors (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or one of the following depending on the trial: stroke or nonfatal cardiac arrest) similarly in patients with and without diabetes mellitus.

	Low	▪ ARB therapy (telmisartan) impacts the composite efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure similarly to placebo in those with or without diabetes mellitus (p-value for interaction = 0.311). No significant benefits are seen with ARB therapy vs. placebo in either subgroup.
	Low	▪ ACE inhibitor therapy (ramipril) provides similar efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) to ARB therapy (telmisartan) in those with or without diabetes mellitus.
	Low	▪ When ACE inhibitor therapy (ramipril) is compared to combination therapy with ACE inhibitors and ARBs (ramipril + telmisartan), there is a nonsignificant indication that combination therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) than ACE inhibitor therapy in those with diabetes mellitus, but similar efficacy occurs between treatments in those without diabetes mellitus (p-value for interaction = 0.15).
	Low	▪ ACE inhibitor therapy (enalapril, imidapril, lisinopril[1]) provides similar efficacy to calcium channel blocker (nifedipine) therapy in those with diabetes mellitus.
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with or without diabetes mellitus cannot be determined at this time.
KQ7i. Renal dysfunction	Low	▪ ACE inhibitor therapy (perindopril, ramipril, trandolapril) may prevent cardiovascular events and total mortality better in those with mild to moderate renal dysfunction than those without it.
	Insufficient	▪ The impact of ARB therapy on cardiovascular events and total mortality in those with or without renal dysfunction cannot be determined at this time.
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with or without renal dysfunction cannot be determined at this time.
KQ7j. Hypertension	Moderate	▪ ACE inhibitor therapy (perindopril, ramipril) reduces composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or of one of the following depending on the trial: stroke or nonfatal cardiac arrest) similarly in those with or without hypertension.

	Low	▪ ARB therapy (telmisartan) impacts the composite efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure similarly to placebo in those with systolic blood pressures of <135mmHg, 135-149mmHg, or >149mmHg (p-value for interaction = 0.796).
	Low	▪ When ACE inhibitor (ramipril) and ARB (telmisartan) therapy are directly compared, there is a nonsignificant indication that ACE inhibitor therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in those with baseline systolic blood pressures above 134mmHg, while ARBs might provide greater efficacy in those with baseline systolic blood pressures of 134mmHg or below (p-value for interaction = 0.10).
	Low	▪ When ACE inhibitor therapy (ramipril) is compared to combination therapy with ACE inhibitors and ARBs (ramipril + telmisartan), there is a nonsignificant indication that combination therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in those with baseline systolic blood pressures of 134mmHg of less and those with a baseline systolic blood pressure of 150mmHg or more. ACE inhibitor therapy alone tends to provide greater efficacy in the middle blood pressure range (p-value for interaction = 0.15).
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with or without hypertension cannot be determined at this time.
KQ7k. Baseline risk	Low	▪ ACE inhibitors (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or one of the following depending on the trial: stroke or nonfatal cardiac arrest) in low, medium, and high baseline risk categories vs. placebo. As the baseline risk is increased, the benefits from ACE inhibitor therapy might be accentuated.
	Low	▪ ARB therapy (telmisartan) might provide greater efficacy than placebo in low baseline risk patients than in those with medium or high risk for the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure (p-value for interaction = 0.462).

	Low	▪ ACE inhibitor therapy (ramipril) may provide greater efficacy than ARB therapy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in those at medium to high baseline risk, while ARB therapy (telmisartan) may provide more efficacy than ACE inhibitors in those at lower baseline risk (p-value for interaction = 0.21).
	Low	▪ Combination therapy with an ACE inhibitor plus an ARB (ramipril + telmisartan) provides similar efficacy as an ACE inhibitor alone regardless of baseline risk (p-value for interaction = 0.97).
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with different baseline risk cannot be determined at this time.
KQ7l. Antiplatelet therapy	Moderate	▪ ACE inhibitor therapy (perindopril, ramipril) is significantly better than placebo at reducing the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and stroke in patients without antiplatelet therapy vs. those with antiplatelet therapy (p-value for interaction < 0.003).
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with antiplatelet therapy cannot be determined at this time.
KQ7m. History of revascularization	Moderate	▪ ACE inhibitor therapy (perindopril, ramipril) is likely better than placebo at reducing the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and stroke in patients without a history of revascularization vs. those with such a history (p-value for interaction = 0.078).
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with or without a history of revascularization cannot be determined at this time.
KQ7n. Beta-blockers	Moderate	▪ ACE inhibitors (perindopril, ramipril) have ability similar to placebo in reducing the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with or without beta-blockers (p-value for interaction = 0.134)
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with or without beta-blockers cannot be determined at this time.
KQ7o. Lipid lowering therapy	Moderate	▪ ACE inhibitors (perindopril, ramipril) provide a similar ability to reduce the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and stroke vs. placebo in patients with or without lipid lowering therapy (p-value for interaction = 0.651)

	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with or without lipid lowering therapy cannot be determined at this time.
KQ7p. Vitamin E therapy	Low	▪ ACE inhibitors (ramipril) provide similar ability to reduce the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and stroke vs. placebo in patients with or without vitamin E therapy
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with or without vitamin E therapy cannot be determined at this time.

[1]The JMIC-B (Japan Multicenter Investigation for Cardiovascular Diseases-B) trial compared the calcium channel blocker nifedipine to one of three ACE inhibitors (enalapril, imidapril, or lisinopril), while the CAMELOT (Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis) trial compared the calcium channel blocker amlodipine to the ACE inhibitor enalapril.

Abbreviations: ACE=angiotension-converting enzyme; ARB= angiotensin receptor blocker.

Remaining Issues

While the trials included in the review were not designated as effectiveness trials, many were multicenter and multinational trials with long-term followup and included numerous subgroup analyses based on gender, age, comorbidities, and concurrent therapies. The use of run-in periods in several of these trials detracts from applicability, since those unable to tolerate therapy were eliminated before entering the trial. In addition, the TRANSCEND trial was limited to those who could not tolerate ACE inhibitors and represents a select group of subjects. This reduces applicability to the overall population, but the applicability to those unable to tolerate ACE inhibitors is high. While the participants in the trials were not ubiquitously receiving aspirin, statins, and beta-blockers (important components of standard medical therapy), they received benefits from ACE inhibitors regardless of the use of these agents in subgroup analyses. In addition, patients in the United States seldom receive all of the agents associated with mortality and morbidity reductions. So even with these limitations, we have confidence in the applicability of many of the efficacy results to populations with ischemic heart disease and preserved left ventricular function. However, for the evaluation of ACE inhibitors or ARBs vs. calcium channel blockers and the evaluation of ACE inhibitors or ARBs in patients with ischemic heart disease risk equivalents, we do not have the same degree of confidence in the applicability of the efficacy results. We also have less confidence in the applicability of the harms result, given the lack of data for several outcomes in many trials, the use of run-in periods, and the differing or unexplained definitions of harms outcomes.

Future Research

We believe that the following areas of future research are of particular importance to patient care.

- An individual patient data meta-analysis of major placebo-controlled ACE inhibitor or ARB trials or future trials is needed to provide insight into the benefits and harms in African Americans and Latinos. We cannot determine the comparative benefits and harms associated with the use of these drugs in these populations based on the data provided to date.

- Either (1) an individual patient data meta-analysis of major placebo-controlled ACE inhibitor or ARB trials or (2) future trials are needed to provide insight into the benefits and harms in patients with single vs. multivessel disease, and specifically to determine if left anterior descending artery disease is more important than disease in other vessels in predicting efficacy and harms.
- An individual patient data meta-analysis of major placebo-controlled ACE inhibitor or ARB trials is needed to determine if an association exists with a baseline ejection fraction between 40 percent and 70 percent and the benefits or harms associated with therapy.
- An individual patient data meta-analysis is needed to determine if ACE inhibitors provide greater benefits in patients taking adenosine diphosphate inhibiting drugs than in those taking no antiplatelet therapy to find out whether the interaction noted between antiplatelets and ACE inhibitors is applicable to all antiplatelets or just to aspirin. Determining the impact of antiplatelet therapy on ARB therapy efficacy is also needed.
- An individual patient data meta-analysis is needed to determine if a history of revascularization significantly reduces the benefits associated with ACE inhibitor or ARB therapy and to elucidate the impact on harms associated with these therapies in this population.
- Future trials are needed to discern if adding ACE inhibitors or ARBs to standard medical therapy in patients with stable ischemic heart disease and preserved left ventricular function is superior or inferior to adding other cardiovascular drugs such as calcium channel blockers. Information on the applicability of these results to subjects of different genders, age, comorbidities, and medications is needed.
- Future trials are needed to determine the benefits and harms associated with adding ACE inhibitors or ARBs to standard medical therapy in patients without proven stable ischemic heart disease but with ischemic heart disease risk equivalents. Information on the applicability of these results to subjects of different genders, age, comorbidities, and medications is needed.
- Future studies are needed to determine if the dosing intensity of ACE inhibitor or ARB therapy is related to the extent of efficacy and harms that patients receive.
- Future trials are needed to determine the impact of genetic polymorphisms within the ACE gene or the angiotensin II type 1 receptor and the benefits or harms associated with ACE inhibitors or ARBs in this population.

A review of trials registered at www.clinicaltrials.gov [Accessed January 8th, 2009] revealed no ongoing trials that would have matched our inclusion criteria or answered any of the remaining clinical questions proposed in this section.

Introduction

Background

This is an evidence report prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC) concerning the benefits and harms associated with using angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), either alone or in combination, in people with stable ischemic heart disease or ischemic heart disease risk equivalents and intact left ventricular systolic function.

While the role of ACE inhibitors and ARBs in patients with post-myocardial infarction left ventricular dysfunction or chronic heart failure is well established, the role for these modalities in patients with stable ischemic heart disease or ischemic heart disease risk equivalents and preserved left ventricular systolic function is not as clear. The aim of this report is to acquire, assess, and summarize the current evidence about the benefits and harms associated with the use of ACE inhibitors and ARBs, either alone or in combination, in this patient population. The information is intended to inform clinicians, payors, and the public, while helping to define avenues for future research.

Health Impact of Cardiovascular Disease in the United States

Nearly 2,400 Americans die of cardiovascular disease each day, an average of one death every 36 seconds. Cardiovascular disease claims more lives each year than cancer, chronic lower respiratory diseases, accidents and diabetes mellitus combined.[1] An estimated 79,400,000 American adults (one in three) have one or more types of cardiovascular disease, of whom 37,500,000 are estimated to be age 65 or older; approximately 8,900,000 adults suffer from angina. In every year since 1900, except 1918, cardiovascular disease accounted for more deaths than any other single cause or group of causes of death in the United States.[1]

Stable Ischemic Heart Disease With Preserved Left Ventricular Function

People with stable ischemic heart disease have advanced atherosclerosis reducing the maximal ability of the coronary arteries to supply blood to the myocardium.[2] Stable ischemic heart disease can run the gamut from those with asymptomatic ischemic episodes to those with severely debilitating symptoms and from focused large vessel disease to those with diffuse microvascular disease.[2] People with stable ischemic heart disease may or may not have had an acute coronary syndrome in the past but are at increased risk of such an event in the future.[2]

In people without a previous acute coronary syndrome but with stable ischemic heart disease, antiplatelet therapy with a single agent (aspirin or clopidogrel) and statin therapy (if the low density lipoprotein and non-high density lipoprotein concentrations are above 100mg/dL and 130mg/dL, respectively) can reduce the risk of cardiovascular events.[2,3] Other drugs such as fast acting nitrates (nitroglycerin tablets or spray), negative chronotropic agents (beta-blockers, non-dihydropyridine calcium channel blockers), and vasodilators (calcium channel blockers, long acting nitrates) are for symptomatic relief but do not impact the risk of cardiovascular events. In people with a myocardial infarction but with preserved left ventricular function, dual antiplatelet therapy, statin therapy (if the low density lipoprotein and non-high density lipoprotein concentrations are above 70-100mg/dL and 130mg/dL, respectively), and beta-blockers can reduce the risk of subsequent cardiovascular events. The aforementioned symptomatic relief

agents can similarly be used in this population as well.[2,3] As such, it is important to evaluate new therapeutic modalities that may impact cardiovascular events in ischemic heart disease patients in addition to standard medical therapy.

ACE Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors have been shown to reduce the risk of morbidity and mortality amongst patients who have chronic heart failure or those after a myocardial infarction with left ventricular dysfunction.[4-6] In patients with either chronic heart failure or post-myocardial infarction with left ventricular dysfunction, ARBs have been shown to be a reasonable substitute for ACE inhibitors for patients with these indications as well.[7-11] In fact, in the Losartan Heart Failure Survival Study (ELITE II), patients with class II-IV heart failure and ejection fractions of <40 percent showed no difference between the ACE inhibitor captopril or the ARB losartan in terms of all cause mortality or sudden death.[8] Additionally, a recent systematic review reported no significant differences in either blood pressure lowering ability or clinical outcomes in patients with essential hypertension between ACE inhibitors and ARBs.[12] American College of Cardiology and American Heart Association practice guidelines support the use of ACE inhibitors in patients who have chronic heart failure or those with myocardial infarction and left ventricular dysfunction while ARBs are reserved for those who cannot tolerate ACE inhibitors.[13,14] Combined ACE inhibitor and ARB therapy has been shown to provide additional benefits (17 percent reduction in mortality and 17 percent reduction in heart failure hospitalization) over that of an ACE inhibitor alone among patients with heart failure in the Candesartan in Heart failure Assessment of Reduction in Mortality (CHARM)-added trial.[11] However, in the Valsartan in Acute Myocardial infarction (VALIANT) trial the combined use of an ACE inhibitor and ARB in post-myocardial infarction patients with left ventricular dysfunction or heart failure was no better than captopril alone for mortality or the composite endpoint (death from cardiac causes, reinfarction, or hospitalization for heart failure) with an increased risk of harms (adverse events resulting in dose reduction, 34.8 percent vs. 28.4 percent).[12] As such, the aforementioned practice guidelines recommend the adjuvant use of ARBs in patients with heart failure who are still symptomatic on ACE inhibitors and beta-blockers but not in patients after a myocardial infarction with left ventricular dysfunction.[13,14]

Studies have been conducted that evaluate the use of ACE inhibitors and ARBs, either alone or in combination, in patients who have ischemic heart disease or an ischemic heart disease risk equivalent but without heart failure or left ventricular dysfunction. From this body of evidence, the benefits and harms associated with use of these therapies in this population of patients may be discerned. This is the focus of our current report.

Pharmacology and Analytic Framework

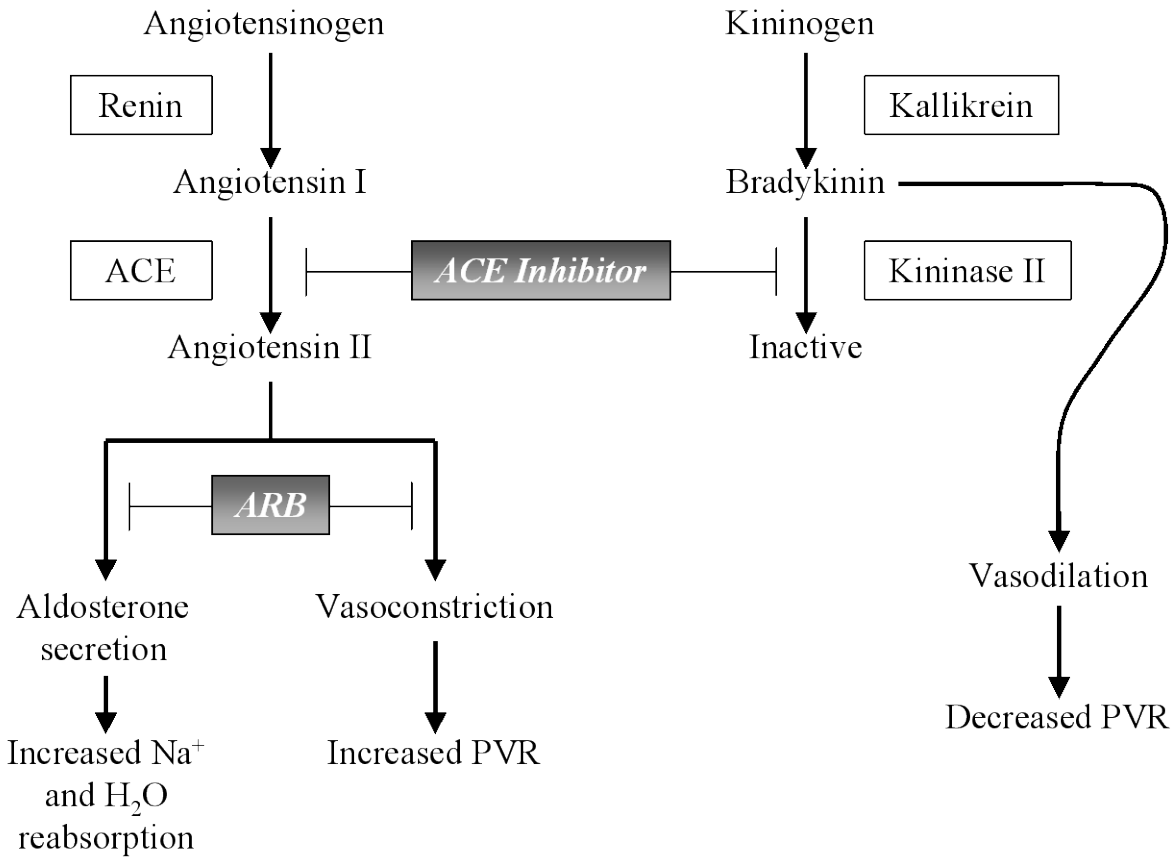
Through the stimulation of angiotensin II type-1 receptors, angiotensin II increases systemic vascular resistance (afterload) elevating blood pressure and causing left ventricular hypertrophy. Angiotensin II promotes pathogenic remodeling (atherosclerosis and fibrosis) through the production of free radicals and subsequent promotion of inflammatory mediator release. These mediators participate in the recruitment of lymphocytes, the accumulation of macrophages with subsequent conversion to foam cells, and the propagation of atherosclerosis.[15,16] Angiotensin II causes the release of aldosterone promoting pathogenic remodeling and also activates the sodium-potassium pump in the distal convoluted tubule promoting hypokalemia and fluid retention. Angiotensin II may increase the production of

endogenous inhibitors of fibrinolysis. Finally, through production of free radicals, angiotensin II also decreases the availability of nitric oxide, inducing a state of endothelial dysfunction that may impact endothelial wall integrity and lead to ischemia.[15,17]

ACE inhibitors inhibit ACE, blocking the conversion of angiotensin I to angiotensin II, while preserving bradykinin (Figure 1).[18] ARBs block the angiotensin II type-1 receptor and reduce the pharmacologic effects of angiotensin II regardless of whether angiotensin II is created by ACE or non-ACE pathways (Figure 1).[19] As such, ACE inhibitors and ARBs can provide several pharmacological effects, over and above that of blood pressure reduction alone, which may impact cardiovascular events.

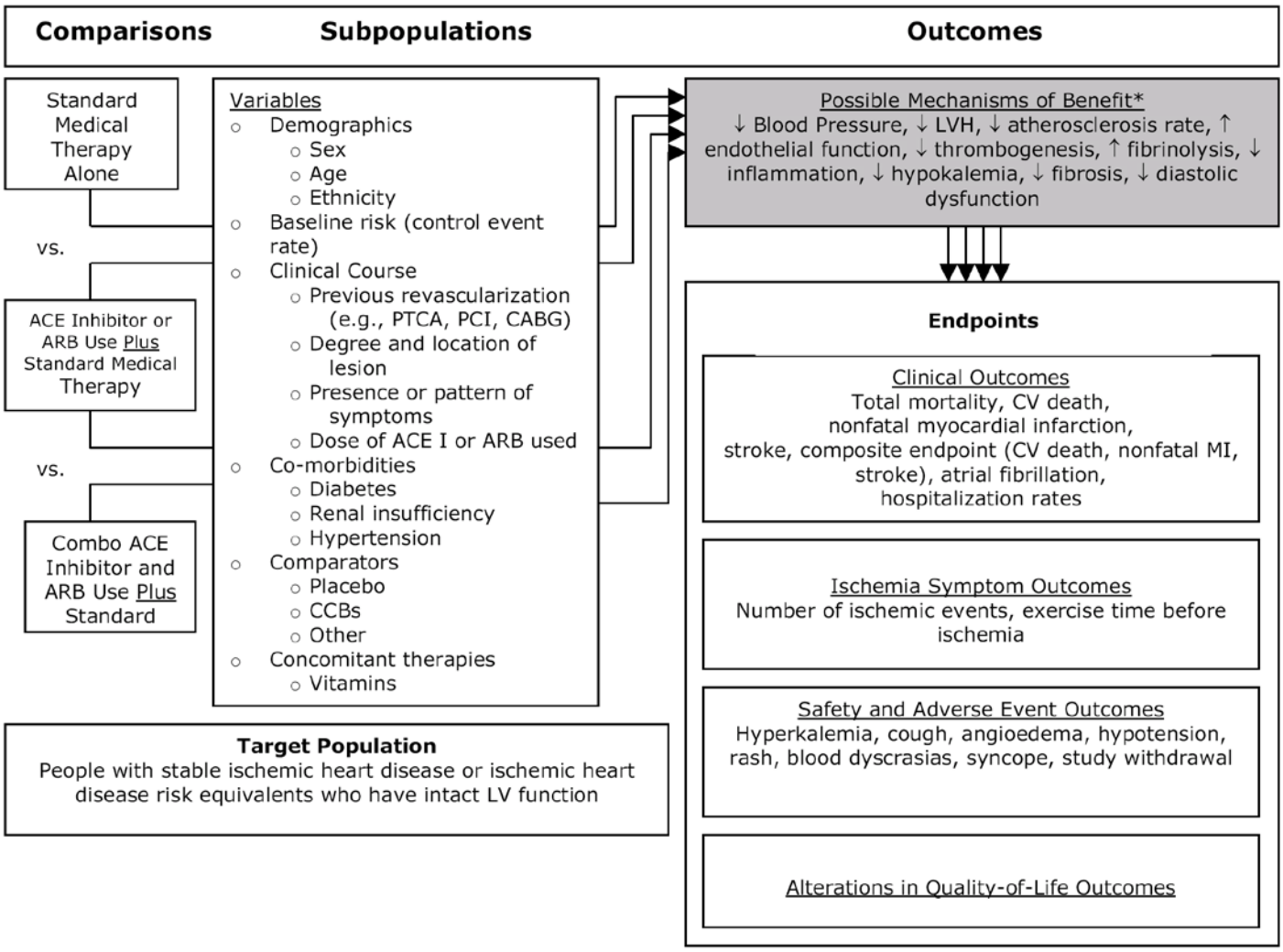
Figure 1. Pharmacologic effects of antagonists of the renin-angiotensin system[18,19]

PVR = peripheral vascular resistance



To guide our assessment of studies examining the association between ACE inhibitors, ARBs, or the combination of agents from the two classes on benefits and harms in our target population, we developed an analytic framework mapping specific linkages from comparisons to subpopulations of interest, mechanisms of benefit, and outcomes of interest (Figure 2). It is a logic chain that supports the link from the intervention to the outcomes of interest.

Figure 2. Analytic framework for the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with stable ischemic heart disease and preserved systolic function



Scope and Key Questions

This comparative effectiveness review was commissioned by the Agency for Healthcare Research and Quality (AHRQ) to focus on a population with stable ischemic heart disease or ischemic heart disease risk equivalents[20-22] who have preserved left ventricular systolic function.

The key questions center around the comparative effectiveness of ACE inhibitors or ARBs added to standard medical therapy versus standard medical therapy alone; or center around the combined use of ACE inhibitors and ARBs added to standard medical therapy versus either an ACE inhibitor or ARB alone added to standard medical therapy. Amongst the total number of studies in this general category, some studies have been conducted where recent coronary revascularization procedures were a prerequisite for enrollment. These studies were evaluated separately from those where this was not a prerequisite.

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 combination 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?

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 versus 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, co-morbidities (diabetes, renal dysfunction, hypertension), and other medications (vitamins, lipid lowering drugs, beta-blockers, anti-platelet agents)?

Table 1. Characteristics and current indications of ACE inhibitors and ARBs evaluated in this review[23-27]

Drug	Trade name(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
ACE Inhibitors					
Captopril	Capoten	$T_{1/2}$ = 2 hours	HTN, HF, LVD post MI, diabetic nephropathy	6.25 – 100 mg three times daily	Use lower initial doses in patients with renal impairment; titrate slowly
Cilazopril	Various	$T_{1/2}$ = 32 – 45 hours	Not FDA approved	1 – 5 mg daily	Start with 0.5 mg if CrCl 10 – 40 mL/min or if HF
Enalapril	Vasotec	$T_{1/2}$ = 11 hours	HTN, HF, asymptomatic LVD	5 – 40 mg divided once or twice daily	Start with 2.5 mg daily in patients with CrCl ≤ 30 mL/min, HF, or hyponatremia
Fosinopril	Monopril	$T_{1/2}$ = 11.5 – 14 hours	HTN, HF as adjunctive therapy	10 – 80 mg divided once or twice daily	Use close medical supervision in patients with HF; consider 5mg if renal impairment also present or if diuresed
Perindopril	Aceon	$T_{1/2}$ = 3 – 10 hours (active metabolite)	Stable CAD, HTN	4 – 8 mg daily; max 16 mg daily if normal renal function	Start with 2 mg daily if > 70 years old or renal insufficiency, 2 mg – 4 mg if on diuretic; Not studied in CrCl < 30 mL/min
Quinapril	Accupril	$T_{1/2}$ = 3 hours (active metabolite)	HTN, HF as adjunctive therapy	10 – 80 mg divided once or twice daily	Start with 2.5 mg if CrCl 10 – 30 mL/min or 5 mg if CrCl 30 – 60 mL/min
Ramipril	Altace	$T_{1/2}$ = 13 – 17 hours (active metabolite)	Reduce risk of MI, stroke, and death from CV causes, HTN, HF post MI	2.5 – 20 mg divided once or twice daily	Start with 1.25 mg in patients with renal impairment; only 25% of normal doses may be needed if CrCl < 40mL/min
Trandolapril	Mavik	$T_{1/2}$ = 6 hours (parent drug); 10 hours (active metabolite)	HTN, HF or LVSD post MI	1 – 4 mg daily up to 4 mg twice daily	Start with 0.5 mg if concomitant diuretic, CrCl < 30 mL/min, or cirrhosis
Zofenopril	Various	$T_{1/2}$ = 5 hours	Not FDA approved	7.5 – 60 mg daily	Titrate slowly in HF
ARBs					
Candesartan	Atacand	$T_{1/2}$ = 9 hours	HTN, HF in patients with LVD	2 – 32 mg daily	Start at lower doses if moderate hepatic impairment or volume depleted
Telmisartan	Micardis	$T_{1/2}$ = 24 hours	HTN	20 – 80 mg daily	Use under close medical supervision if volume depleted or hepatic or biliary disorders

Abbreviations: CrCl=creatinine clearance; FDA=Food and Drug Administration; HF=heart failure; HTN=hypertension; LVSD=left ventricular systolic dysfunction; mg=milligram; MI=myocardial infarction; mL/min=milliliters per minute; $T_{1/2}$=half-life

Methods

Topic Development

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) for the AHRQ Effective Health Care Program drafted the initial key questions and, after approval from AHRQ, posted them to a public Web site. The public was invited to comment on these questions. After reviewing the public commentary, the SRC drafted final key questions and submitted them to AHRQ for approval.

This comparative effectiveness review (CER) of ACE inhibitors or ARBs for stable ischemic heart disease is based on a systematic review of the literature. The University of Connecticut/Hartford Hospital EPC received input from a Technical Expert Panel (TEP) formed for this project as well as the task order officer (TOO). The TEP as well as the TOO served in an advisory capacity for this report, helping to refine key questions, identifying important issues, reviewing our proposed methods, and defining parameters for the review of evidence. The TEP included cardiologists, a cardiovascular pharmacist/pharmacologist, and a health policy pharmacist. All of the methods described below were determined *a priori*.

The methods for this CER follows the methods suggested in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 published by AHRQ (available at http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf). See **Abbreviations** for a list of abbreviations used for the entire document.

Search Strategy

For primary studies, two independent investigators conducted systematic literature searches of MEDLINE (1966 to February 2009) using the Cochrane Highly Sensitive and Specific Search Strategy (Sensitivity and Precision Maximizing Version 2008),[28] Embase (1974 to February 2009) using the McMaster Health Information Research Unit (HiRU) strategy for minimizing differences between sensitivity and specificity,[29] and the Cochrane Central Register of Controlled Trials (1966 to February 2009). Separate searches for 'clinical outcomes' (key questions 1, 2, 3, 7; RCTs only) and 'harm' (key question 4, 5, 6; observational studies to supplement RCT search) data were conducted. For systematic reviews, two independent investigators conducted systematic literature searches of MEDLINE (1966 to February 2009) using the McMaster Health Information Research Unit (HiRU) strategy to minimize differences between sensitivity and specificity) and the Cochrane Database of Systematic Reviews (1st Quarter 2009). No language restrictions were imposed. A manual search of references from reports of clinical trials or review articles and major cardiology meeting (American Heart Association, American College of Cardiology, European Society of Cardiology) abstract books from June 2006 – February 2009 was performed to identify relevant trials. Clinical trial registry Web sites (including www.clinicaltrials.gov) were used to identify ongoing or soon to be published clinical trials of interest.

When applicable, we contacted investigators for clarification and additional data. Our exact search terms for each database are included in Appendix 1.

Study Selection

The results of our searches were imported into RefWorks® version 16 (CSA, Bethesda, MD). We scanned for duplicate citations, identified the number of duplicates and then eliminated them. We imported the remaining citations into a custom designed Microsoft Access® database version 9.0.6926 SP-3 (Microsoft Corporation, Washington, DC) for title and abstract review. Two independent reviewers conducted this review in a parallel fashion. Citations at this 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. For a citation to be eliminated both reviewers had to indicate that it was ineligible for the same reason. A query report was generated identifying citations 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. Given the robust RCT data known to exist on the subject, we felt that excluding smaller RCTs with less than 75 patients was justified. We also felt that, for harms specifically, only observational studies of greater than 1000 patients would provide reliable data. These search restrictions were discussed and approved by the TOO prior to the search being performed.

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, hypotension, rash, blood dyscrasias, syncope).

Data Extraction

Through use of a standardized data abstraction tool, two reviewers independently collected data, with disagreement resolved through discussion. The following information was obtained from each trial: author identification, year of publication, source of study funding, study design characteristics and below-mentioned methodological quality criteria, study population (including study inclusion and exclusion criteria, run-in period, study withdrawals, ACE inhibitor, ARB or combination utilized, dose utilized, length of study, and duration of patient followup), patient baseline characteristics (sex, age, ethnicity, LVEF), co-morbidities (coronary disease history, myocardial infarction, stable angina, unstable angina, stroke or transient ischemic attack, peripheral vascular disease, diabetes mellitus, renal insufficiency, hypertension, left ventricular hypertrophy, microalbuminuria, smoking), revascularization procedures recently conducted or scheduled as an entry criteria, baseline cardiac health assessment values [systolic and diastolic blood pressure, body mass index, cholesterol levels (total LDL, HDL, triglycerides)], blood glucose, serum creatinine, serum potassium, coronary lesion location (left main, left anterior descending, left circumflex, right coronary artery), and use of concurrent standard medical therapies (beta-blockers, calcium channel blockers, anti-platelet agents including aspirin and clopidogrel/ticlopidine, diuretics, nitrates, lipid-lowering therapies including statins, digitalis). Clinical outcome endpoints include: total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, composite endpoint (cardiovascular death, nonfatal-myocardial infarction, stroke), total myocardial infarction, fatal myocardial infarction, atrial fibrillation, symptom reporting, hospitalization rates (including total hospitalization, hospitalization for angina, and hospitalization for heart failure), revascularization, and quality of life measures. Harms endpoints include: (hyperkalemia, cough, angioedema, hypotension, rash, blood dyscrasias, syncope, and study withdrawal due to adverse events).

Individual Study and Systematic Review Validity Assessment

As they are inherent controls of bias, the use of randomization, double-blinding, use of an intention-to-treat methodology, and other study methodologies for reducing bias (such as prospective study conduction, propensity score matching or adjustment, multivariate analysis) were used to assess the methodological quality of included studies.

The eleven-item "Assess the Methodological quality of SysteMAtic Review" (AMSTAR) checklist was used to assess methodological quality of systematic reviews. Two independent reviewers evaluated each systematic review with discrepancies resolved through discussion. Quality criteria set by AMSTAR include 'a priori' study design, duplication of study selection and data extraction, comprehensive literature search of at least two databases, inclusion of grey literature, list of both excluded and included studies, study characteristics, quality assessment,

quality discussion, appropriate combining of data, publication bias assessment, and statement of conflicts of interest.[31]

Applicability

Throughout this report, we discuss the applicability by following the population, intervention, comparator, outcomes, timing of outcomes measurement, and setting (PICOTS) format. Additionally, we report on differences in study design including run-in periods and durations of followup, as well as use subgroup and sensitivity analyses to identify potential differences in results based on PICOTS criteria. Key Question 7 is also used to discuss the applicability of study results to various patient populations.

Rating the Strength of a Body of Evidence

We used the EPC methodology for grading, which is based on the criteria and methods of GRADE (Grading of Recommendations Assessment, DEvelopment), to assess the strength of evidence. This system uses four required domains – risk of bias, consistency, directness, and precision.[32] Additional domains were not utilized because they were deemed not relevant to this review. All assessments were made by two investigators (with disagreements resolved through discussion). The evidence pertaining to each key question was classified into three broad categories: (1) "high", (2) "moderate", or (3) "low" grade (see Table 2). Below we describe in more detail the features that determined the strength of evidence for the different outcomes evaluated in this report.

Table 2. Definitions for grading the strength of evidence

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Risk of Bias

Risk of bias is the degree to which the included studies for any given outcome or comparison have a high likelihood of adequate protection against bias. This can be assessed through the evaluation of both design and study limitations. The study design for each trial was recorded as either a randomized controlled trial or an observational study. Studies were also ranked as no limitations, serious limitations, or very serious limitations. Because all of the included studies were randomized controlled trials with few limitations, they were considered to have a low risk of bias.

Consistency

Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. This was assessed in two main ways: (1) the effect

sizes had the same sign, in that they were on the same side of unity; (2) the range of effect sizes was narrow. We ranked this domain as no inconsistency, serious inconsistency, and very serious inconsistency. For outcomes whereby only a single study was included, consistency would not be judged. We also considered measures of heterogeneity from out meta-analyses in evaluating consistency.

Directness

Directness refers to whether the evidence links the compared interventions directly with health outcomes, and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is required to link interventions to the most important health outcomes. We ranked this domain as no indirectness, serious indirectness, and very serious indirectness.

Precision

Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. For example, when a meta-analysis was performed, we evaluated the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g. both clinically important superiority and inferiority), a circumstance that will preclude a conclusion.

Data Synthesis

For the purposes of the following analyses, a class effect for all ACE inhibitors and ARBs was made. In order to quantitatively evaluate the comparative effectiveness between ACE inhibitors and/or ARBs versus control (standard medical therapy), meta-analysis was performed when sufficient data existed (two or more studies). As an analytical tool, trials evaluating either an ACE inhibitor or an ARB versus control were pooled together in the base-case analyses. ACE inhibitor and ARB trials were then evaluated separately to determine the individual impact of each class of drugs. Although trials that evaluated patients both with established stable ischemic heart disease, as well as heart disease risk equivalents [including diabetes mellitus or chronic kidney disease, or mixed vascular atherosclerotic disorders (coronary disease, peripheral artery disease, carotid atherosclerosis)] were included, they were not statistically pooled together. Although the risk of some future cardiovascular sequella might be similar between those with ischemic heart disease and ischemic heart disease risk equivalents, we do not have confidence that the risks of many of the outcomes in interest are similar. Similarly, we analyzed placebo controlled trials separately from active controlled trials because of the potential benefits that could be derived from other cardiovascular therapy. We believed that pooling all of these disparate types of trials together would unnecessarily increase the statistical heterogeneity of our analyses. Thus, where applicable, four separate base-case analyses could be run for clinical outcomes: randomized, double-blind, controlled trials in ischemic heart disease comparing ACE inhibitor and/or ARB versus (1) placebo and (2) active-controls; and randomized controlled trials in heart disease risk equivalents [including diabetes mellitus or chronic kidney disease, or mixed vascular atherosclerotic disorders (coronary disease, peripheral artery disease, carotid atherosclerosis)] comparing ACE inhibitor and/or ARB versus (3) placebo and (4) active-controls.

For dichotomous endpoints, data were reported as pooled relative risks (RRs) with associated 95 percent confidence intervals (CIs). As heterogeneity between included studies was expected, a DerSimonian and Laird random-effects model was used which utilizes a variation of the inverse variance method.[33] A random-effects model assumes that the variation of effect from study-to-study is related not just to random error (chance) but also to other real differences (including clinical or methodological differences). It also assumes that there is a normal distribution of effect sizes (a bell shaped curve) among constituent studies for which the pooled effect is in the center of the distribution. The result is a more conservative estimate of the confidence interval around the point estimate of effect size. When pooling continuous endpoints, a weighted mean difference (WMD) was calculated, again using a DerSimonian and Laird random-effects model. Statistics were performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd, Cheshire, England) and MIX statistical software,[34] version 1.7 (Kitasato Clinical Research Center, Sagamihara, Kanagawa, Japan, freely accessible at www.mix-for-meta-analysis.info). A p-value of <0.05 was considered statistically significant for all analyses, except where otherwise specified.

Statistical heterogeneity was assessed using the Q Statistic (a p-value <0.10 was considered representative of significant statistical heterogeneity) and the I^2 (which assesses the degree of inconsistency across studies and ranges from 0-100 percent with the higher percentage representing a higher likelihood of the existence of heterogeneity).[35] While categorization of values for I^2 may not be appropriate in all situations, I^2 values of 25-49 percent, 50-74 percent and greater than 75 percent have been regarded as representative of low, medium and high statistical heterogeneity, respectively. In order to evaluate the impact of statistical, clinical or methodological heterogeneity (when present), we conducted various subgroup and sensitivity analyses differing by key question. For Key Questions 1, 2, 4, and 5, we meta-analyzed trials that evaluated ACE inhibitors and ARBs separately. Methodological quality of the included studies was assessed via sensitivity analysis whereby both double-blind as well as open-label trials were pooled, in addition to separately assessing studies that reported using intention-to-treat (ITT) methodologies.

For Key Questions 3 and 6, we also conducted subgroup analysis analyzing ACE inhibitors and ARBs separately. Similar to above, methodological quality of the included studies was assessed via sensitivity analysis whereby both double-blind as well as open-label trials were pooled, in addition to separately assessing studies that reported using ITT methodologies. In addition, we performed subgroup analysis whereby trials conducted in patients undergoing coronary artery bypass graft surgery and percutaneous procedures were analyzed separately.

Visual inspection of funnel plots and Egger's weighted regression statistics were used to assess for the presence of publication bias.[36] In order to assess the potential effect of any publication bias on the meta-analysis results, the Trim and Fill method was used.[37] The Trim and Fill method uses funnel plot symmetry to estimate the number of "missing" studies and the magnitudes of their effects. It re-estimates the overall effect size after imputing potentially "missing" studies into the meta-analysis to determine if the results of the original analysis were replicated.

For some key questions, or portions of some key questions, studies that can provide insight into the answers to key questions could not be pooled with others. In this case the studies were described qualitatively.

Peer Review and Public Commentary

A draft of this Evidence Report was sent to peer reviewers, the representatives of the AHRQ and the SRC at Oregon Health and Science University. Based on comments from AHRQ, revisions were made to the draft report and posted to a website for public comment. In response to the comments of the peer reviewers and the public, revisions were made to the Evidence Report, and a summary of the comments and their disposition was submitted to AHRQ.

Results

Results of Primary Literature Review

A summary of the search results for the primary literature review is presented in Figures 3 and 4.

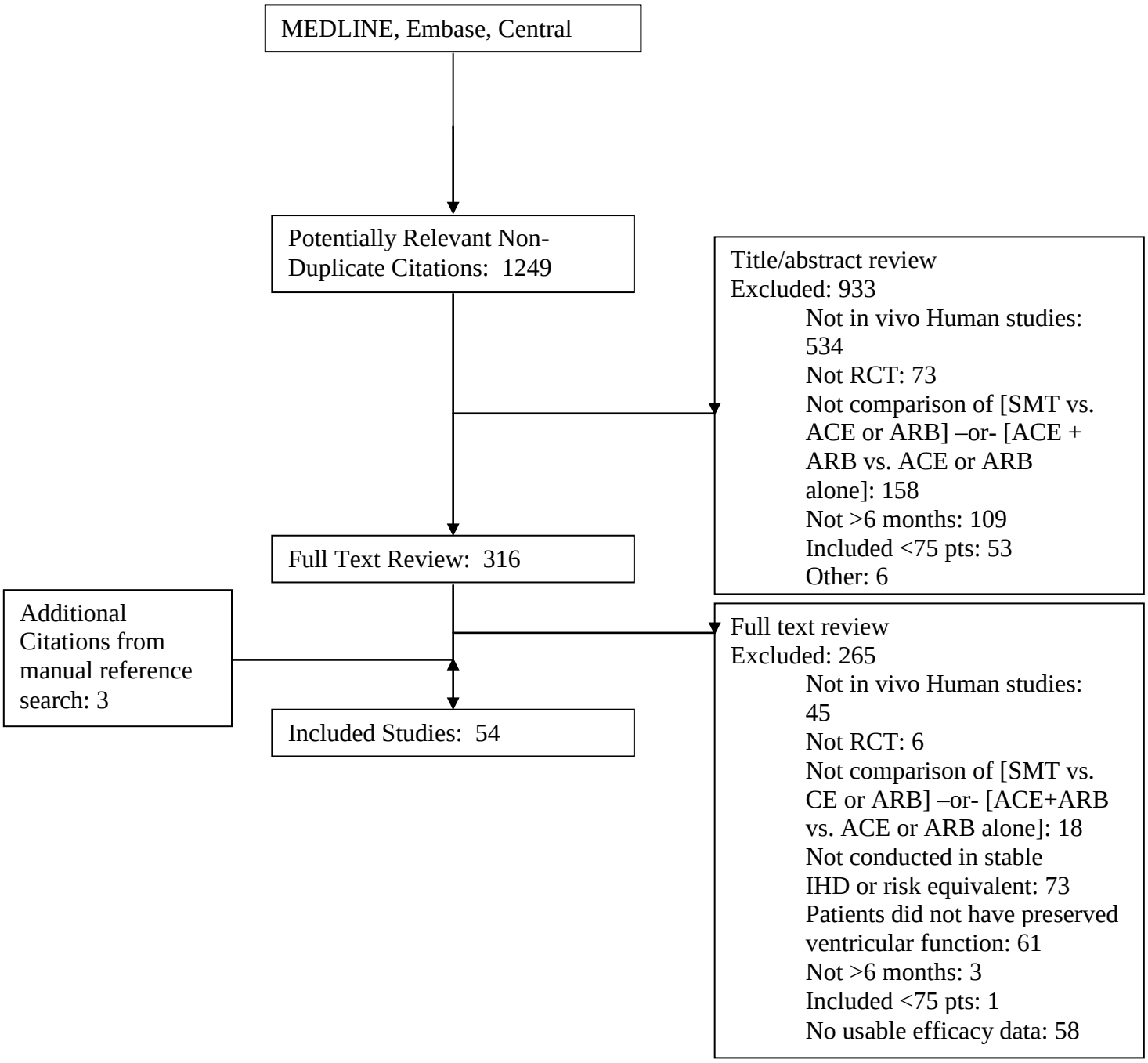
From the clinical outcomes literature search, we retrieved 1249 unique citations. After a review of the titles and abstracts, 316 were deemed eligible for further review, and the full articles were retrieved. A total of 54 primary literature articles were found to match our inclusion criteria.[38-91]

From the harms literature search, we retrieved 93 unique citations. After a review of the titles and abstracts, 35 were deemed eligible for further review, and the full articles were retrieved. A total of 27 citations that were excluded from the efficacy search for lack of clinical outcome data were included in the full text review step of the harms search. A total of one primary literature article was included in this review.[82]

Results of Search and Quality of Existing Systematic Reviews

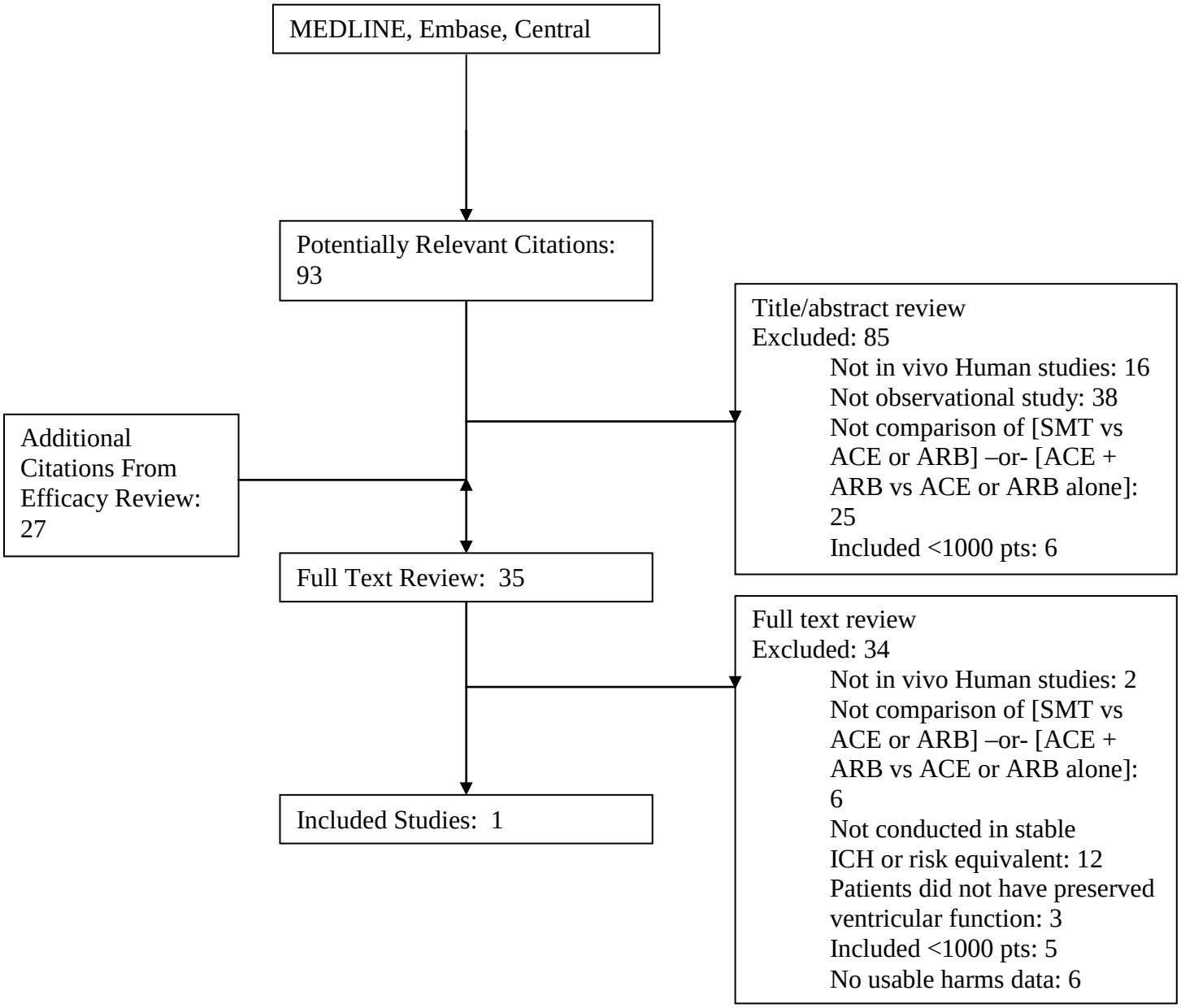
A summary of the search results for the systematic review literature review is presented in Figure 5. From the search, 123 reviews were deemed eligible for further review, and the full articles were retrieved. A total of six systematic reviews were included in this review (Appendix Table 1).[92-97] With the exception of one existing systematic review, the use of these other existing systematic reviews would not be comprehensive enough or of sufficient quality to substitute for a de novo process. However, the individual patient data meta-analysis conducted by Degenais and colleagues did provide useful information on subgroups for Key Question 7.[93]

Figure 3. Summary of clinical outcomes literature search



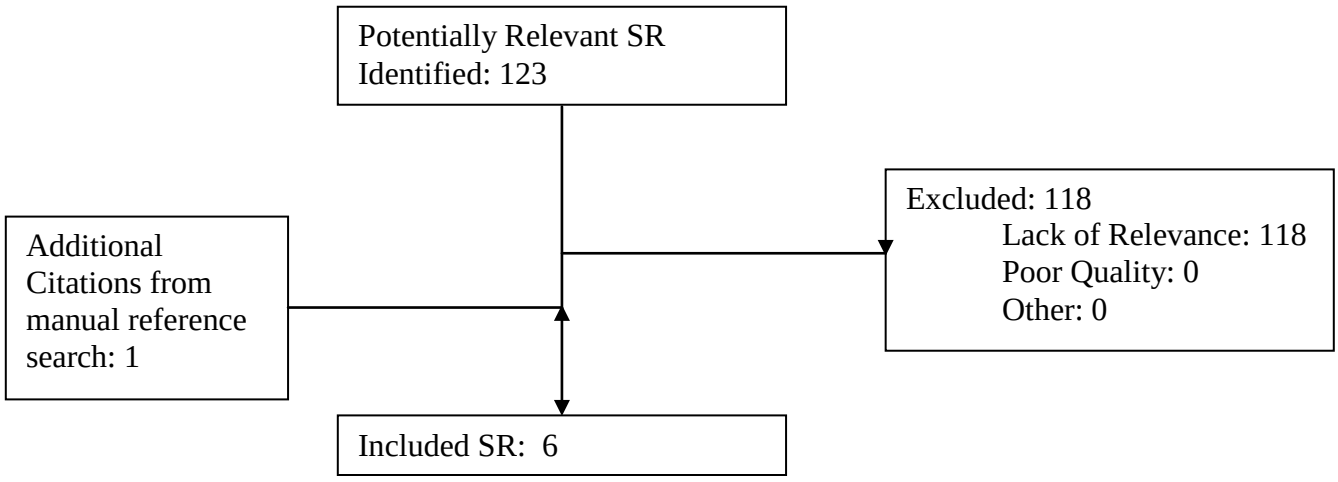
ACE=angiotensin converting enzyme; ARB=angiotensin II receptor blocker; IHD=ischemic heart disease; RCT=randomized controlled trial; SMT=standard medical therapy

Figure 4. Summary of harms literature search



ACE=angiotensin converting enzyme; ARB=angiotensin II receptor blocker; IHD=ischemic heart disease; RCT=randomized controlled trial; SMT=standard medical therapy

Figure 5. Summary of systematic review literature search



SR=systematic review

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 Points

- For trials to be included, ACE inhibitors or ARBs needed to be studied in patients with preserved left ventricular systolic function who either had stable ischemic heart disease or an ischemic heart disease risk equivalent.
- Twelve trials were included, 9 evaluating ACE inhibitors (ramipril, enalapril, perindopril, imidapril, lisinopril, trandolapril, fosinopril, zofenopril) and 3 evaluating ARBs (candesartan, telmisartan).
- Three base case analyses were conducted for each outcome: (1) ACE inhibitor or ARB therapy versus placebo in patients with ischemic heart disease; (2) ACE inhibitor therapy versus calcium channel blocker therapy in patients with ischemic heart disease; (3) ACE inhibitor or ARB therapy versus placebo in patients with ischemic heart disease risk equivalents.

- ACE inhibitor or ARB therapy significantly reduced total mortality (ramipril, enalapril, perindopril, trandolapril, telmisartan), nonfatal myocardial infarction (ramipril, enalapril, perindopril, trandolapril), stroke (ramipril, enalapril, perindopril, trandolapril, telmisartan), and the composite endpoint (cardiovascular mortality, nonfatal myocardial infarction, and stroke) (ramipril, trandolapril, telmisartan) versus placebo in patients with stable ischemic heart disease.
- ACE inhibitor (ramipril, enalapril, perindopril, trandolapril) or ARB therapy (telmisartan) did not significantly reduce cardiovascular mortality versus placebo in patients with stable ischemic heart disease with moderate statistical heterogeneity. ACE inhibitor therapy (ramipril, enalapril, perindopril, trandolapril) significantly reduced cardiovascular mortality versus placebo in patients with stable ischemic heart disease with lower statistical heterogeneity.
- ACE inhibitor therapy (enalapril, imidapril, lisinopril) did not significantly reduce total mortality, cardiovascular mortality, nonfatal myocardial infarction, or stroke versus calcium channel blockers in patients with stable ischemic heart disease.
- ACE inhibitor or ARB therapy did not significantly reduce total mortality (fosinopril, candesartan), cardiovascular mortality (fosinopril), nonfatal myocardial infarction (fosinopril), stroke (fosinopril), or the composite endpoint (cardiovascular mortality, nonfatal myocardial infarction, and stroke) (fosinopril) versus placebo in patients with ischemic heart disease risk equivalents.
- ACE inhibitor (ramipril) or ARB therapy (telmisartan) did not significantly reduce atrial fibrillation versus placebo in patients with stable ischemic heart disease. No trials were available comparing ACE inhibitors or ARBs versus active comparators in ischemic heart disease or versus placebo or active comparators in ischemic heart disease risk equivalents.
- In the only trial to evaluate the impact of ACE inhibitor therapy on ischemia, zofenopril therapy significantly increased the time to onset of ischemic symptoms via treadmill exercise test versus placebo in patients with stable ischemic heart disease.
- ACE inhibitor or ARB therapy did not significantly reduce the risk for all cause hospitalizations (ramipril, telmisartan), or hospitalizations due to angina (ramipril, enalapril, telmisartan), but did reduce the risk for hospitalizations for heart failure (ramipril, enalapril, perindopril, trandolapril) versus placebo in patients with stable ischemic heart disease.
- ACE inhibitor (enalapril, imidapril, lisinopril) therapy did not significantly increase the risk of hospitalizations due to angina or the risk of hospitalizations for heart failure versus calcium channel blockers (amlodipine, nifedipine) in subjects with stable ischemic heart disease.
- No trials were available comparing ACE inhibitor or ARB therapy versus placebo on total hospitalizations, or hospitalizations for angina or heart failure in patients with ischemic heart disease risk equivalents.
- ACE inhibitor (ramipril, enalapril, perindopril, trandolapril) or ARB therapy (telmisartan) significantly reduced the need for revascularization versus placebo in patients with stable ischemic heart disease; no difference was seen for ACE inhibitors (enalapril, imidapril, lisinopril) versus calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease, and no trials evaluated patients with ischemic heart disease risk equivalents.

Detailed Analysis

Study Design and Population Characteristics

Trials meeting inclusion criteria for Key Question 1 included those investigating ACE inhibitors or ARBs added to standard medical therapy in patients with stable ischemic heart disease or ischemic heart disease risk equivalents and preserved left ventricular systolic function. Patients could not have a recent myocardial infarction or have therapy initiated in close proximity to a revascularization procedure. A total of 12 trials (n=41672 participants) met our inclusion criteria (Tables 3-7).[38-59] Ten of the trials were conducted in patients with established ischemic heart disease[38-47,50,51] and two trials were in patients with kidney disease, an ischemic heart disease risk equivalent.[48,49] Nine of the trials were double-blind,[38-43,45,47,48,50,51] and three were open-label.[44,46,49] Eight of the trials were placebo-controlled,[38-43,45,47,48,50,51] two had no comparator,[44,49] and two trials had CCB active comparators[45,46] with one of the two trials having both an active and placebo arm.[45] Seven of the trials received funding from foundations,[38-42,46,47,50,51] seven of the trials received funding from industry,[38-43,47,48,51] and two of the trials did not report their funding source.[44,49] It should be noted that five of the trials received both foundation as well as industry funding to conduct their studies.[34-42,47,51]

Four of the 12 trials were conducted, in part, in the United States. The average LVEF was reported in 4 of the 12 trials, ranging from 53-66 percent.[44,47,49,50] In the eight trials that did not report average LVEF,[38-43,45,46,48,51] six excluded patients with a LVEF less than 40 percent[38-41,42,45,46,48] and two trials excluded patients with signs or symptoms of heart failure.[43,51] One of the 12 trials reported 6 months of patient follow-up,[50] with the remainder of the trials having follow-up times ranging from 19.4 months to 4.8 years.[38-49,51] Nine of the 12 trials evaluated ACE inhibitors,[38-43,45-47,50] with two using enalapril,[42,45] two using ramipril,[38-41] and one each using fosinopril,[48] perindopril,[43] trandolapril,[47] and zofenopril.[50] The ACE inhibitor group of the JMIC-B trial could have received enalapril, imidapril or lisinopril at the investigators discretion.[46] Three of the 12 trials evaluated ARBs,[44,49,51] with two using candesartan[44,49] and one using telmisartan.[51] Males constituted a majority of the patients studied, ranging from 51-89 percent of the total number of subjects. Ethnicity was not routinely reported. The CAMELOT[45] and PEACE[47] trials reported that Caucasian subjects constituted 89-93 percent of patients. The TRANSCEND[51] trial reported the following ethnicity breakdown: Asian = 21 percent, Arab = 1.3 percent, African = 1.7-1.9 percent, European = 61 percent, Native/Aboriginal = 13 percent, other = 1.3 percent. The JMIC-B,[46] Kondo et al,[44] and Takahashi et al[49] trials were entirely conducted in Japan and likely had a high Asian population. Baseline blood pressures ranged from 127-153 mmHg systolic and 76-85 mmHg diastolic. Three of the 12 trials had systolic blood pressures greater than 140 mmHg,[46,48,51] and one had systolic blood pressures greater than 150 mmHg at baseline.[49]

Baseline medical therapies, although not routinely reported, differed between the included studies (Table 6). Amongst trials including patients with ischemic heart disease, baseline medical therapy usage was as follows: beta-blockers ranged from 10 to 79 percent; CCBs ranged from 5 to 49 percent; diuretics ranged from 5 to 33 percent; nitrates ranged from 10 to 67 percent; lipid lowering agents ranged from 26 to 70 percent (studies did not specify which agent was used); statins ranged from 28 to 84 percent. Some studies reported usage of antiplatelet agents (53 to 93 percent) although they did not specify which agent was used, some reported aspirin usage (3 to 95 percent), while others reported clopidogrel/ticlopidine usage (1 to

11 percent). One study also reported the use of digoxin in 4 percent of their population.[47] Many of the lower ranges for the use of these agents resulted from the SMILE-ISCHEMIA trial.[50] When examining the three largest trials (HOPE,[38] EUROPA,[43] and PEACE[47]) baseline therapy use is more homogenous although HOPE[38] study had lower use of beta-blocker, antiplatelet and lipid lowering therapy than did EUROPA[43] or PEACE.[47]

Outcome Evidence Evaluations

Total Mortality

Total mortality data was available in 11 trials (3425 events in 41323 patients; 8.3 percent).[38-49,51] Three separate base case analyses, and four subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril, enalapril, perindopril, imidapril, lisinopril, trandolapril, fosinopril) or ARB (candesartan, telmisartan) therapy on total mortality in this population.

Seven trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 2).[38-43,45,47,51] Therapy with ACE inhibitors (ramipril, enalapril, perindopril, trandolapril) or ARBs (telmisartan) significantly reduced the risk of total mortality as compared with placebo [RR 0.91 (0.84 to 0.98)](Figure 6). A low level of statistical heterogeneity was seen (I^2 = 21.5 percent), and publication bias was not expected (Egger's p=0.81, no imputed studies via Trim and Fill). Two trials were included in the second base case analysis evaluating randomized, active controlled trials in patients with stable ischemic heart disease, both of which compared ACE inhibitors with CCBs.[45,46] In one trial enalapril was compared with amlodipine where in the other, therapy with enalapril, imidapril, or lisinopril was compared with nifedipine. ACE inhibitors did not impact total mortality versus CCBs [RR 1.21 (0.66 to 2.21)](Figure 7). A single trial was included in the third base case analysis evaluating randomized, placebo controlled trials in patients with ischemic heart disease risk equivalents.[48] In this trial, the ACE inhibitor fosinopril did not impact total mortality versus placebo [RR 1.08 (0.78 to 1.52)]. Due to the low number of trials, statistical heterogeneity and publication bias was not assessed in these last two base case analyses.

When inclusion was restricted to the six randomized, placebo controlled trials evaluating ACE inhibitors in patients with stable ischemic heart disease, ACE inhibitors (ramipril, enalapril, perindopril, trandolapril) significantly reduced the risk of total mortality as compared with placebo [RR 0.87 (0.81 to 0.94)](Appendix Figure 1).[38-43,45,47] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ARB telmisartan in patients with stable ischemic heart disease, ARB therapy did not impact total mortality [RR 1.05 (0.91 to 1.20)].[51]

In order to assess the impact of study quality on results in the first base case analysis, inclusion was broadened to include a combined total of eight open label or placebo controlled trials evaluating the impact of ACE inhibitors (ramipril, enalapril, perindopril, trandolapril) or ARBs (telmisartan, candesartan) on total mortality in patients with stable ischemic heart disease.[38-45,47,51] Similarly, ACE inhibitors or ARBs significantly reduced the risk of total mortality as compared with placebo [RR 0.90 (0.82 to 0.99)](Appendix Figure 2). When the inclusion criteria in the second base case analysis were broadened to include open label or placebo controlled trials, no additional trials were found. When inclusion was broadened to include the two open label or placebo controlled trials evaluating patients with ischemic heart

disease risk equivalents in the third base case analysis, no significant impact on total mortality was seen with ACE inhibitor (fosinopril) or ARB (candesartan) therapy versus placebo [RR 0.34 (0.02 to 6.49)](Appendix Figure 3).[48,49] As all of the trials included in Key Question 1 utilized intention-to-treat methodologies, its impact on mortality could not be assessed.

Cardiovascular Mortality

Cardiovascular mortality data was available in eight trials (1983 events in 39133 patients; 5.1 percent).[38-41,43-45,47,48,51] Cardiac mortality was also reported in two trials,[42,46] although their results were not reported in this analysis as we felt that cardiovascular mortality and cardiac mortality should not be pooled. Three separate base case analyses and four subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril, perindopril, enalapril, imidapril, lisinopril, trandolapril, fosinopril) or ARB (telmisartan, candesartan) therapy on cardiovascular mortality in this population.

Six trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 3).[38-41,43,45,47,51] Therapy with ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) or ARBs (telmisartan) did not impact cardiovascular mortality as compared with placebo [RR 0.87 (0.75 to 1.02)](Figure 8). Moderate statistical heterogeneity was seen (I^2 = 57.9 percent), and publication bias was not expected (Egger's p=0.86, one study was imputed via Trim and Fill with no difference in outcome [RR 0.86 (0.74 to 1.02)]). Two trials were included in the second base case analysis evaluating randomized, active controlled trials in patients with stable ischemic heart disease, both of which compared ACE inhibitors with CCBs.[45,46] In one trial enalapril was compared with amlodipine where in the other, therapy with enalapril, imidapril, or lisinopril was compared with nifedipine. ACE inhibitors did not impact cardiovascular mortality versus CCBs [RR 1.00 (0.43 to 2.29)](Figure 9). A single trial was included in the third base case analysis evaluating randomized, placebo controlled trials in patients with ischemic heart disease risk equivalents.[48] In this trial the ACE inhibitor fosinopril did not impact cardiovascular mortality versus placebo [RR 1.06 (0.67 to 1.67)]. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed in these last two base case analyses.

When inclusion was restricted to the five randomized, placebo controlled trials evaluating ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) on cardiovascular mortality in patients with stable ischemic heart disease, ACE inhibitors significantly reduced the risk of cardiovascular mortality as compared with placebo [RR 0.83 (0.70 to 0.98)](Appendix Figure 4).[38-41,43,45,47] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ARB (telmisartan) in patients with stable ischemic heart disease, ARB therapy did not impact cardiovascular mortality [RR 1.02 (0.86 to 1.22)].[51]

In order to assess the impact of study quality on results in the first base case analysis, inclusion was broadened to include a combined total of seven open label or placebo controlled trials evaluating the impact of ACE inhibitors or ARBs on cardiovascular mortality in patients with stable ischemic heart disease.[38-41,43-45,47,51] Similarly, ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) or ARBs (telmisartan, candesartan) did not impact cardiovascular mortality as compared with placebo [RR 0.86 (0.72 to 1.02)](Appendix Figure 5). When the inclusion criteria in the second and third base cases were broadened to include open label or placebo controlled trials, no additional trials were found. As all of the trials included in Key Question 1 utilized intention-to-treat methodologies, its impact on cardiovascular mortality could not be assessed.

Nonfatal Myocardial Infarction

Nonfatal myocardial infarction data was available in eight trials (1827 events in 33667 patients; 5.4 percent).[38-45,47,48] Three separate base case analyses, and four subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril, perindopril, enalapril, trandolapril, fosinopril) or ARB (candesartan) therapy on nonfatal myocardial infarction in this population.

Six trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 4).[38-43,45,47] Therapy with ACE inhibitor (ramipril, perindopril, enalapril, trandolapril) or ARB (none evaluated) therapy significantly reduced the risk of nonfatal myocardial infarction as compared with placebo [RR 0.83 (0.73 to 0.94)](Figure 10). A moderate level of statistical heterogeneity was seen (I^2 = 30.5 percent), and publication bias was not expected (Egger's p=0.68, one study was imputed via Trim and Fill with no difference in outcome [RR 0.84 (0.74 to 0.95)]). A single trial was included in the second base case analysis evaluating randomized, active controlled trials in patient with stable ischemic heart disease, which evaluated ACE inhibitors with CCBs.[45] ACE inhibitor therapy with enalapril did not impact nonfatal myocardial infarction versus the CCB amlodipine [RR 0.77 (0.35 to 1.69)]. A single trial was included in the third base case analysis evaluating randomized, placebo controlled trials in patients with ischemic heart disease risk equivalents.[48] ACE inhibitor (fosinopril) or ARB (none evaluated) therapy did not impact nonfatal myocardial infarction versus placebo [RR 1.31 (0.50 to 3.47)]. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed in the last two base case analyses.

Since all of the randomized, placebo controlled trials evaluating nonfatal myocardial infarction in patients with stable ischemic heart disease utilized ACE inhibitors, result of this subgroup analysis are the same as the first base case analysis (Appendix Figure 6).[38-43,45,47] No trials evaluating ARBs were included in our analysis of placebo controlled trials, and thus their impact on nonfatal myocardial infarction could not be assessed.

In order to assess the impact of study quality on results in the first base case analysis, inclusion was broadened to include a combined total of seven open label or placebo controlled trials evaluating the impact of ACE inhibitor (ramipril, perindopril, enalapril, trandolapril) or ARB (candesartan) therapy on nonfatal myocardial infarction in patients with stable ischemic heart disease.[38-45,47] ACE inhibitors or ARBs significantly reduced the risk of nonfatal myocardial infarction as compared with placebo [RR 0.83 (0.74 to 0.94)] (Appendix Figure 7). When the inclusion criteria in the second and third base cases were broadened to include open label or placebo controlled trials, no additional trials were found. As all of the trials included in Key Question 1 utilized intention-to-treat methodologies, its impact on nonfatal myocardial infarction could not be assessed.

Stroke

Stroke data was available in nine trials (1102 events in 40846 patients; 2.7 percent).[38-43,45-48,51] The exact definition for stroke used in each trial was not routinely provided. Two of the trials defined stroke as either a stroke, transient ischemic attack or a more broad cerebrovascular accident.[45,46] Whether the events were fatal or nonfatal was also not reported, with the exception of one trial which reported only nonfatal stroke requiring hospital admission.[41] Three separate base case analyses, and four subgroup/sensitivity analyses were

conducted to discern the impact of ACE inhibitor (ramipril, perindopril, enalapril, imidapril, lisinopril, trandolapril, fosinopril) or ARB (telmisartan) therapy on stroke in this population.

Seven trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 5).[38-43,45,47,51] Therapy with ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) or an ARB (telmisartan) significantly reduced the risk of stroke as compared with placebo [RR 0.79 (0.67 to 0.93)](Figure 11). A moderate level of statistical heterogeneity was seen (I^2 = 27.6 percent), and publication bias was not expected (Egger's p=0.91, one study was imputed via Trim and Fill with no difference in outcome [RR 0.81 (0.67 to 0.97)]). Two trials were included in the second base case analysis evaluating randomized, active controlled trials in patients with stable ischemic heart disease, both of which evaluated ACE inhibitors with CCBs.[45,46] In one trial enalapril was compared with amlodipine where in the other, therapy with enalapril, imidapril, or lisinopril was compared with nifedipine. ACE inhibitors did not impact stroke versus CCBs [RR 1.09 (0.61 to 1.94)](Figure 12). A single trial was included in the third base case analysis evaluating randomized, placebo controlled trials in patients with ischemic heart disease risk equivalents.[48] The ACE inhibitor fosinopril did not impact stroke versus placebo [RR 1.68 (0.81 to 3.46)]. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed in the last two base case analyses.

When inclusion was restricted to the six randomized, placebo controlled trials evaluating ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) in patients with stable ischemic heart disease, ACE inhibitors significantly reduced the risk of stroke as compared with placebo [RR 0.78 (0.63 to 0.97)] (Appendix Figure 8).[38-43,45,47] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ARB telmisartan in patients with stable ischemic heart disease, ARB therapy did not impact stroke [RR 0.83 (0.65 to 1.06)].[51]

In order to assess the impact of study quality on results in the first base case analysis, inclusion was broadened to include a combined total of seven open label or placebo controlled trials evaluating the impact of ACE inhibitor (ramipril, perindopril, enalapril, trandolapril) or ARBs (telmisartan) on stroke in patients with stable ischemic heart disease.[38-43,45,47,51] Similar to the first base case analysis, ACE inhibitor or ARB therapy significantly reduced the risk of stroke as compared with placebo [RR 0.79 (0.67 to 0.93)] (Appendix Figure 9). When the inclusion criteria in the second and third base cases were broadened to include open label or placebo controlled trials, no additional trials were found. As all of the trials included in Key Question 1 utilized intention-to-treat methodologies, its impact on stroke could not be assessed.

Composite of Cardiovascular Mortality, Nonfatal Myocardial Infarction, and Stroke

Data on the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and stroke was available in four trials (3206 events in 23910 patients; 13.4 percent).[38,47,48,51] Three separate base case analyses, and four subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril, trandolapril, fosinopril) or ARB (telmisartan) therapy on the composite outcome in this population.

Three trials were included in the base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 6).[38,47,51] Therapy with ACE inhibitors (ramipril, trandolapril) or the ARB telmisartan significantly reduced the risk of the composite outcome as compared with placebo [RR 0.86 (0.77 to 0.95)](Figure 13). A moderate level of statistical heterogeneity was seen (I^2 = 58 percent). Due to the low number of included studies, publication bias could not be assessed. No trials

evaluated ACE inhibitors or ARBs versus active therapy. Thus, their impact on the composite outcome could not be assessed. A single trial was included in the base case analysis evaluating randomized, placebo controlled trials in patients with ischemic heart disease risk equivalents.[48] The ACE inhibitor fosinopril did not impact the composite outcome versus placebo [RR 1.20 (0.83 to 1.73)]. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed.

When inclusion was restricted to the two randomized, placebo controlled trials evaluating ACE inhibitors (ramipril, trandolapril) in patients with stable ischemic heart disease, ACE inhibitors reduced the risk of the composite outcome as compared with placebo, although statistical significance was not reached [RR 0.85 (0.72 to 1.01)](Appendix Figure 10).[38,47] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ARB telmisartan in patients with stable ischemic heart disease, ARB therapy significantly reduced the risk of the composite outcome as compared with placebo [RR 0.88 (0.77 to 1.00)].[51]

Because all of the included trials were double-blinded, the impact of open label trials was not assessed. Similarly, all of the trials included in Key Question 1 utilized intention-to-treat methodologies, thus its impact on the composite outcome could not be assessed.

Atrial Fibrillation

Atrial fibrillation data was available in two trials (539 events in 14261 patients; 3.8 percent).[40,51] Three separate base case analyses, and four subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril) or ARB (telmisartan) therapy on atrial fibrillation in this population.

Both trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 7).[40,51] Therapy with the ACE inhibitor ramipril or the ARB telmisartan had no impact on atrial fibrillation as compared with placebo [RR 0.98 (0.83 to 1.15)](Figure 14). Due to the low number of included studies, statistical heterogeneity and publication bias could not be assessed. None of the included trials use active therapy as a comparator and no trial evaluated ACE inhibitors or ARBs in patients with ischemic heart disease risk equivalents. Thus, their impact on atrial fibrillation could not be assessed.

When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ACE inhibitor ramipril in patients with stable ischemic heart disease, the ACE inhibitor did not impact atrial fibrillation as compared with placebo [RR 0.89 (0.67 to 1.19)].[38] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ARB telmisartan in patients with stable ischemic heart disease, ARB therapy had no impact on atrial fibrillation as compared with placebo [RR 1.02 (0.83 to 1.24)].[51]

Because both of the included trials were double-blinded, the impact of open label trials was not assessed. Similarly, all of the trials included in Key Question 1 utilized intention-to-treat methodologies, thus its impact on atrial fibrillation could not be assessed.

Angina Symptoms: Treadmill Exercise Test

Only the randomized, double blind, placebo controlled SMILE-ISCHEMIA trial provided data on the time to onset of ischemic symptoms.[50] When a treadmill test was performed 6 months following a myocardial infarction, patients receiving the ACE inhibitor zofenopril had a significantly improved exercise time as compared with placebo [WMD 3.5 minutes (2.82 to 4.18)].[50]

Hospitalizations

Hospitalization data was available in two trials (3571 events in 6543 patients; 54.6 percent).[41,51] This endpoint represents total hospitalizations reported rather than hospitalization for a specific indication (see next sections related to hospitalization for angina and heart failure). Three separate base case analyses, and four subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril) or ARB (telmisartan) therapy on hospitalizations in this population.

Both trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 8).[41,51] Therapy with the ACE inhibitor ramipril or the ARB telmisartan did not impact hospitalizations as compared with placebo [RR 0.97 (0.94 to 1.00); p=0.09](Figure 15). Due to the low number of included studies, statistical heterogeneity and publication bias could not be assessed. None of the included trials used active therapy as a comparator and none evaluated ACE inhibitors or ARBs in patients with ischemic heart disease risk equivalents. Thus, their impact on hospitalizations could not be assessed.

When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ACE inhibitor ramipril in patients with stable ischemic heart disease, ACE inhibitor therapy did not impact hospitalizations as compared with placebo [RR 0.97 (0.92 to 1.01)].[41] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ARB telmisartan in patients with stable ischemic heart disease, ARB therapy did not impact hospitalizations as compared with placebo [RR 0.97 (0.93 to 1.02)].[51]

Because all of the included trials were double-blinded, the impact of open label trials was not assessed. Similarly, all of the trials included in Key Question 1 utilized intention-to-treat methodologies, thus its impact on hospitalizations could not be assessed.

Hospitalization for Angina

Hospitalization for angina data was available in seven trials (2165 events in 20338 patients; 10.6 percent).[38-42,44-46,51] Three separate base case analyses, and four subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril, enalapril, imidapril, lisinopril) or ARB (telmisartan, candesartan) therapy on hospitalizations for angina in this population.

Five trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 9).[38-42,45,51] Therapy with ACE inhibitors (ramipril, enalapril) or the ARB telmisartan did not impact hospitalizations for angina as compared with placebo [RR 0.97 (0.89 to 1.06)](Figure 16). A low level of statistical heterogeneity was seen (I^2 = 2.3 percent), and publication bias was not expected (Egger's p=0.29, 2 studies were imputed via Trim and Fill with no difference in outcome [RR 0.95 (0.86 to 1.05)]). Two trials were included in the second base case analysis evaluating randomized, active controlled trials in patient with stable ischemic heart disease, both evaluating ACE inhibitors with CCBs.[45,46] In one trial enalapril was compared with amlodipine where in the other, therapy with enalapril, imidapril, or lisinopril was compared with nifedipine. ACE inhibitors did not impact hospitalizations for angina versus CCBs [RR 1.38 (0.95 to 2.02)](Figure 17). None of the included trials evaluated ACE inhibitors or ARBs in patients with ischemic heart disease risk equivalents. Thus, their impact on hospitalizations for angina could not be assessed. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed in the first two base case analyses.

When inclusion was restricted to the four randomized, placebo controlled trials evaluating ACE inhibitors in patients with stable ischemic heart disease, ACE inhibitors (ramipril, enalapril) did not impact hospitalizations for angina as compared with placebo [RR 1.01 (0.91 to 1.11)](Appendix Figure 11).[38-42,45] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ARB telmisartan in patients with stable ischemic heart disease, ARB therapy did not impact hospitalizations for angina [RR 0.89 (0.75 to 1.04)].[51]

In order to assess the impact of study quality on results in the first base case analysis, inclusion was broadened to include a combined total of six open label or placebo controlled trials evaluating the impact of ACE inhibitors (ramipril, enalapril) or ARBs (telmisartan, candesartan) on hospitalizations for angina in patients with stable ischemic heart disease.[38-42,44,45,51] Similarly, ACE inhibitors or ARBs had no impact on hospitalizations for angina as compared with placebo [RR 0.97 (0.89 to 1.05)](Appendix Figure 12). When the inclusion criteria in the second base case were broadened to include open label or placebo controlled trials, no additional trials were found. As all of the trials included in Key Question 1 utilized intention-to-treat methodologies, its impact on hospitalizations for angina could not be assessed.

Hospitalization for Heart Failure

Hospitalization for heart failure data was available in eight trials (1020 events in 40386 patients; 2.5 percent).[38-41,43-47,51] Three separate base case analyses, and four subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril, perindopril, enalapril, imidapril, lisinopril, trandolapril) or ARB (candesartan, telmisartan) therapy on hospitalizations for heart failure in this population.

Six trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 10).[38-41,43,45,47,51] Therapy with ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) or the ARB telmisartan significantly reduced the risk of hospitalizations for heart failure as compared with placebo [RR 0.83 (0.70 to 0.98)](Figure 18). A moderate level of statistical heterogeneity was seen (I^2 = 36.3 percent). Although publication bias was not expected using Egger's weighted regression statistic (p=0.64), the Trim and Fill method imputed two studies that resulted in a similar point estimate, but statistical significance was lost [RR 0.89 (0.74 to 1.08)]. Two trials were included in the second base case analysis evaluating randomized, active controlled trials in patient with stable ischemic heart disease, both comparing ACE inhibitors with CCBs.[45,45] In one trial enalapril was compared with amlodipine where in the other, therapy with enalapril, imidapril, or lisinopril was compared with nifedipine. ACE inhibitors did not impact hospitalizations for heart failure versus CCBs [RR 0.87 (0.41 to 1.83)](Figure 19). None of the included trials evaluated ACE inhibitors or ARBs in patients with ischemic heart disease risk equivalents. Thus, their impact on hospitalizations for heart failure could not be assessed. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed in the other two base case analyses.

When inclusion was restricted to the five randomized, placebo controlled trials evaluating ACE inhibitors in patients with stable ischemic heart disease, ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) significantly reduced the risk of hospitalization for heart failure as compared with placebo [RR 0.78 (0.67 to 0.90)](Appendix Figure 13).[38-41,43,45,47] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the

ARB telmisartan in patients with stable ischemic heart disease, ARB therapy did not impact hospitalizations for heart failure [RR 1.04 (0.83 to 1.32)].[51]

In order to assess the impact of study quality on results in the first base case analysis, inclusion was broadened to include a combined total of seven open label or placebo controlled trials evaluating the impact of ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) or ARBs (telmisartan, candesartan) on hospitalizations for heart failure in patients with stable ischemic heart disease.[38-41,43-45,47,51] Similar to the first base case analysis, ACE inhibitors or ARBs significantly reduced the risk of hospitalization for heart failure as compared with placebo [RR 0.83 (0.70 to 0.98)](Appendix Figure 14). When the inclusion criteria in the second base case were broadened to include open label or placebo controlled trials, no additional trials were found. As all of the trials included in Key Question 1 utilized intention-to-treat methodologies, its impact on hospitalizations for heart failure could not be assessed.

Need for Revascularization

Need for revascularization data was available in eight trials (4572 events in 40229 patients; 11.4 percent).[38-40,42-47,51] Three separate base case analyses, and six subgroup/sensitivity analyses were conducted to discern the impact of ACE inhibitor (ramipril, perindopril, enalapril, imidapril, lisinopril, trandolapril) or ARB (telmisartan, candesartan) therapy on revascularizations in this population.

Five trials were included in the first base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 11).[38-40,42,43,45,51] Therapy with ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) or the ARB telmisartan significantly reduced the risk of need for revascularization as compared with placebo [RR 0.90 (0.85 to 0.96)](Figure 20). No statistical heterogeneity was seen (I^2 = 0 percent), and publication bias was not expected (Egger's p=0.47, three studies were imputed via Trim and Fill with no significant difference in outcome [RR 0.94 (0.88 to 0.99)]). Two trials were included in the second base case analysis evaluating randomized, active controlled trials in patient with stable ischemic heart disease, both evaluating ACE inhibitors with CCBs.[45,46] In one trial enalapril was compared with amlodipine where in the other, therapy with enalapril, imidapril, or lisinopril was compared with nifedipine. ACE inhibitors did not impact the need for revascularization versus CCBs [RR 1.06 (0.83 to 1.36)](Figure 21). None of the included trials evaluated ACE inhibitors or ARBs in patients with ischemic heart disease risk equivalents. Thus, their impact on the need for revascularization could not be assessed. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed in this base case analysis.

When inclusion was restricted to the four randomized, placebo controlled trials evaluating ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) in patients with stable ischemic heart disease, ACE inhibitors significantly reduced the risk of need for revascularization as compared with placebo [RR 0.90 (0.84 to 0.96)] (Appendix Figure 15).[38-40,42,43,45] When inclusion was restricted to the single randomized, placebo controlled trial evaluating the ARB telmisartan in patients with stable ischemic heart disease, ARB therapy did not impact the need for revascularization [RR 0.90 (0.79 to 1.03)].[51]

When inclusion was restricted to the two randomized, placebo controlled trials evaluating ACE inhibitors (enalapril, trandolapril) or ARBs (none evaluated) in patients with stable ischemic heart disease, therapy did not impact the need for coronary artery bypass grafting surgery as compared with placebo [RR 0.92 (0.78 to 1.07)] (Appendix Figure 16).[42,47] When

inclusion was restricted to the two randomized, placebo controlled trials evaluating ACE inhibitors (enalapril, trandolapril) or ARBs (none evaluated) in patients with stable ischemic heart disease, therapy did not impact the need for percutaneous coronary interventions as compared with placebo [RR 0.91 (0.59 to 1.40)](Appendix Figure 17).[42,47]

In order to assess the impact of study quality on results in the first base case analysis, inclusion was broadened to include a combined total of six open label or placebo controlled trials evaluating the impact of ACE inhibitors (ramipril, perindopril, enalapril, trandolapril) or ARBs (telmisartan, candesartan) on revascularizations in patients with stable ischemic heart disease.[38-40,42-45,51] Similar to the first base case analysis, ACE inhibitors or ARBs significantly reduced the risk of need for revascularization as compared with placebo [RR 0.90 (0.85 to 0.95)] (Appendix Figure 18). When the inclusion criteria in the second and third base cases were broadened to include open label or placebo controlled trials, no additional trials were found. As all of the trials included in Key Question 1 utilized intention-to-treat methodologies, its impact on need for revascularization could not be assessed.

Quality of Life

None of the eligible trials reported the impact of ACE inhibitor or ARB therapy on quality of life.

Discussion

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 using calcium channel blockers in addition to standard medical therapy. Although the baseline medical therapies were somewhat heterogeneous between studies, the lack of statistical heterogeneity and agreement of effect size suggests that the effects seen are related to the ACE inhibitor or ARB regardless of the standard medical therapy used. While there were no significant differences between the ACE inhibitor versus the calcium channel blocker groups, future research is needed to determine the comparative efficacy of ACE inhibitors or ARBs versus other vasoactive drugs such as calcium channel blockers and thiazide diuretics in patients receiving standard medical therapy. Key Question 2 provides the only direct evidence on the comparative efficacy of ACE inhibitors versus ARBs in patients with stable ischemic heart disease and preserved left ventricular function. This data will be discussed in detail later.

When we evaluated ACE inhibitors and ARBs versus placebo in patients with ischemic heart disease risk equivalents and preserved left ventricular function, no significant benefits were found. However, only a limited number of trials were available to assess these outcomes. Future research is needed to determine if ACE inhibitors and ARBs provide benefits in this target population.

The lack of impact of ACE inhibitors and ARBs on the occurrence of atrial fibrillation is similar to what has been demonstrated previously. A meta-analysis of nine randomized trials of ACE inhibitors and ARBs in patients both with and without left ventricular systolic dysfunction showed an 18 percent reduction in the risk of new-onset atrial fibrillation [RR 0.82 (0.70 to 0.97)].[98] However, when they subgrouped the included studies by patient population, they found no effect in hypertension [RR 0.94 (0.72 to 1.23)] or post-myocardial infarction trials [RR 0.73 (0.43 to 1.26)], but significant reductions in atrial fibrillation in the heart failure trials [RR 0.57 (0.37 to 0.89)].[98] Thus it appears that ACE inhibitors and ARBs may not be protective against

atrial fibrillation in patients outside of those with documented left ventricular dysfunction. Our results confirm this since no effect on atrial fibrillation was seen in these patients with ischemic heart disease and preserved left ventricular systolic function.

It has long been thought that lowering either systolic or diastolic blood pressure in patients with coronary heart disease would lower a patients' subsequent risk for major clinical outcomes.[22] Thus, it has been postulated that differences in the blood pressure lowering ability of pharmacologic agents may, at least partially, explain differences in outcomes seen in clinical trials. This contention is supported by the results of the CAMELOT trial which showed similar blood pressure-lowering ability between the ACE inhibitor enalapril and the calcium channel blocker amlodipine, with resultant similar effects on clinical outcomes.[45] The relationship between blood pressure lowering ability and clinical outcomes has been examined in a number of the trials included in this Key Question. The HOPE trial demonstrated that, although significant reductions in outcomes were seen with the ACE inhibitor ramipril, only a small portion of this benefit could be attributed to a reduction in blood pressure since most patients did not have hypertension at baseline and only marginal blood pressure reductions were seen (3/2 mmHg).[38] Similarly, the EUROPA trial did not show any significant difference in treatment outcomes with the ACE inhibitor perindopril whether patients either had or did not have hypertension at baseline.[43] In addition, the magnitude of reductions seen in the primary efficacy outcome could not be fully explained by the reductions in blood pressure seen in the study (5/2 mmHg).[43] A prior systematic review of the impact of ACE inhibitors on coronary artery disease in patients with preserved left ventricular function showed similar effects on clinical outcomes in studies that reduced systolic blood pressure either less than or greater than 5 mm Hg.[92] ARBs appear to have similar blood-pressure independent effects. The TRANSCEND trial showed that the impact of the ARB telmisartan on clinical outcomes was likely independent of its blood pressure lowering ability, with no differences in the point estimates seen when differences in blood pressure between telmisartan and placebo were adjusted for.[51] Thus it seems that the beneficial effects seen in the current Key Question are potentially separate from their blood pressure lowering ability.

While a more in-depth review of applicability will be conducted in Key Question 7, some general points can be made here. HOPE, EUROPA, PEACE and TRANSCEND were the largest trials evaluating the impact of ACE inhibitor (ramipril, perindopril, trandolapril) or ARB (telmisartan) therapy versus placebo.[38,43,47,51] Each of these trials include patients with preserved left ventricular function that had either established ischemic heart disease or a heart disease risk equivalent including stroke, peripheral vascular disease and diabetes mellitus. Although the average age of patients in these trials ranged from 60-67 years, their inclusion criteria differed somewhat. Whereas HOPE[38] and TRANSCEND[51] included patients greater than 55 years of age, EUROPA[43] included patients greater than 18 years and PEACE[47] greater than 50 years. Thus, there may be less applicability to younger patients with ischemic heart disease or heart disease risk equivalents. Since only 6-7 percent of patients with coronary heart disease are below age 60, a majority of the general population with ischemic heart disease and preserved left ventricular function would most likely have qualified for at least one of these major trials base on their age.[1] However, people may develop diabetes mellitus and hypertension at younger ages and might not be as well represented by the current trials. Since the TRANSCEND trial[51] included only patients with ischemic heart disease and preserved left ventricular function who were intolerant to ACE inhibitor therapy, the results of that trial are only applicable to that population. Only some of the ACE inhibitors and two ARBs were assessed in this population in

clinical trials and therefore, the applicability of the results to other ACE inhibitors and ARBs cannot be firmly established. Additionally, the duration of followup differed between the included studies for many of the outcomes. Thus, the optimal duration of treatment to derive the greatest benefit is currently unknown.

Table 3. KQ1—Quality of randomized controlled trials

Study, year	Randomized	Randomization Adequate	Double-Blinded	Double-Blinding Adequate	Intention-to-Treat
HOPE, 2000[38]	Yes	Yes	Yes	Yes	Yes
PART-2, 2000[41]	Yes	Yes	Yes	Yes	Yes
SCAT, 2000[42]	Yes	Yes	Yes	Yes	Yes
EUROPA, 2003[43]	Yes	NR	Yes	Yes	Yes
Kondo et al, 2003[44]	Yes	NR	No	N/A	Yes
CAMELOT, 2004[45]	Yes	Yes	Yes	Yes	Yes
JMIC-B, 2004[46]	Yes	Yes	No	N/A	Yes
PEACE, 2004[47]	Yes	Yes	Yes	Yes	Yes
FOSIDIAL, 2006[48]	Yes	Yes	Yes	Yes	Yes
Takahashi et al, 2006[49]	Yes	Yes	No	N/A	Yes
SMILE-ISCHEMIA, 2007[50]	Yes	Yes	Yes	NR	Yes
TRANSCEND, 2008[51]	Yes	Yes	Yes	NR	Yes

Abbreviations: N/A=Not applicable; NR=Not reported

Table 4. KQ1—Study design characteristics and population

Study, year	Study Design	Country	Study Funding	Duration of Follow-up	Inclusion Criteria	Exclusion Criteria
HOPE, 2000[38]	RCT	Europe, North & South America	Industry, Foundation	4.5 years	Age >55 years old, history of CAD, stroke, PVD, or DM plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, LDL, cigarette smoking, or documented microalbuminuria	HF, known low LVEF (<0.40), currently taking ACEI or vitamin E, uncontrolled hypertension or overt nephropathy, MI or stroke within four weeks before the study began
PART-2, 2000[41]	RCT	New Zealand	Industry, Foundation	4.7 years	Age 75 years or younger, had a hospital diagnosis (within five years of enrollment) of any of the following: MI, angina with coronary disease confirmed by angiography or exercise electrocardiogram, TIA or IC	HF or any other definite indication for treatment with an ACEI, a contraindication to treatment with an ACEI, serious nonvascular disease, a DBP>100 mm Hg, a SBP>160 mm Hg or <100 mm Hg during the prerandomization run-in period, or were of childbearing potential without adequate contraception
SCAT, 2000[42]	RCT	Canada	Industry, Foundation	4 years	Age>21years old, TC between 160-240 mg/dL, HDL<85 mg/dL, TG<350 mg/dL, angiographically detectible coronary atherosclerosis in >3 major coronary segments, LVEF>35%, >6mo from coronary angioplasty or bypass surgery	Clear indications for, or contraindications to, study drugs, clinical instability, imminent need for intervention, other significant cardiac or systemic diseases, potential noncompliance, inability to give informed consent
EUROPA, 2003[43]	RCT	Europe	Industry	4.2 years	Age≥18 years with evidence of CHD, documented by: previous MI (>3 months before screening), percutaneous or surgical coronary revascularisation (>6 months before screening), or angiographic evidence of at least 70% narrowing of one or more major coronary arteries.	Clinical evidence of HF, planned revascularisation, hypotension (sitting SBP <110 mm Hg), uncontrolled hypertension (SBP >180 mm Hg, DBP >100 mm Hg, or both), recent (<1 month) use of ACEI or ARB, renal insufficiency (creatinine >150 mol/L), and serum potassium > 5.5 mmol/L
Kondo et al, 2003[44]	RCT	Japan	NR	24 months	History of coronary intervention with no significant coronary stenosis on followup angiography 6 months after intervention	HF (LVEF<0.40), malignancy, patients receiving dialysis treatment

Table 4 Continued. KQ1—Study design characteristics and population

Study, year	Study Design	Country	Study Funding	Duration of Follow-up	Inclusion Criteria	Exclusion Criteria
CAMELOT, 2004[45]	RCT	US, Canada, Europe	Industry	2 years	Age 30-79 years, requiring coronary angiography for evaluation for chest pain or PCI, DBP<100 mm Hg, with or without treatment. Angiographic inclusion criteria required >1 lesions in a native coronary artery with greater than 20% stenosis by visual (angiographic) estimation	Patients with a left main coronary artery obstruction greater than 50%, LVEF<40%, or moderate to severe CHF
JMIC-B, 2004[46]	RCT	Japan	Foundation	3 years	Age <75 years, hypertension & CAD	Patients with acute MI or unstable angina, LVEF<40%[†]
PEACE, 2004[47]	RCT	US, Canada, Italy, Puerto Rico	Industry, Foundation	4.8 years	Age>50 years, documented CAD, LVEF>40%	Current use of ACEI/ARB, UA hospitalization w/in 2mo, valvular heart Dz, CABG w/in 3mo, planned PCI, SCr>2.0 mg/dL, serum K>5.5 mmol/L, limited 5-yr survival, condition precluding long-term adherence, female of childbearing potential not using contraception, current inclusion in a research trial of non-FDA approved medication
FOSIDIAL, 2006[48]	RCT	France	Industry	4.8 years	Men or postmenopausal women 50–80 years with LVEF>40%[†], hemodialysis for at least 6 months with three sessions per week, and LVH defined by a cardiac mass index >130 g/m^2 for men and 100 g/m^2 for women within 3 months of enrollment	ACEI use, hyperkalemia (>6 mmol/L), or hypersensitivity to ACEI
Takahashi et al, 2006[49]	RCT	Japan	NR	19.4 months	Age>35 years and: (i) those who were in stable condition and asymptomatic for at least the previous 6 months; (ii) those with interdialytic increase of body weight <5% and with stable dry weight, defined as regularly reached end-dialysis weight without the signs of dehydration or overhydration, for at least 3 months; (iii) those with post-haemodialytic cardiothoracic ratio on chest X-ray <50% in males and <55% in females	History of MI, angina pectoris and cardiac revascularization, valvular heart disease, CHF, severe arrhythmia and pulmonary, hepatic, renal, active inflammatory and malignant diseases.

Table 4 Continued. KQ1—Study design characteristics and population

Study, year	Study Design	Country	Study Funding	Duration of Follow-up	Inclusion Criteria	Exclusion Criteria
SMILE-ISCHEMIA, 2007[50]	RCT	Italy, Germany	Foundation	6 months	LVEF>40%, MI within preceding 6±1 weeks, SBP>100 mmHg, prior thrombolytic therapy, previous 6 week treatment with ACEI	(a) Cardiogenic shock during the acute phase (Killip class IV), (b) SCr>2.5 mg/dL (221 mmol/L), (c) history of congestive heart failure, (d) EF<40%, (e) contraindications to ACEI, (f) angina or asymptomatic ischemic electrocardiographic abnormalities at enrollment, (g) scheduled PCI, or (h) physical incapacity to perform exercise (treadmill) test
TRANSCEND, 2008[51]	RCT	Europe, Asia, North, Central & South America, South Africa, Russia, United Arab Emerates, Australia	Industry, Foundation	4.7 years	Patients intolerant to ACEI with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	HF, significant primary valvular or cardiac outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, unexplained syncope, planned cardiac surgery or revascularization w/in 3 months, SBP>160 mmHg, heart transplantation, subarachnoid hemorrhage, significant renal artery stenosis, SCr>265 μmol/L, proteinuria, or hepatic dysfunction

† Heart failure exclusion was not included in the main manuscript, and was provided by a personal communication with the corresponding author

Abbreviations: ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CABG=coronary artery bypass grafting; CAD=coronary artery disease; CHD=coronary heart disease; DBP=diastolic blood pressure; DM=diabetes mellitus; Dz=disease; FDA=food and drug administration; HDL=high-density lipoprotein; HF=heart failure; IC=intermittent claudication; LDL=low-density lipoprotein; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy; MI=myocardial infarction; NR=not reported; PCI=percutaneous coronary intervention; PVD=peripheral vascular disease; RCT=randomized controlled trial; SBP=systolic blood pressure; Scr=serum creatinine; TC=total cholesterol; TG=triglycerides; TIA=transient ischemic attack; UA=unstable angina

Table 5. KQ1—Initial and target dosing regimens

Study, year	Group	Initial Dose	Target Dose
HOPE, 2000[38]	Ramipril Placebo	2.5mg/d X 7 days, then 5mg/d X 21 days, then 10 mg/d	10mg/d
PART-2, 2000[41]	Ramipril Placebo	5mg/d X 7 days, then 10mg/d X 7 days (run-in), then 5-10mg/d depending on tolerability	5-10mg/d
SCAT, 2000[42‡]	Enalapril Placebo	5mg/d (divided twice daily), then upward dose titration during the first 3 monthly visits	20mg/d
EUROPA, 2003[43]	Perindopril Placebo	4mg/d X 14 days, then 8mg/d X 14 days (run-in), then 4-8mg/d depending on tolerability	4-8mg/d
Kondo et al, 2003[44]	Candesartan Control	4mg/d	4mg/d
CAMELOT, 2004[45]	Enalapril Amlodipine Placebo	10mg/d X 14 days, then 20 mg/d 5mg/d X 14 days, then 10 mg/d	20mg/d 10mg/d
JMIC-B, 2004[46]	ACEI Nifedipine	Enalapril 5-10mg/d, imidapril 5-10mg/d, or lisinopril 10-20mg/d 20-40mg/d (divided twice daily)	ACEI 20-40mg/d
PEACE, 2004[47]	Trandolapril Placebo	2mg/d X 6 months, then 4mg/d	4mg/d
FOSIDIAL, 2006[48]	Fosinopril Placebo	5mg/d (run-in), then increased weekly by 5mg/d up to a target of 20mg/d	20mg/d
Takahashi et al, 2006[49]	Candesartan Control	4-8mg/d	4-8mg/d
SMILE-ISCHEMIA, 2007[50]	Zofenopril Placebo	15mg/d (divided twice daily), then progressively doubled up to total dose of 60mg/d (divided twice dialy)	60mg/d
TRANSCEND, 2008[51]	Telmisartan Placebo	80mg/d	80mg/d

Abbreviations: ACEI=angiotensin converting enzyme inhibitor
‡ SCAT was a 2X2 factorial design with simvastain 40mg

Table 6. KQ1—Baseline characteristics

Study, year	Group	Ave Age (SD)	Male (%)	Ave LVEF % (SD)	Clinical History (%)											
					CAD	MI	CABG	PCI-PTCA	Stable Angina	Unstable Angina	Stroke or TIA	PVD	DM	HTN	RI	LVH
HOPE, 2000[38]	Ramipril 10mg/d	66 (7)	72		80	52	26	18	55	25	11	42	39	48		8
	Placebo	66 (7)	74		81	53	26	17	56	26	11	45	38	46		9
PART-2, 2000[41]	Ramipril 5-10mg/d	60 (8)	82			43					11	20	8			
	Placebo	61 (8)	82			41					9	20	9			
SCAT, 2000[42‡]	Enalapril 20mg/d	60 (10)	89		100	70							11	39		
	Placebo	62 (9)	89		100	71							11	32		
EUROPA, 2003[43]	Perindopril 8mg/d	60 (9)	86		60	65	29	29			3	7	12	27		
	Placebo	60 (9)	85		61	65	29	30			3	7	13	27		
Kondo et al, 2003[44]	Candesartan 4mg/d	65 (9)	74	63 (10)		67							27	48		
	Control	65 (10)	77	62 (10)		70							23	39		
CAMELOT, 2004[45]	Enalapril 20mg/d	59 (10)	72			40	7	29			5		18	60		
	Amlodipine 10mg/d	57 (10)	76			37	8	26			4		17	61		
	Placebo	57 (10)	73			38	8	30			4		20	60		
JMIC-B, 2004[46]	ACEI∝	64 (9)	70			46							21	100		
	Nifedipine 10-20mg/d	65 (8)	68			38							24	100		
PEACE, 2004[47]	Trandolapril 4mg/d	64 (8)	81	58 (10)	61	54	38	42			7		18	46		
	Placebo	64 (8)	83	58 (9)	61	56	40	41			6		16	45		
FOSIDIAL, 2006*[48]	Fosinopril 20mg/d	67 (8)	54	>40%*	16	100					9	18	35			
	Placebo	67 (8)	51	>40%*	10	100					6	14	28			
Takahashi et al, 2006[49]	Candesartan 4-8mg/d	60 (13)	61	66 (10)									35	84	100	
	Control	62 (12)	57	61 (17)									30	78	100	
SMILE-ISCHEMIA, 2007[50]	Zofenopril 60mg/d	58 (10)	81	55 (10)		100							18	45		
	Placebo	58 (10)	85	53 (8)		100							17	45		
TRANSCEND, 2008[51]	Telmisartan 80mg/d	67 (7)	57		75	47	19	27	37	16	22	12	36	77		13
	Placebo	67 (7)	57		74	46	19	26	37	15	22	11	36	76		14

* The corresponding author for the FOSIDIAL trial reported that all trial participants had normal LVEF, although specific data was not provided

∝ = Patients in the ACEI group were given enalapril 5-10mg/d, imidapril 5-10mg/d, or lisinopril 10-20mg/d

‡ SCAT was a 2X2 factorial design with simvastain 40mg

Abbreviations: ACEI= angiotensin converting enzyme inhibitor; CABG=coronary artery bypass grafting; CAD=coronary artery disease; DM=diabetes mellitus; HTN=hypertension; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy; MI=myocardial infarction; PCI=percutaneous coronary intervention; PTCA=percutaneous transluminal coronary angioplasty; PVD=peripheral vascular disease; RI=renal insufficiency; SD=standard deviation; TIA=transient ischemic attack

Table 6 Continued. KQ1—Baseline characteristics

Study, year	Group	SBP mmHg (SD)	DBP mmHg (SD)	BMI (kg/m^2)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	Serum Creatinine (mg/dL)	Serum Potassium (mEq/L)
HOPE, 2000[38†]	Ramipril 10mg/d	139 (20)	79 (11)	28 (4)							
	Placebo	139 (20)	79 (11)	28 (4)							
PART-2, 2000[41]	Ramipril 5-10mg/d	133 (17)	79 (9)		240 (43)	162 (39)	46 (12)	159 (106)			
	Placebo	133 (16)	79 (10)		236 (39)	159 (35)	43 (12)	159 (97)			
SCAT, 2000[42]	Enalapril 20mg/d	128 (19)	77 (11)								
	Placebo	132 (20)	78 (10)								
EUROPA, 2003[43]	Perindopril 8mg/d	137 (16)	82 (8)								
	Placebo	137 (15)	82 (8)								
Kondo et al, 2003[44]	Candesartan 4mg/d	129 (13)	76 (8)	24 (2)	187 (28)	114 (25)	49 (12)	126 (73)	118 (32)		
	Control	128 (14)	76 (8)	23 (2)	187 (31)	112 (30)	49 (14)	127 (77)	117 (38)		
CAMELOT, 2004[45]	Enalapril 20mg/d	129 (16)	77 (9)	30 (6)		101 (31)					
	Amlodipine 10mg/d	130 (16)	78 (9)	30 (6)		104 (32)					
	Placebo	129 (16)	78 (9)	30 (5)		100 (32)					
JMIC-B, 2004[46]	ACEI[∝]	145 (20)	82 (12)	24 (3)	198 (33)					1.1 (0.4)	
	Nifedipine 10-20mg/d	147 (19)	82 (11)	24 (3)	203 (37)					1.1 (0.4)	
PEACE, 2004[47]	Trandolapril 4mg/d	134 (17)	78 (10)		192 (39)					1.0 (0.2)	
	Placebo	133 (17)	78 (10)		192 (40)					1.0 (0.2)	
FOSIDIAL, 2006*[48]	Fosinopril 20mg/d	146 (19)	77 (11)	26 (5)		120 (39)	43 (12)				4.9 (0.8)
	Placebo	145 (20)	77 (11)	27 (6)		120 (39)	43 (12)				4.9 (0.8)
Takahashi et al, 2006[49]	Candesartan 4-8mg/d	153 (20)	82 (13)	20 (4)							4.8 (0.9)
	Control	152 (24)	85 (18)	20 (4)							4.4 (1.3)
SMILE-ISCHEMIA, 2007[50]	Zofenopril 60mg/d	127 (14)	78 (8)	28 (4)	232 (40)	159 (20)	38 (2)	169 (15)			
	Placebo	129 (14)	79 (8)	28 (4)	227 (39)	156 (19)	37 (2)	167 (19)			
TRANSCEND, 2008[51]	Telmisartan 80mg/d	141 (17)	82 (10)	28 (5)	197 (46)	117 (39)	49 (14)	159 (116)	117 (44)	1.04 (0.3)	4.4 (0.4)
	Placebo	141 (16)	82 (10)	28 (5)	196 (45)	117 (39)	50 (16)	157 (97)	117 (44)	1.04 (0.3)	4.4 (0.5)

‡ SCAT was a 2X2 factorial design with simvastain 40mg

∝ = Patients in the ACEI group were given enalapril 5-10mg/d, imidapril 5-10mg/d, or lisinopril 10-20mg/d

Abbreviations: ACEI=angiotensin converting enzyme inhibitor; BMI=body mass index; DBP=diastolic blood pressure; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SBP=systolic blood pressure; SD=standard deviation; TC=total cholesterol; TG=triglycerides

Table 7. KQ1 - Baseline medical therapies

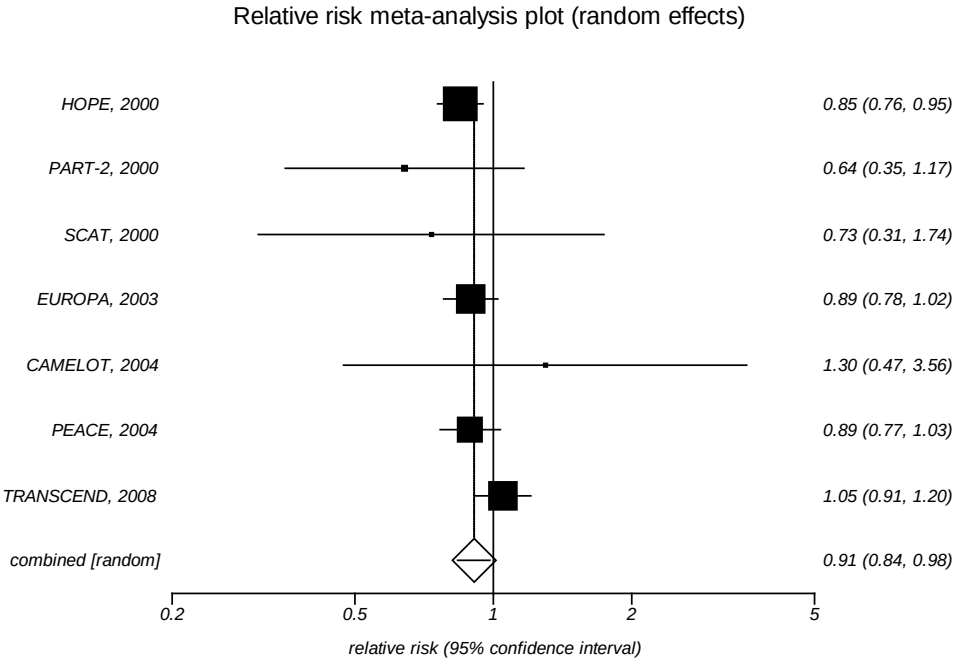
Study, year	Group	BB	CCB	ASA	Clopidogrel or Ticlopidine	Antiplatelet	Diuretic	Nitrate	Statin	Lipid Lowering	Digitalis
HOPE, 2000[38]	Ramipril 10mg/d	39	46			75	15			28	
	Placebo	40	48			77	15			29	
PART-2, 2000[41]	Ramipril 5-10mg/d	42	25			83				29	
	Placebo	43	25			79				28	
SCAT, 2000[42]	Enalapril 20mg/d	49	16	91				62	49		
	Placebo	46	13	89				66	51		
EUROPA, 2003[43]	Perindopril 8mg/d	62	32			92	9	43		58	
	Placebo	61	31			93	9	43		57	
Kondo et al, 2003[44]	Candesartan 4mg/d	14		68					37		
	Control	14		67					32		
CAMELOT, 2004[45]	Enalapril 20mg/d	75	6	95			27		82		
	Amlodipine 10mg/d	74	5	94			32		83		
	Placebo	79	12	95			33		84		
JMIC-B, 2004[46]	ACEI∝	19	49			57	5	65		26	
	Nifedipine 10-20mg/d	21	53			53	5	67		29	
PEACE, 2004[47]	Trandolapril 4mg/d	60	36			90	13			70	4
	Placebo	60	35			91	13			70	4
FOSIDIAL, 2006*[48]	Fosinopril 20mg/d									26	
	Placebo									24	
Takahashi et al, 2006[49]	Candesartan 4-8mg/d	23	77	16			33	33			
	Control	8	59	8			16	14			
SMILE-ISCHEMIA, 2007[50]	Zofenopril 60mg/d	10	3	3	1			10	28		
	Placebo	12	6	10	7			23	32		
TRANSCEND, 2008[51]	Telmisartan 80mg/d	59	40	75	11	80	33		56		
	Placebo	57	40	74	11	79	33		55		

‡ SCAT was a 2X2 factorial design with simvastain 40mg

∝ = Patients in the ACEI group were given enalapril 5-10mg/d, imidapril 5-10mg/d, or lisinopril 10-20mg/d

Abbreviations: ACEI=angiotensin converting enzyme inhibitor; ASA=aspirin; BB=beta-blocker; CCB=calcium channel blocker

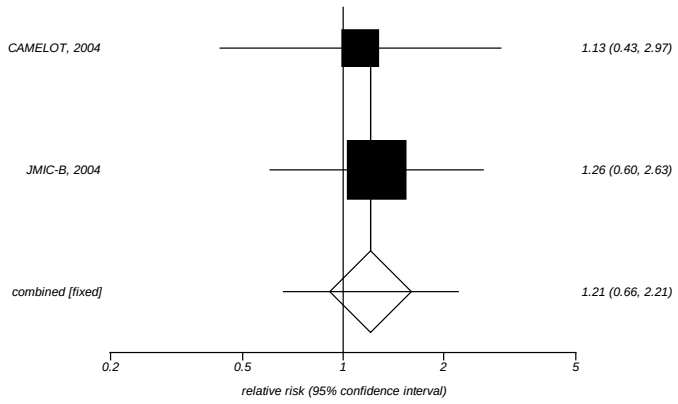
Figure 6. KQ1 Total mortality first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=7.639539 (df=6) p=0.2657; I^2 statistic=21.5%

Figure 7. KQ1 Total mortality second base case analysis—Meta-analysis of randomized placebo-controlled trials comparing ACEI or ARB with CCB in patients with stable ischemic heart disease

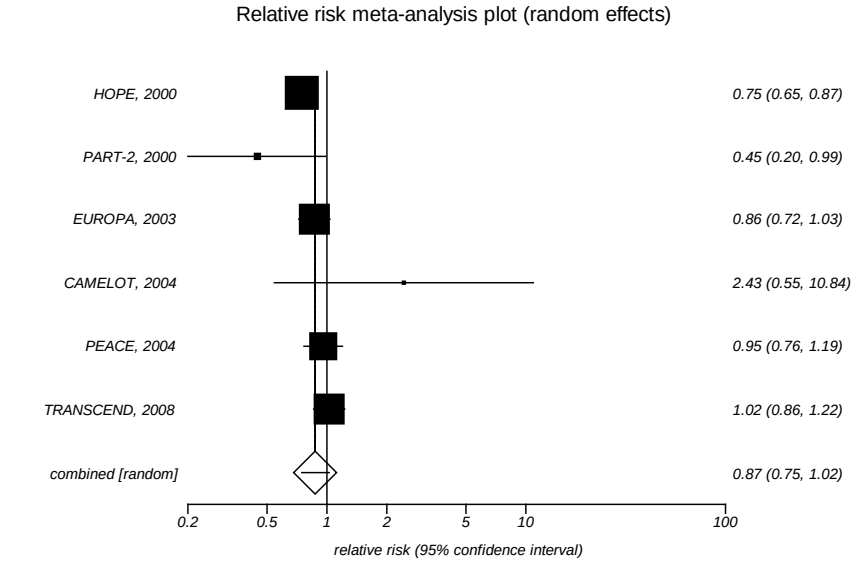


Favors ACEI/ARB Favors CCB

Test for heterogeneity: Cochran Q=0.030336 (df=1) p=0.8617; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

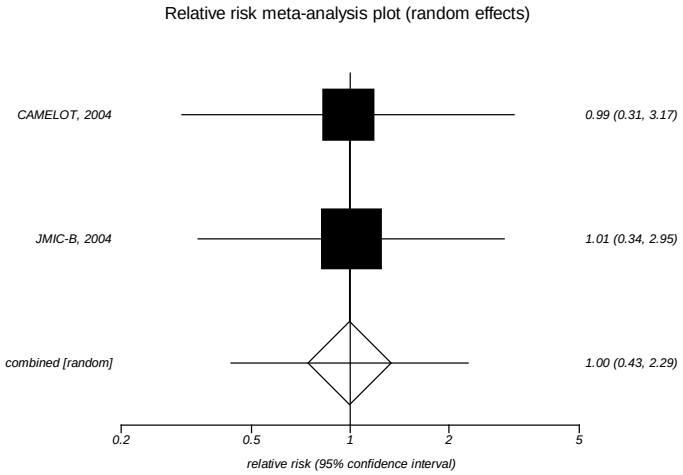
Figure 8. KQ1 Cardiovascular mortality first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=11.863251 (df=5) p=0.0367; I^2 statistic=57.9%

Figure 9. KQ1 Cardiovascular mortality second base case analysis—Meta-analysis of randomized placebo-controlled trials comparing ACEI or ARB with CCB in patients with stable ischemic heart disease

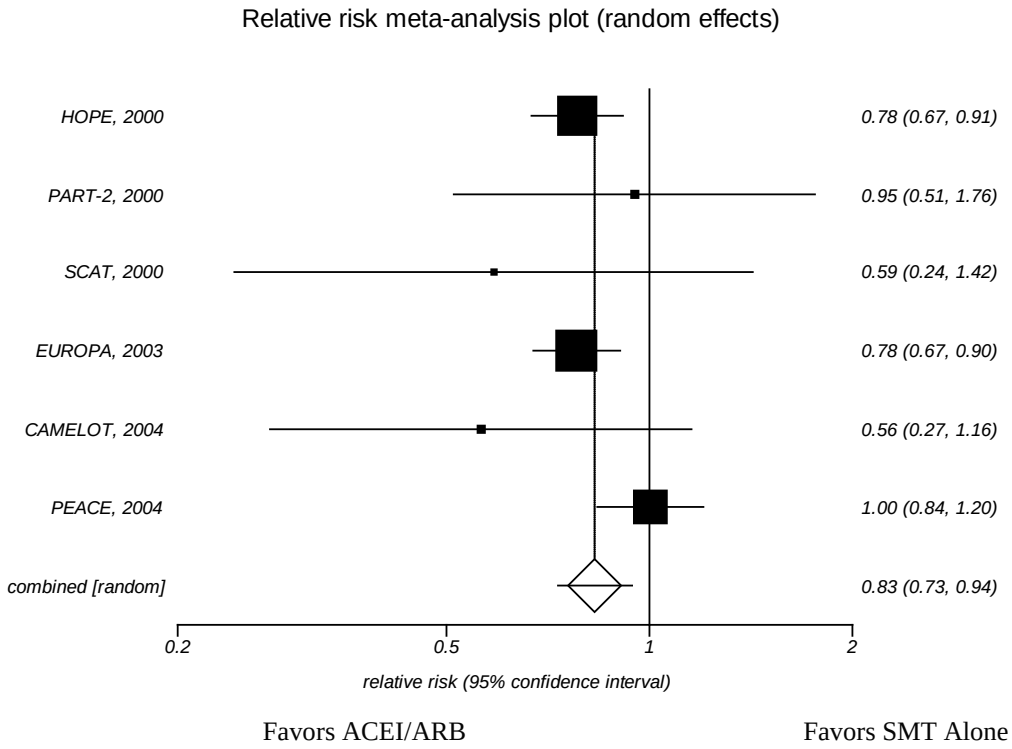


Favors ACEI/ARB Favors CCB

Test for heterogeneity: Cochran Q=0.00068 (df=1) p=0.9792; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 10. KQ1 Nonfatal myocardial infarction first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease

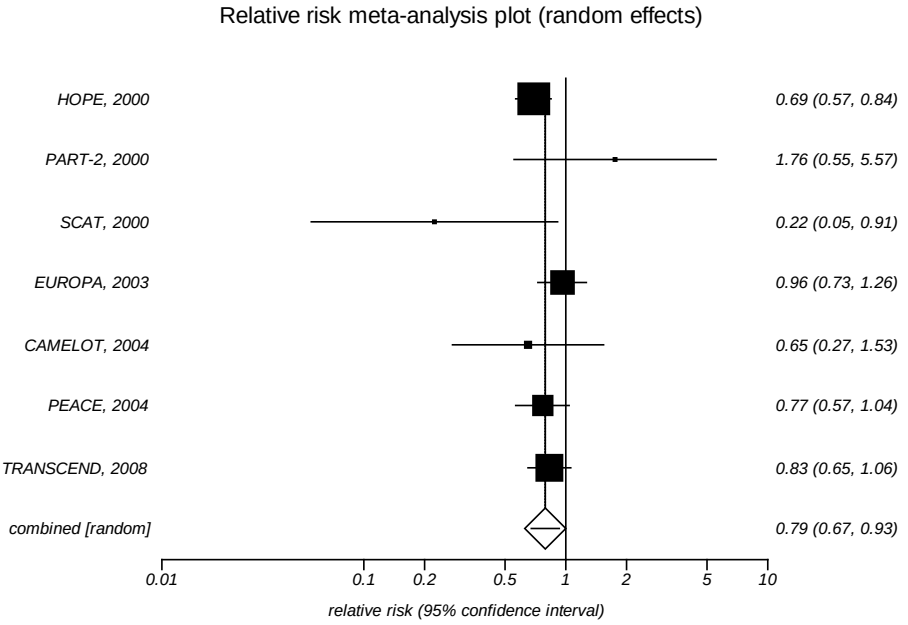


Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=7.189476 (df=5) p=0.2069
I^2 statistic=30.5%

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

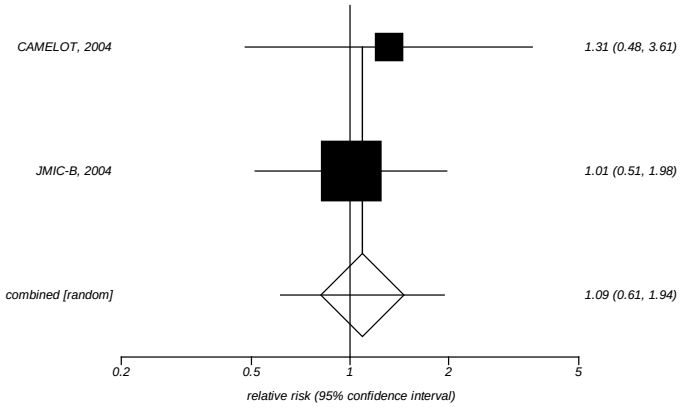
Figure 11. KQ1 Stroke first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=8.291835 (df=6) p=0.011848; I^2 statistic=27.6%

Figure 12. KQ1 Stroke second base case analysis—Meta-analysis of randomized placebo-controlled trials comparing ACEI or ARB with CCB in patients with stable ischemic heart disease

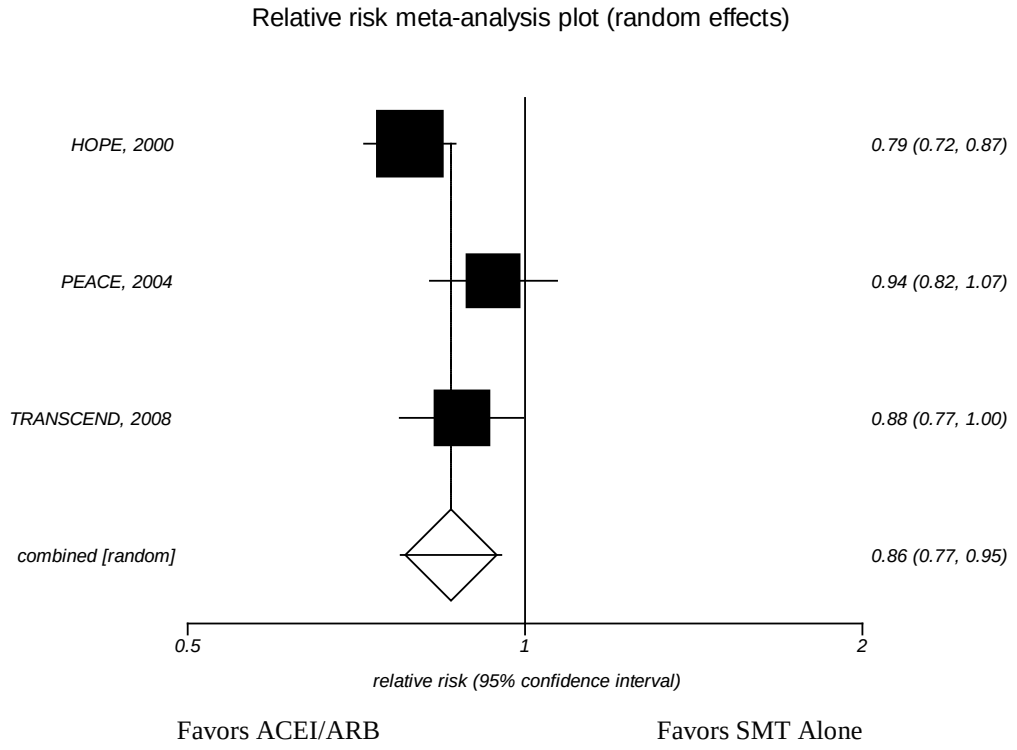


Favors ACEI/ARB Favors CCB

Test for heterogeneity: Cochran Q=0.171342 (df=1) p=0.6789; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 13. KQ1 Composite of cardiovascular mortality, nonfatal myocardial infarction and stroke first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease

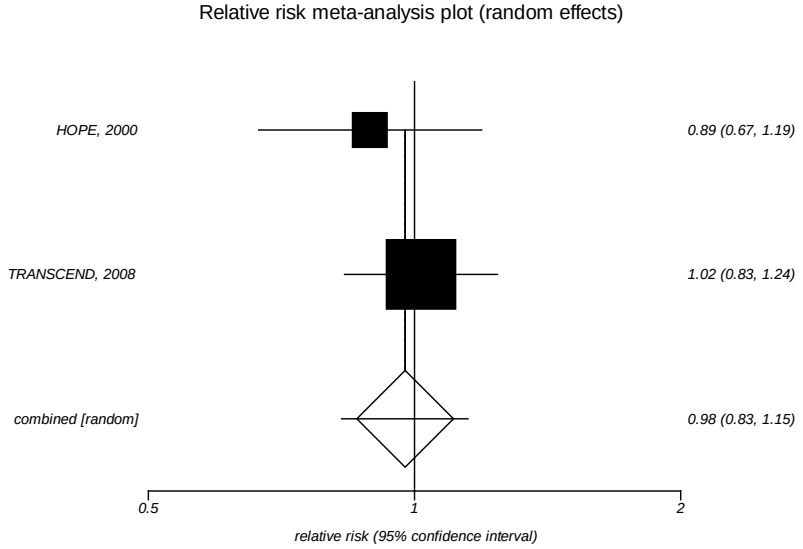


Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=4.760357 (df=2) p=0.0925
I^2 statistic=58%

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

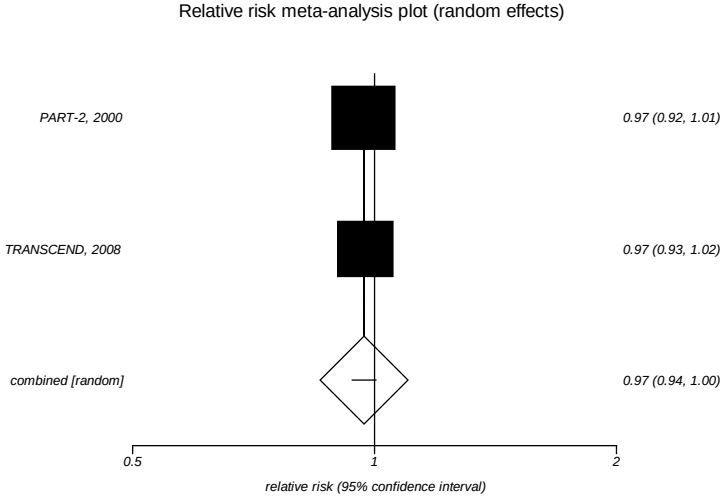
Figure 14. KQ1 Atrial fibrillation first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=0.543657 (df=1) p=0.4609; I^2 statistic=N/A

Figure 15. KQ1 Hospitalizations first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease

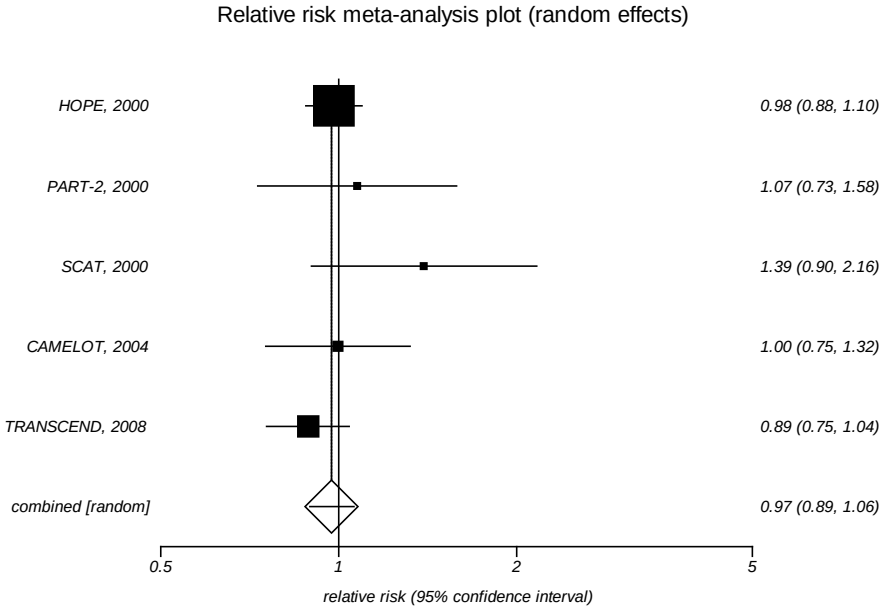


Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=0.038012 (df=1) p=0.8454; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

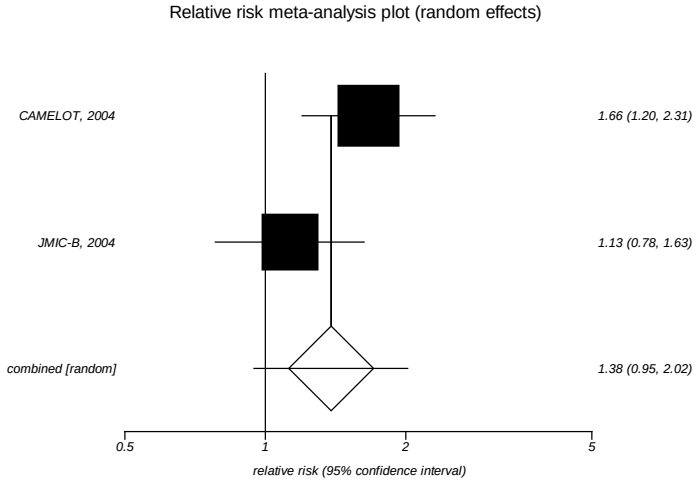
Figure 16. KQ1 Hospitalization for angina first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=4.094188 (df=4) p=0.3934; I^2 statistic=2.3%

Figure 17. KQ1 Hospitalization for angina second base case analysis—Meta-analysis of randomized placebo-controlled trials comparing ACEI or ARB with CCB in patients with stable ischemic heart disease

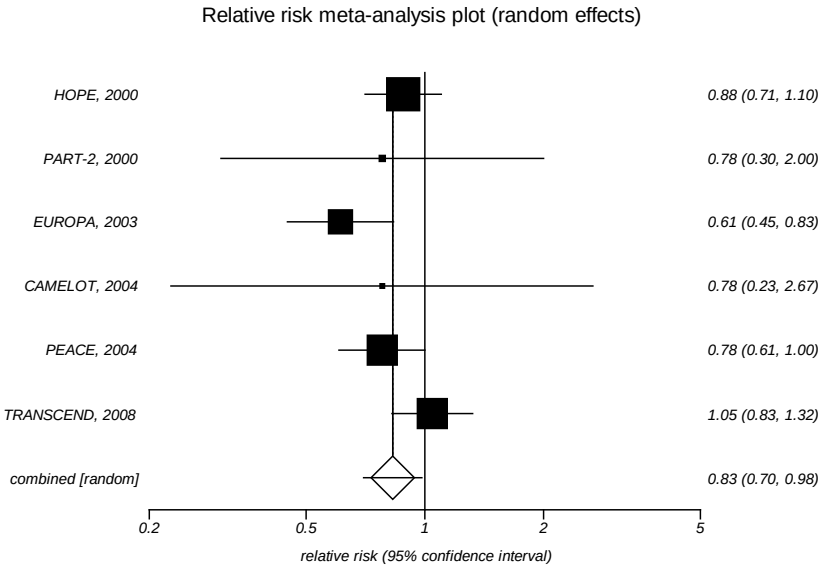


Favors ACEI/ARB Favors CCB

Test for heterogeneity: Cochran Q=2.351502 (df=1) p=0.1252; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

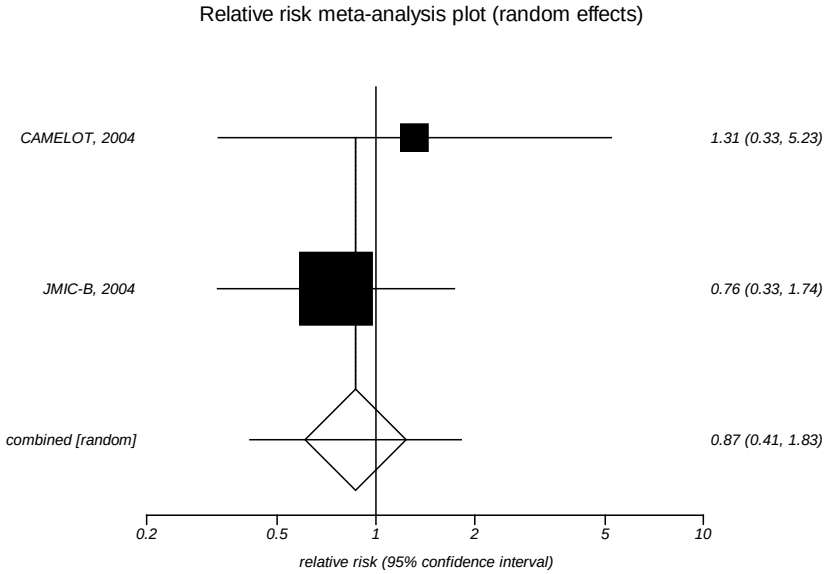
Figure 18. KQ1 Hospitalization for heart failure first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=7.845356 (df=5) p=0.165; I^2 statistic=36.3%

Figure 19. KQ1 Hospitalization for heart failure second base case analysis—Meta-analysis of randomized placebo-controlled trials comparing ACEI or ARB with CCB in patients with stable ischemic heart disease

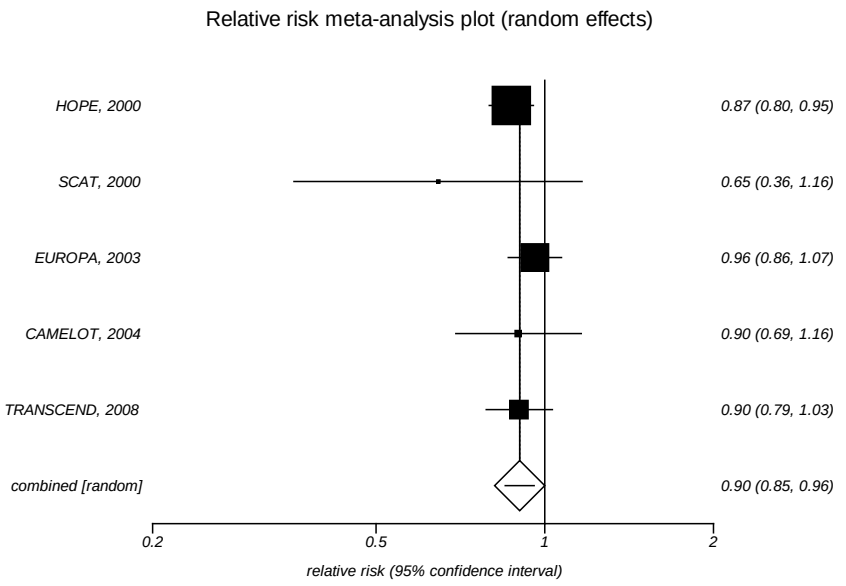


Favors ACEI/ARB Favors CCB

Test for heterogeneity: Cochran Q=0.396129 (df=1) p=0.5291; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

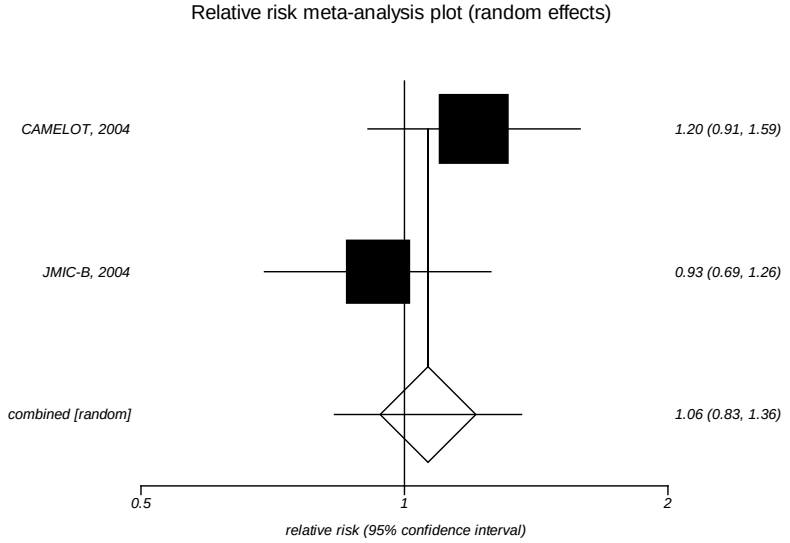
Figure 20. KQ1 Revascularization first base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=2.990188 (df=4) p=0.5595; I^2 statistic=0%

Figure 21. KQ1 Revascularization second base case analysis—Meta-analysis of randomized placebo-controlled trials comparing ACEI or ARB with CCB in patients with stable ischemic heart disease



Favors ACEI/ARB Favors CCB

Test for heterogeneity: Cochran Q=1.455372 (df=1) p=0.2277; I^2 statistic=N/A
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

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?

Key Points

- One multicenter clinical trial is available to assess the comparative effectiveness of the combination of ACE inhibitor plus ARB therapy to ACE inhibitor therapy alone in this population.
- The ACE inhibitor ramipril reduced total mortality similarly to the combination of ACE inhibitor plus ARB.
- The ACE inhibitor ramipril reduced cardiovascular mortality, fatal + nonfatal myocardial infarction, fatal + nonfatal stroke, the composite of the three items, as well as atrial fibrillation similarly to the combination of the two agents.
- The ACE inhibitor ramipril reduced new or worsening angina, hospitalizations due to angina, hospitalizations due to heart failure, and need for a revascularization procedure similarly to the combination of the two agents but quality of life was not assessed.

Detailed Analysis

The randomized, double-blinded, active-controlled Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) was the only trial providing insight into the comparative effectiveness of adding an ACE inhibitor to an ARB versus using an ACE inhibitor or ARB alone in patients with stable vascular disease (coronary, peripheral, or carotid) or diabetes with evidence of end organ damage. This trial was funded by both foundation as well as industry sources.[52]

Study Design and Population Characteristics

Like trials included in Key Question 1, subjects with signs or symptoms of chronic heart failure were excluded from the ONTARGET trial. As a randomized controlled trial, ONTARGET provides more direct evidence of efficacy than effectiveness.[52]

After the run in period, 25,620 patients were recruited from 733 centers around the world (including centers in the United States) and randomly assigned to one of three groups: (1) ramipril 5mg per day initially and increased to 10mg daily after two weeks (ACE inhibitor); (2) telmisartan 80mg daily (ARB); or (3) a combination of the two drugs. Ramipril was the

active comparator to which both the telmisartan and combination ramipril + telmisartan arms were being compared.[52]

The median duration of followup in the ONTARGET trial was 56 months.[52] The three groups were well matched for baseline characteristics. The study population included 27 percent women, 73 percent European, 14 percent Asian, 9 percent Native or aboriginal, 2 percent African, and 1 percent Arab. Overall, 85 percent of patients had cardiovascular disease, 69 percent had hypertension, and 38 percent had diabetes. There was appreciable baseline use of other therapies proven to impact morbidity or mortality in atherosclerotic vascular disease including antiplatelet therapy (81 percent), statin therapy (62 percent), and beta-blocker therapy (57 percent).[52]

Outcome Evidence Evaluations

As seen in Table 8, both combination therapy as well as telmisartan therapy alone provided comparable efficacy when compared to ramipril therapy alone for all of the outcomes of interest we could evaluate. For the endpoint of myocardial infarction, data were only available on the combination of fatal and nonfatal events; thus the intended outcome of nonfatal myocardial infarction could not be evaluated. Similarly, we could not evaluate hospitalizations for any cause but did have comparative data on hospitalizations for heart failure and for angina. Reports of worsening or new angina were compared between groups. No evaluation of patient perceived quality of life was reported.[52]

The primary endpoint of ONTARGET was the composite of cardiovascular mortality, myocardial infarction, stroke, and hospitalization for heart failure. While not listed as an outcome of interest in this Key Question, this composite outcome occurred in 16.5 percent of ramipril patients, 16.3 percent of combination therapy patients [0.99 (0.92 to 1.07) versus ramipril], and 16.7 percent of telmisartan patients [RR 1.01 (0.94 to 1.09) versus ramipril].[52]

Discussion

Given the available evidence, solely from the ONTARGET trial, ACE inhibitors provide similar efficacy as the combination of ACE inhibitors and ARBs. While only one trial provided data for this analysis, it was a large, multicenter, randomized, active controlled trial. The use of a run-in period would typically tend to overemphasize the efficacy by eliminating those less likely to benefit from therapy, but this would have been applied across all treatment groups. Ramipril and/or telmisartan were the only agents to which subjects were randomized in this trial. Ramipril has been used in previous placebo controlled trials including the HOPE trial,[38-40] described in Key Question 1, and was found to be effective at reducing the composite endpoint of interest. Telmisartan appears to reduce blood pressure to the same extent as other ARBs in the class and may be better than losartan, but this was not determined as a result of a systematic review.[99-101] As such, this was a reasonable comparison of an ACE inhibitor to an ARB. Interestingly, patients receiving either telmisartan or the combination telmisartan/ramipril had improved blood pressure lowering as compared with ramipril (although statistical comparisons were not made). However, despite these differences in blood pressure, no differences in clinical outcomes were seen.

In Key Question 1, only the TRANSCEND trial was available to evaluate major efficacy outcomes for ARB therapy versus placebo in patients with stable ischemic heart disease and preserved left ventricular function. Subjects had to be intolerant to ACE inhibitor therapy to be eligible for inclusion in TRANSCEND. As such, the TRANSCEND trial is characteristically

different than the major placebo controlled ACE inhibitor trials. In TRANSCEND, ARB therapy with telmisartan was associated with similar reductions in the composite endpoint of cardiovascular mortality, nonfatal myocardial infarction, and stroke as the pooled results from the HOPE and PEACE trials comparing ACE inhibitors versus placebo (Figure 12, KQ1). While the benefits of ARB therapy in TRANSCEND are driven more by reductions in stroke than cardiovascular mortality, it would be difficult to say that subjects derive differential benefits from ACE inhibitor and ARB therapy. In Key Question 2, there is direct comparative evidence from the ONTARGET trial that ACE inhibitors and ARBs provide similar benefits in major outcomes of interest in this population.

Table 8. KQ2—Results of the ONTARGET Trial comparing an ACE inhibitor to an ARB or to a combination with an ACE inhibitor + ARB[52]

Outcomes	Ramipril (n=8576)	Combination Therapy (n=8502)	Telmisartan (n=8502)	Combination vs. Ramipril	Telmisartan vs. Ramipril
	N (%)			Relative Risk (95% CI)	
Total Mortality	1014 (11.8)	1065 (12.5)	989 (11.6)	1.07 (0.98-1.16)	0.98 (0.90-1.07)
Cardiovascular Mortality	603 (7.0)	620 (7.3)	598 (7.0)	1.04 (0.93-1.17)	1.00 (0.89-1.12)
Myocardial Infarction†	413 (4.8)	438 (5.2)	440 (5.2)	1.08 (0.94-1.23)	1.07 (0.94-1.22)
Stroke†	405 (4.7)	373 (4.4)	369 (4.3)	0.93 (0.81-1.07)	0.91 (0.79-1.05)
Composite*	1210 (14.1)	1200 (14.1)	1190 (13.9)	1.00 (0.93-1.09)	0.99 (0.91-1.07)
New Atrial Fibrillation	570 (6.9)	537 (6.5)	550 (6.7)	0.96 (0.85-1.07)	0.97 (0.86-1.09)
Worsening or New Angina	567 (6.6)	538 (6.3)	536 (6.3)	0.96 (0.85-1.08)	0.95 (0.84-1.07)
Hospitalization for Angina	925 (10.8)	952 (11.2)	954 (11.2)	1.04 (0.95-1.14)	1.04 (0.95-1.14)
Hospitalization for Heart Failure	354 (4.1)	332 (3.9)	394 (4.6)	0.95 (0.82-1.10)	1.12 (0.97-1.29)
Need for Revascularization Procedure	1269 (14.8)	1303 (15.3)	1290 (15.1)	1.04 (0.97-1.13)	1.03 (0.95-1.11)

† Includes both fatal and nonfatal events;* Cardiovascular mortality, myocardial infarction, or stroke
Abbreviations: ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; CI=confidence interval; N=number

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 Points

- For trials to be included, ACE inhibitors or ARBs needed to be started in close proximity to a revascularization procedure.
- Seven small (n=91) to moderate size (n=2553) trials were included.
- ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy significantly increased the need for revascularizations versus placebo.
- ACE inhibitor (cilazapril, ramipril, quinapril) or ARB (candesartan) therapy did not have any significant impact on total mortality versus placebo.
- ACE inhibitor or ARB therapy did not have any significant impact on cardiovascular mortality (ramipril, quinapril, candesartan), nonfatal myocardial infarction (cilazapril, quinapril, candesartan), stroke (ramipril, quinapril), or the composite of the three items (quinapril) versus placebo.
- ACE inhibitor therapy (quinapril) did not have any significant impact on new onset atrial fibrillation versus placebo and ARB therapy was not evaluated.
- ACE inhibitor (ramipril, quinapril) did not have any significant impact on hospitalization for angina, or hospitalization for heart failure versus placebo and ARB therapy was not evaluated.
- ACE inhibitor or ARB therapy was not evaluated for impact on quality of life.

Detailed Analysis

Study Design and Population Characteristics

Trials included in this section are characteristically different from those included in Key Question 1 because experimental therapy with ACE inhibitors or ARBs were given in close proximity to a revascularization procedure to determine the impact of therapy on outcomes of interest (Tables 9-12). Revascularization procedures could include percutaneous coronary intervention (coronary angioplasty with or without stenting or arthrectomy) or coronary artery bypass graft surgery. Seven trials met our inclusion criteria;[53-59] six were placebo controlled,[53,54,56-59] and one was open label.[55] No direct comparative trials were included

although standard medical therapy for ischemic heart disease was applied to experimental and control groups in all studies. Two of the trials were foundation funded,[54,56] five of the trials were industry funded,[53,56-59] and the Kondo, et al study did not report their funding source.[55] It should be noted that two of the trials, APRES and QUIET, were funded by both foundation and industry funding sources.[54,56]

Two of the seven trials were conducted, in part, in the United States.[53,57] The average LVEF was reported in four of seven trials.[54,56,57,59] With the exception of the APRES trial,[54] where the LVEF was approximately 42 percent, LVEFs were close to 60 percent. Three trials did not provide average LVEF data, although they did exclude patients with signs or symptoms of heart failure.[53,55,58] Four of the seven included trials had 6 months of followup[53,55,56,58] while the other three trials had mean followup periods between 2.3 and 3.0 years.[54,57,59] Quinapril was the ACE inhibitor used in four of seven trials[55-57,59] with cilazapril[53] and ramipril[54] being used in two other studies. Candesartan was the only ARB evaluated for this indication.[58] Males constituted 76-91 percent of the total number of subjects in six of these trials, with the MARCATOR trial not reporting data on gender.[53] Ethnicity was only reported in the QUIET[57] and IMAGINE[59] trials, with Caucasian subjects accounting for 94 percent and 96 percent of the total, respectively. However, the Kondo trial[55] was conducted in Japan and likely had a high Asian population. Baseline blood pressures were well controlled in the three trials where it was determined with mean readings ranging from 121 to 130mmHg systolic and 70 to 79mmHg diastolic.[54,57,59]

Only three of the trials included in this Key Question reported the percentage of patients receiving standard medical therapies at baseline.[54,57,58] The APRES trial reported 30 percent use of beta blockers, 100 percent use of aspirin and 26 to 34 percent use of statins.[54] The QUIET study reported 25 to 27 percent use of beta blockers, 71 to 74 percent use of aspirin, 0.1 percent use of lipid lowering therapy (one patient in each group), and 41 to 42 percent use of nitrates.[57] In addition, the AACHEN study reported 46 to 54 percent use of statins.[58]

Outcome Evidence Evaluations

Total Mortality

Total mortality was rarely experienced in the seven included trials (128 total deaths in 6208 total subjects; 2.1 percent).[53-59] We conducted seven different analyses to discern the impact of ACE inhibitor (cilazapril, ramipril, quinipril) or ARB (candesartan) therapy on total mortality in this population.

The six trials included into our base case analysis were randomized, placebo-controlled trials evaluating the impact of ACE inhibitors or ARBs on total mortality in patients who initiated their therapy in close proximity to a revascularization procedure.[53,54,56-59] Therapy with ACE inhibitors (cilazapril, ramipril, quinipril) or the ARB candesartan did not impact total mortality versus placebo [RR 0.94 (0.67 to 1.34)](Appendix Table 12 and Figure 22). Statistical heterogeneity was not seen (I^2 = 0 percent), and publication bias was not expected (Egger's p=0.75; no imputed studies via Trim and Fill).

When inclusion was restricted to the five randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (cilazapril, ramipril, quinipril) on total mortality in patients who initiated their therapy in close proximity to a revascularization procedure, no significant effect was seen [RR 0.94 (0.66 to 1.34)](Appendix Figure 19).[53,54,56,57,59] When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact

of an ARB (candesartan) on total mortality in patients who initiated their therapy in close proximity to a revascularization procedure, no significant effect was seen [RR 0.91 (0.02 to 44.90)].[58]

In order to assess the impact of study quality on results, inclusion was broadened to include a combined total of seven open label or placebo-controlled trials evaluating the impact of ACE inhibitor (cilazapril, ramipril, quinipril) or ARB (candesartan) therapy on total mortality in patients who initiated their therapy in close proximity to a revascularization procedure; no significant effect was seen [RR 0.95 (0.67 to 1.34)](Appendix Figure 20).[53-59] When inclusion was restricted to the five randomized, placebo-controlled trials that utilized ITT methodologies, similar results to the base-case analysis were seen [RR 0.94 (0.66 to 1.34)](Appendix Figure 21).[53,54,56,57,59]

When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) or ARB (none evaluated) therapy on total mortality in patients who initiated their therapy in close proximity to coronary artery bypass grafting surgery, no significant effect was seen [RR 0.99 (0.59 to 1.67)].[59] When inclusion was restricted to the four randomized, placebo-controlled trials evaluating the impact of ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy on total mortality in patients who initiated their therapy in close proximity to a percutaneous coronary intervention, no significant effect was seen [RR 1.04 (0.63 to 1.72)](Appendix Figure 22).[53,56-58]

Cardiovascular Mortality

Cardiovascular mortality was rarely experienced in the six trials reporting results for this endpoint (69 cardiovascular deaths in 4772 subjects; 1.4 percent).[54-59] We conducted seven different analyses to discern the impact of ACE inhibitor (ramipril, quinipril) or ARB (candesartan) therapy on cardiovascular mortality in this population.

The five trials included into our base case analysis were randomized, placebo-controlled trials evaluating the impact of ACE inhibitor (ramipril, quinipril) or ARB (candesartan) therapy on cardiovascular mortality in patients who initiated their therapy in close proximity to a revascularization procedure.[54,56-59] Therapy with ACE inhibitors or ARBs did not impact cardiovascular mortality versus placebo [RR 0.91 (0.53 to 1.57)](Appendix Table 13 and Figure 23). Statistical heterogeneity was low (I^2 = 8.1 percent) and publication bias was not expected (Eggers p=0.40; no imputed studies via Trim and Fill).

When inclusion was restricted to the four randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (ramipril, quinipril) on cardiovascular mortality in patients who initiated their therapy in close proximity to a revascularization procedure, no significant effect was seen [RR 0.85 (0.43 to 1.69)](Appendix Figure 23).[54,56,57,59] Moderate statistical heterogeneity was seen (I^2 = 31.1 percent). Three[56,57,59] of the four trials showed a consistent lack of effect with the exception of the APRES trial[54] which showed a significant reduction in cardiovascular mortality with ACE inhibitor (ramipril) therapy. When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of an ARB (candesartan) on cardiovascular mortality in patients who initiated their therapy in close proximity to a revascularization procedure, no significant effect was seen [RR 0.91 (0.02 to 44.90)].[58]

In order to assess the impact of study quality on results, inclusion was broadened to include a combined total of six open label or placebo-controlled trials evaluating the impact of ACE inhibitor (ramipril, quinipril) or ARB (candesartan) therapy on cardiovascular mortality in

patients who initiated their therapy in close proximity to a revascularization procedure, no significant effect was seen [RR 0.94 (0.58 to 1.52)](Appendix Figure 24).[54-59] When inclusion was restricted to the four randomized, placebo-controlled trials that utilized ITT methodologies, similar results to the base-case analysis were seen [RR 0.85 (0.43 to 1.69](Appendix Figure 25).[54,56,57,59]

When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) or ARB (none evaluated) therapy on cardiovascular mortality in patients who initiated their therapy in close proximity to coronary artery bypass grafting surgery, no significant effect was seen [RR 1.19 (0.60 to 2.36)].[59] When inclusion was restricted to the three randomized, placebo-controlled trials evaluating the impact of ACE inhibitor (quinapril) or ARB (candesartan) therapy on cardiovascular mortality in patients who initiated their therapy in close proximity to a percutaneous coronary intervention, no significant effect was seen [RR 0.92 (0.45 to 1.90)](Appendix Figure 26).[56-58]

Nonfatal Myocardial Infarction

Nonfatal myocardial infarction was rarely experienced in the five trials reporting this endpoint (152 total nonfatal myocardial infarctions in 5950 total subjects; 2.6 percent).[53,56-59] We conducted seven different analyses to discern the impact of ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy on nonfatal myocardial infarction in this population.

The five trials included into our base case analysis were randomized, placebo-controlled trials evaluating the impact of ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy on nonfatal myocardial infarction in patients who initiated their therapy in close proximity to a revascularization procedure.[53,56-59] Therapy with ACE inhibitors or ARBs did not significantly impact nonfatal myocardial infarction versus placebo [RR 0.89 (0.65 to 1.24)](Appendix Table 14 and Figure 24). Statistical heterogeneity was not seen (I^2 = 0 percent) and publication bias was not expected (Egger's p=0.75, no imputed studies via Trim and Fill).

When inclusion was restricted to the four randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (cilazapril, quinapril) on nonfatal myocardial infarction in patients who initiated their therapy in close proximity to a revascularization procedure, no significant effect was seen [RR 0.90 (0.65 to 1.26)](Appendix Figure 27).[53,56,57,59] When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of an ARB (candesartan) on nonfatal myocardial infarction in patients who initiated their therapy in close proximity to a revascularization procedure, no significant effect was seen [RR 0.45 (0.04 to 4.86)].[58]

In order to assess the impact of study quality on results, inclusion was broadened to include both open label and placebo-controlled trials evaluating the impact of ACE inhibitors or ARBs on nonfatal myocardial infarction in patients who initiated their therapy in close proximity to a revascularization procedure. Since no open label trials reported on nonfatal myocardial infarction, this analysis included the same trials and had the same results as the base case analysis (Appendix Figure 28).[53,59-59] When inclusion was restricted to the three randomized, placebo-controlled trials that utilized ITT methodologies, similar results to the base-case analysis were seen [RR 0.90 (0.65 to 1.26)](Appendix Figure 29).[53,56,57,59]

When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) or ARB (none evaluated) therapy on nonfatal myocardial infarction in patients who initiated their therapy in close proximity to coronary artery bypass grafting surgery, no significant effect was seen [RR 0.76 (0.40 to 1.45)].[59] When

inclusion was restricted to the four randomized, placebo-controlled trials evaluating the impact of ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy on nonfatal myocardial infarction in patients who initiated their therapy in close proximity to a percutaneous coronary intervention, no significant effect was seen [RR 0.94 (0.65 to 1.37)](Appendix Figure 30).[53,56-58]

Stroke

Stroke was only reported in two of the seven trials and rarely occurred (30 total strokes in 2712 subjects; 1.1 percent).[54,59] While the key question focused on nonfatal stroke, the APRES trial (ramipril) only reported fatal stroke and the IMAGINE trial (quinapril) did not define stroke suggesting that fatal + nonfatal stroke was included.

Both trials were included into our base case analysis and were randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (ramipril, quinapril) or ARBs (none included) on stroke in patients who initiated their therapy in close proximity to a revascularization procedure.[54,59] Therapy with ACE inhibitors did not impact stroke versus placebo [RR 1.01 (0.50 to 2.04)](Appendix Table 15 and Figure 25). Because of the low number of included studies, statistical heterogeneity and publication bias could not be determined.

When inclusion was restricted to the two randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (ramipril, quinapril) on stroke in patients who initiated their therapy in close proximity to a revascularization procedure, results were the same as in the base case analysis (Appendix Figure 31).[54,59] No trials were conducted evaluating the impact of an ARB on stroke in patients who initiated their therapy in close proximity to a revascularization procedure.

When assessing the impact of study quality on results, results were the same as the base case when including open label trials, and those utilizing ITT methodologies (the same studies were used in each analysis)(Appendix Figures 32-33).[54,59]

When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) or ARB (none evaluated) therapy on stroke in patients who initiated their therapy in close proximity to coronary artery bypass grafting surgery, no significant effect was seen [RR 0.99 (0.59 to 1.67)].[59] Because no trials evaluated the impact of ACE inhibitor or ARB therapy on stroke in patients who initiated their therapy in close proximity to a percutaneous coronary intervention, this outcome could not be assessed.

Composite of Cardiovascular Mortality, Myocardial Infarction, and Stroke

Only the IMAGINE trial provided data on this composite endpoint, which occurred in 90 of 2553 subjects (3.5 percent).[59] ACE inhibitor therapy with quinapril did not significantly impact the composite endpoint in this randomized, placebo-controlled trial [RR 0.99 (0.66 to 1.49)](Appendix Table 16).[59]

Atrial Fibrillation

Only the IMAGINE trial provided data on new onset atrial fibrillation, which occurred in 215 of 2553 subjects (8.4 percent).[59] ACE inhibitor therapy with quinapril did not significantly impact new onset atrial fibrillation in this randomized, placebo-controlled trial [RR 1.12 (0.87 - 1.45)] (Appendix Table 17).[59]

Angina Symptoms/Hospitalizations

None of the eligible trials reported the impact of ACE inhibitor or ARB therapy on time to onset of ischemic symptoms via treadmill exercise test or total hospitalizations.

Hospitalization for Angina

Three trials evaluated the impact of ACE inhibitor or ARB therapy on hospitalization for angina, which occurred in 201 of 4462 subjects (4.5 percent).[54,57,59]

All three trials were included into our base case analysis.[54,57,59] They were randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (ramipril, quinapril) or ARBs (none evaluated) on hospitalization for angina in patients who initiated their therapy in close proximity to a revascularization procedure. Therapy with ACE inhibitors did not impact hospitalization for angina versus placebo [RR 1.02 (0.78 to 1.34)](Appendix Table 18 and Figure 26). Statistical heterogeneity was not seen (I^2 = 0 percent) and publication bias could not be determined due to the low number of studies.

When inclusion was restricted to randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (ramipril, quinapril) on hospitalization for angina in patients who initiated their therapy in close proximity to a revascularization procedure, results were the same as in the base case analysis.(Appendix Figure 34).[54,57,59] No trials were conducted evaluating the impact of an ARB on hospitalization for angina in patients who initiated their therapy in close proximity to a revascularization procedure.

When assessing the impact of study quality on this outcome, results were the same as the base case when including open label trials, and those utilizing ITT methodologies (the same studies were used in each analysis)(Appendix Figures 35-36).[54,57,59]

When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) or ARB (none evaluated) therapy on hospitalization for angina in patients who initiated their therapy in close proximity to coronary artery bypass grafting surgery, no significant effect was seen [RR 1.18 (0.77 to 1.80)].[59] When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitors (quinapril) or ARBs (none evaluated) on hospitalization for angina in patients who initiated their therapy in close proximity to a percutaneous coronary intervention, no significant effect was seen [0.86 (0.58 to 1.27)].[57]

Hospitalization for Heart Failure

Two trials evaluated the impact of ACE inhibitor or ARB therapy on hospitalization for heart failure, which occurred in 36 of 2712 subjects (1.3 percent).[54,59]

Both were randomized, placebo-controlled trials that evaluated ACE inhibitors (quinapril, ramipril) and were included into our base case analysis.[54,59] No trials were conducted evaluating the impact of an ARB on hospitalization for heart failure in patients who initiated their therapy in close proximity to a revascularization procedure. Therapy with ACE inhibitors did not impact hospitalization for heart failure versus placebo [RR 0.85 (0.38 to 1.92](Figure 27). Due to the low number of studies, heterogeneity and publication bias could not be determined.

When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) or ARB (none evaluated) therapy on hospitalization for heart failure in patients who initiated their therapy in close proximity to coronary artery bypass grafting surgery, no significant effect was seen [RR 1.07 (0.52 to 2.20)].[59] No trials were included that evaluated the impact of ACE inhibitors or ARBs on hospitalization

for heart failure in patients who initiated their therapy in close proximity to a percutaneous coronary intervention.

When assessing the impact of study quality on this outcome, results were the same as the base case when including open label trials, and those utilizing ITT methodologies (the same studies were used in each analysis as in the base case).[54,59]

Need for Subsequent Revascularization

Five of the seven trials reported the need for a subsequent revascularization procedure during the followup period, which occurred in 836 of 5950 subjects (14.1 percent).[53,56-59] While not directly related to symptom reporting or hospitalization rates, need for subsequent revascularization is tangentially related because: (1) these procedures can occur because of residual or new symptoms of angina either at the lesion that underwent revascularization or another vessel; and (2) these procedures require hospitalization. The QUIET trial[57] reported data on coronary angioplasty and CABG separately, however no aggregate data for total revascularizations was provided. Thus, this study was not included in any base case analysis, but was included in the corresponding subgroup analyses.[57] We conducted seven different analyses to discern the impact of ACE inhibitor or ARB therapy on the need for a subsequent revascularization procedure in this population.

The four trials included into our base case analysis were randomized, placebo-controlled trials evaluating the impact of ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy on the need for subsequent revascularization in patients who initiated their therapy in close proximity to a revascularization procedure.[53,56,58,59] Therapy with ACE inhibitors or ARBs significantly increased the need for subsequent revascularization versus placebo [RR 1.28 (1.03 to 1.59)](Appendix Table 20 and Figure 28). Statistical heterogeneity was not seen ($I^2 = 0$ percent) and publication bias was unlikely (Eggers p=0.85, 1 study was imputed via Trim and Fill with no difference in outcome [RR 1.29 (1.04 to 1.59)]).

When inclusion was restricted to the three randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (cilazapril, quinapril) on the need for subsequent revascularization in patients who initiated their therapy in close proximity to a revascularization procedure, a significant increase was also seen [RR 1.29 (1.03 to 1.60)](Appendix Figure 37).[53,57,59] When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of an ARB (candesartan) on the need for subsequent revascularization in patients who initiated their therapy in close proximity to a revascularization procedure, no significant effect was seen [RR 1.13 (0.32 to 4.01)].[58]

In order to assess the impact of study quality on results, inclusion was broadened to include open label or placebo-controlled trials evaluating the impact of ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy on the need for subsequent revascularization in patients who initiated their therapy in close proximity to a revascularization procedure. The same four trials included in the base case analysis were evaluated, with the same results seen (Appendix Figure 38).[53,56,58,59] When inclusion was restricted to the three randomized, placebo-controlled trials that utilized ITT methodologies, similar results to the base-case analysis were seen [RR 1.29 (1.03 to 1.60)](Appendix Figure 39).[53,56,59]

When inclusion was restricted to the four randomized, placebo-controlled trials (including the QUIET trial[57]) evaluating the impact of ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy on the need for subsequent revascularization in patients who initiated their therapy in close proximity to a percutaneous coronary intervention, no significant effect

was seen [RR 1.08 (0.88 to 1.32)](Appendix Figure 40).[53,56-58] When inclusion was restricted to the two randomized, placebo-controlled trials (including the QUIET trial[57]) evaluating the impact of ACE inhibitor (quinapril) or ARB (none evaluated) therapy on the need for subsequent revascularization in patients who initiated their therapy in close proximity to coronary artery bypass grafting surgery, no significant effect was seen [RR 1.15 (0.93 to 1.42)](Appendix Figure 41).[57,59]

Quality of Life

None of the eligible trials reported the impact of ACE inhibitor or ARB therapy on quality of life.

Discussion

In Key Question 3, the addition of ACE inhibitors or ARBs to standard medical therapy in close proximity to a revascularization procedure were compared to standard medical therapy alone or with placebo in addition to standard medical therapy. For our base case analysis, we limited the trials to those that were randomized and double-blinded comparisons of ACE inhibitors or ARBs to placebo. No active comparator trials were available and thus placebo-controlled trials represented the strongest trials available to answer the questions. Where we could ascertain ethnicity and gender, this body of literature was generally limited to males and Caucasians although one study was conducted in Japan.

ACE inhibitors or ARBs did not significantly impact any of the endpoints evaluated, except for increasing the need for subsequent revascularization versus placebo. However, with the exception of the "need for subsequent revascularization" endpoint, the incidence rates for the endpoints were low. Thus, larger studies are needed in this population to truly determine the impact on results. In addition, a number of the trials were of relatively short duration (e.g. 6 months) which may be too short to demonstrate a benefit. The clinical trials in Key Question 1 showing benefits of ACE inhibitors on clinical outcomes (including HOPE and EUROPA) ranged from 4-5 years of followup. As such, future studies should include not only larger patient numbers but also longer durations of followup.

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, 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 a patient with ischemic heart disease derives benefits from these agents? A majority of the studies included in Key Question 1, including HOPE, PEACE, and EUROPA, included patients that 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 thus more concrete interpretations cannot be made until this evidence becomes available.

Table 9. KQ3—Quality of randomized controlled trials

Study, year	Randomized	Randomization Adequate	Double-Blinded	Double-Blinding Adequate	Intention-to-Treat
MARCATOR, 1995[53]	Yes	NR	Yes	Yes	Yes
APRES, 2000[54]	Yes	Yes	Yes	Yes	Yes
Kondo et al, 2001[55]	Yes	NR	No	N/A	NR
PARIS, 2001[56]	Yes	NR	Yes	Yes	Yes
QUIET, 2001[57]	Yes	Yes	Yes	Yes	Yes
AACHEN, 2006[58]	Yes	NR	Yes	NR	NR
IMAGINE, 2008[59]	Yes	Yes	Yes	NR	Yes

Abbreviations: N/A = Not applicable; NR = Not reported

Table 10. KQ3—Study design characteristics and population

Study, year	Study Design	Country	Study Funding	Duration of Follow-up	Inclusion Criteria	Exclusion Criteria
MARCATOR, 1995[53]	RCT	United States, Canada	Industry	6 months	Patients aged 25-80 years old undergoing coronary angioplasty	History of a recent MI (5 days), severe valve disease, severe hypertension, prior revascularization procedure, recent ACEI treatment
APRES, 2000[54]	RCT	Denmark	Industry, Foundation	2.8 years	Patients undergoing coronary angiography aged 18 to 75 years, had no prior cardiac surgery, had LVEF between 0.30 and 0.50 as determined by ventriculography or echocardiography and were referred for invasive revascularization with CABG or PTCA for angina pectoris after coronary angiography and clinical evaluation	History of recent AMI (3 months) and/or clinical HF, i.e., history of dyspnea relieved by diuretic therapy, ongoing ACEI treatment due to evidenced indications, concomitant valvular disease or geographic restrictions to complete followup, participation in another investigational drug trial, known intolerance to ACEI therapy, childbearing potential and medical conditions (including periprocedural complications) that could have major influence on outcome or known to contraindicate use of the test drug.
Kondo et al, 2001[55]	RCT	Japan	NR	6 months	All patients had functionally significant narrowing in the major coronary arteries, as demonstrated angiographically, and had received elective balloon angioplasty followed by coronary stenting	Patients with renal or liver diseases by standard laboratory screen, unsatisfactory stent implantation, patients with signs/symptoms of heart failure[†]
PARIS, 2001[56]	RCT	France	Industry, Foundation	6 months	PCI with successfully implanted NIR stent	Age ≥75 years, women of childbearing potential, acute myocardial infarction within 48 h before stent implantation, SBP<120 mmHg, needed ACEI or ARB treatment, renal or hepatic impairment, history of bleeding, contraindication to aspirin or ticlopidine, angioplasty of a saphenous-vein-graft lesion, or were participating in another study
QUIET, 2001[57]	RCT	Europe, North America	Industry	2.3 years	Age 18 to 75 years, had undergone successful coronary angioplasty or atherectomy at baseline, and had at least 1 coronary artery that had not been subjected to mechanical revascularization	LDL>165 mg/dl, CABG surgery, SBP<100 mmHg or >160 mmHg and/or DBP>100 mmHg; LVEF<40%; MI within 7 days; prior angioplasty within 3 months; and those receiving lipid-lowering medications, ACEI inhibitors, or CCBs

Table 10 Continued. KQ3 - Study Design Characteristics & Population

Study, year	Study Design	Country	Study Funding	Duration of Follow-up	Inclusion Criteria	Exclusion Criteria
AACHEN, 2006[58]	RCT	Germany	Industry	6 months	Males and females aged >18 years; angina pectoris and/or target vessel–related ischemia documented by noninvasive stress testing; angiographically documented coronary stenosis (N50% diameter stenosis) in native vessels; de novo lesions (type A/B according to AHA/ACC classification); eligibility of the coronary stenosis for elective stent implantation; suitability for emergency CABG; suitability for therapy with an ARB; and written informed consent. Patients were begun 7-14 days prior to intervention	Severe organic risk factors; type 1 DM; unstable angina pectoris (Braunwald class ≥Ib); de novo coronary lesions type C (AHA/ACC classification); AMI <4 weeks before randomization; clinically relevant hypotension <100 mm Hg; LVEF<30%; implantation of coil stents or self-expandable stents (wall stents); lesion length N20 mm; contraindication for candesartan cilexetil, or aspirin, or clopidogrel; therapy with ACEI or ARB (after randomization); increased risk for bleeding, thrombocytopenia, thrombocytopathy; aggressive diuretic therapy; pregnancy or the possibility to get pregnant; breastfeeding; drug/alcohol abuse; reasons that make follow-up or control angiography unlikely or impossible; known or expected poor compliance; and participation in a clinical investigation within 30 days before trial enrolment

Table 10 Continued. KQ3—Study design characteristics and population

Study, year	Study Design	Country	Study Funding	Duration of Follow-up	Inclusion Criteria	Exclusion Criteria
IMAGINE, 2008[59]	RCT	Europe, Canada	Industry	3 years	≤ 7days (10days in France) Post-CABG, Stable after operation (as per investigator judgment) Still in hospital, ≥18 y old, LVEF>40% determined within 6 mo before surgery	Intolerance/contraindication to ACEI or history of angioedema Insulin-dependent DM, or type II DM with microalbuminuria Clinical need for an ACEI or an ARB (investigators' judgment) Current need for post-CABG urgent intervention Valve replacement, not repair, during index CABG Significant valve stenosis or cardiomyopathy Serum K>5.6 mmol/L Primary hyperaldosteronism Scr>2.26 mg/dL (200 mol/L), suspected renal artery, stenosis, single-kidney, or renal transplant, serious concomitant disease, such as cancer, AIDS, or sepsis SBP 160 mm Hg or DBP<90 mm Hg despite treatment SBP<100 mm Hg Significant perioperative myocardial infarction, defined as creatine kinase isoform MB 100 U/L (or 75 g/L), troponin I 20 g/L, or troponin T 15 g/L; or new Q waves or LBBB with corresponding wall-motion abnormality; or prolonged postoperative hypotension (48 h) requiring intravenous inotropic support Pregnancy, breastfeeding, or inadequate contraception; Drug abuse, alcohol abuse, or inability to adhere to protocol

† Heart failure exclusion was not included in the main manuscript, and was provided by a personal communication with the corresponding author

Abbreviations: ACC=American College of Cardiology; ACEI=angiotensin converting enzyme inhibitor; AHA=American Heart Association; AMI=acute myocardial infarction; ARB=angiotensin receptor blocker; CABG=coronary artery bypass grafting; CCB=calcium channel blocker; DBP=diastolic blood pressure; DM=diabetes mellitus; HF=heart failure; LBBB=left bundle branch block; LDL=low-density lipoprotein; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NR=not reported; PCI=percutaneous coronary intervention; PTCA=percutaneous transluminal coronary angioplasty; RCT=randomized controlled trial; SBP=systolic blood pressure; Scr=serum creatinine

Table 11. KQ3—Initial and target dosing regimens

Study, year	Group	Initial Dose	Target Dose
MARCATOR, 199553	Cilazapril Placebo	1mg on the first evening, then 2mg/d (divided twice daily) or 2.5mg on the first evening followed by 10-20mg/d (divided twice daily)	20mg/d
APRES, 200054	Ramipril Placebo	2.5mg X 1 dose, then 5mg/d X 1 month, then 10mg/d	10mg/d
Kondo et al, 200155	Quinapril Control	10-20mg/d	20mg/d
PARIS, 200156	Quinapril Placebo	20mg X 1 dose, then 40mg/d	40mg/d
QUIET, 200157	Quinapril Placebo	10mg X 1 dose, then 20mg/d	20mg/d
AACHEN, 200658	Candesartan Placebo	32mg/d	32mg/d
IMAGINE, 200859	Quinapril Placebo	10-20mg/d (according to investigator), then increased to 40mg/d if tolerated	40 mg/d

Table 12. KQ3—Baseline characteristics

Study, year	Group	Ave Age (SD)	Male (%)	Ave LVEF % (SD)	Clinical History (%)											
					CAD	MI	CABG	PCI-PTCA	Stable Angina	Unstable Angina	Stroke or TIA	PVD	DM	HTN	RI	**LVH**
MARCATOR, 1995[53]	Cilazapril 20mg/d Placebo		80 83			45 48							15 12			
APRES, 2000[54]	Ramipril 10mg/d Placebo	61 61	88 90	41 43		76 77							9 9	25 29		
Kondo et al, 2001[55]	Quinapril 20mg/d Control	66 (9) 64 (9)	80 76			63 46							18 24	35 30		
PARIS, 2001[56]	Quinapril 40mg/d Placebo	58 (11) 59 (10)	91 80	63 (9) 65 (11)		57 40			100 100	20 33			20 11	37 60		
QUIET, 2001[57]	Quinapril 20mg/d Placebo	58 58	82 81	59 59		47 52							14 16	48 47		
AACHEN, 2006[58]	Candesartan 32mg/d Placebo	61 (9) 61 (9)	83 82			29 30							19 28	78 77		
IMAGINE, 2008[59]	Quinapril 40 mg/d Placebo	61 (10) 61 (10)	87 87	60 (10) 60 (10)		39 40	3 2	18 18			2 2		9 10	47 47		

Abbreviations: CABG=coronary artery bypass grafting; CAD=coronary artery disease; DM=diabetes mellitus; HTN=hypertension; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy; MI=myocardial infarction; PCI=percutaneous coronary intervention; PTCA=percutaneous transluminal coronary angioplasty; PVD=peripheral vascular disease; RI=renal insufficiency; SD=standard deviation; TIA=transient ischemic attack

Table 12 Continued. KQ3—Baseline characteristics

Study, year	Group	SBP mmHg (SD)	DBP mmHg (SD)	BMI (kg/m^2)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	Serum Creatinine (mg/dL)	Serum Potassium (mmol/L)
MARCATOR, 1995[53]	Cilazapril 20mg/d Placebo										
APRES, 2000[54]	Ramipril 10mg/d Placebo	129 130	79 78	27 27	246 254						
Kondo et al, 2001[55]	Quinapril 20mg/d Control			23 (3) 24 (3)							
PARIS, 2001[56]	Quinapril 40mg/d Placebo										
QUIET, 2001[57]	Quinapril 20mg/d Placebo	123 123	74 74		194 194	124 124	37 37	167 167		1.3 1.3	4.2 4.2
AACHEN, 2006[58]	Candesartan 32mg/d Placebo			28 (4) 29 (4)							
IMAGINE, 2008[59]	Quinapril 40 mg/d Placebo	122 (14) 121 (14)	70 (9) 70 (9)		188 (45) 188 (44)	111 (39) 111 (39)	43 (11) 44 (15)	163 (93) 167 (89)		1 (0.3) 1 (0.2)	

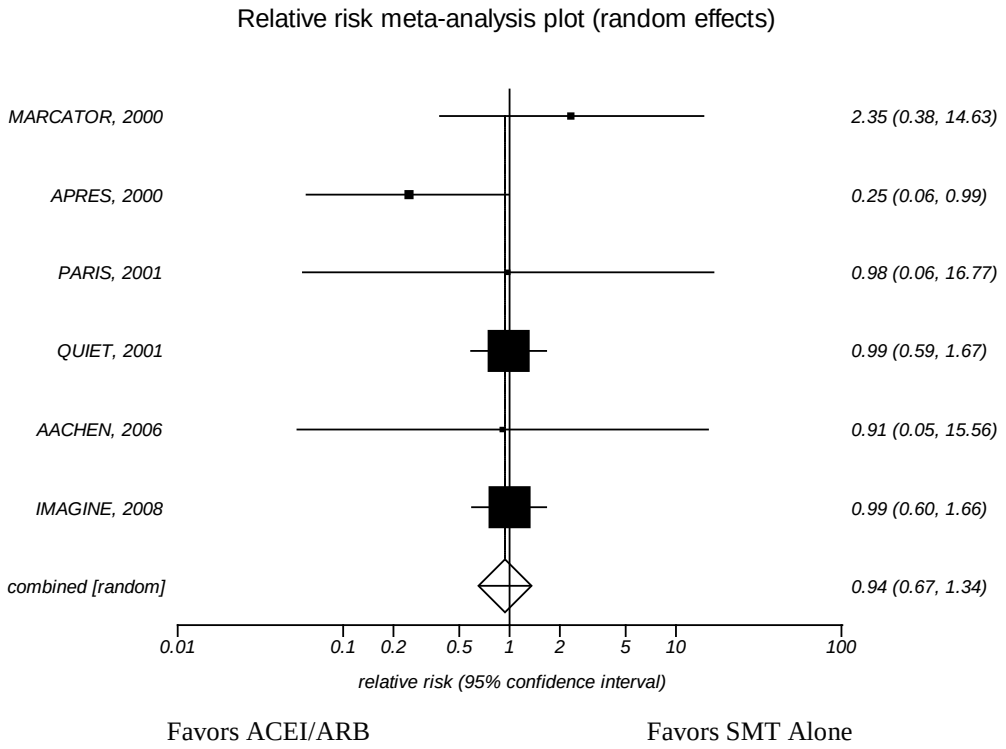
Abbreviations: BMI=body mass index; DBP=diastolic blood pressure; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SBP=systolic blood pressure; SD=standard deviation; TC=total cholesterol; TG=triglycerides

Table 13. KQ3—Baseline medical therapies

Study, year	Group	BB	CCB	ASA	Clopidogrel or Ticlopidine	Antiplatelet	Diuretic	Nitrate	Statin	Lipid Lowering	Digitalis
MARCATOR, 1995[53]	Cilazapril 20mg/d Placebo										
APRES, 2000[54]	Ramipril 10mg/d Placebo	31 29		100 100			20		26 34		
Kondo et al, 2001[55]	Quinapril 20mg/d Control										
PARIS, 2001[56]	Quinapril 40mg/d Placebo										
QUIET, 2001[57]	Quinapril 20mg/d Placebo	27 25	0 0	74 71				42 41		0.1 0.1	
AACHEN, 2006[58]	Candesartan 32mg/d Placebo								54 46		
IMAGINE, 2008[59]	Quinapril 40 mg/d Placebo										

Abbreviations: ASA=aspirin; BB=beta-blocker; CCB=calcium channel blocker

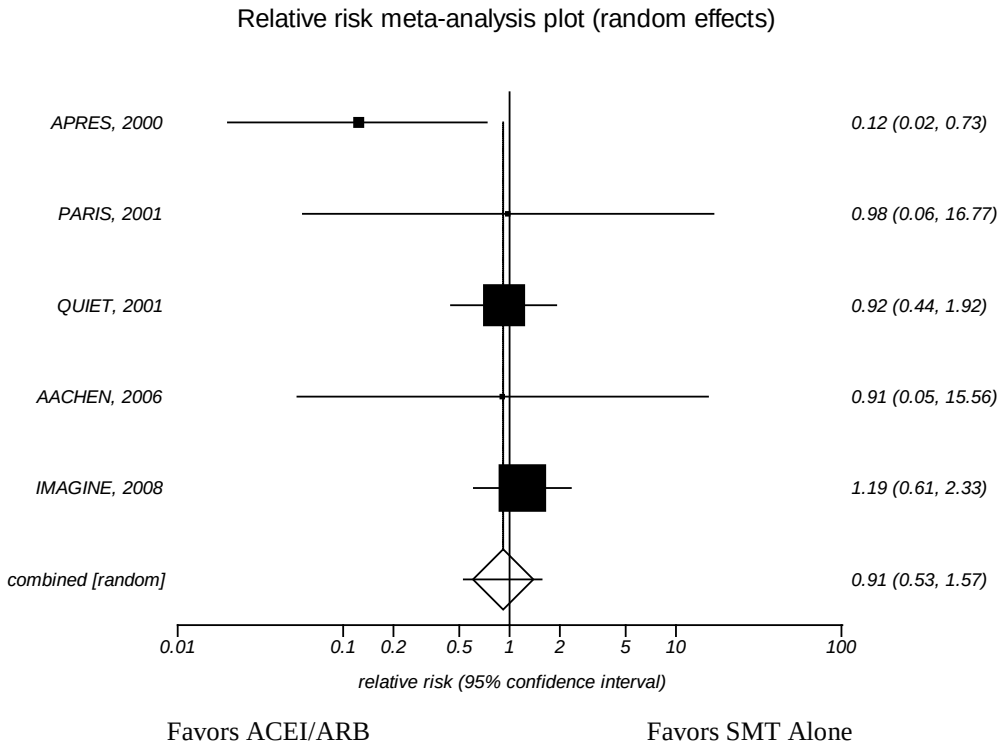
Figure 22. KQ3 Total mortality base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease who have recently undergone, or are set to undergo, a coronary revascularization procedure



Test for heterogeneity: Cochran Q=3.810441 (df=5) p=0.577; I^2 statistic=0%

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

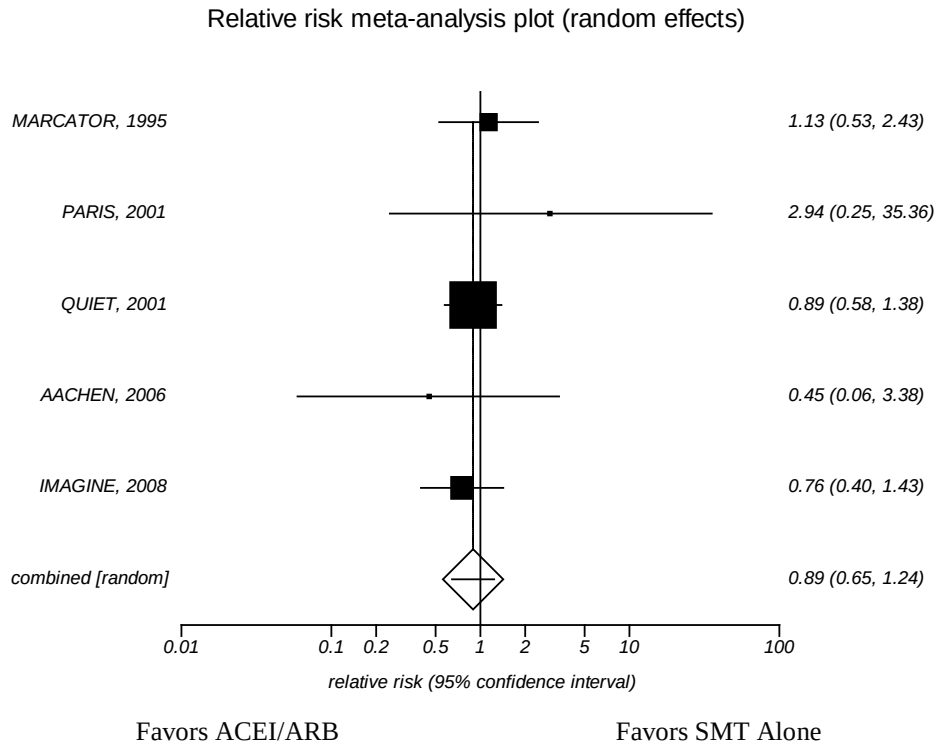
Figure 23. KQ3 Cardiovascular mortality base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease who have recently undergone, or are set to undergo, a coronary revascularization procedure



Test for heterogeneity: Cochran Q=4.350395 (df=4) p=0.3607; I^2 statistic=8.1%

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

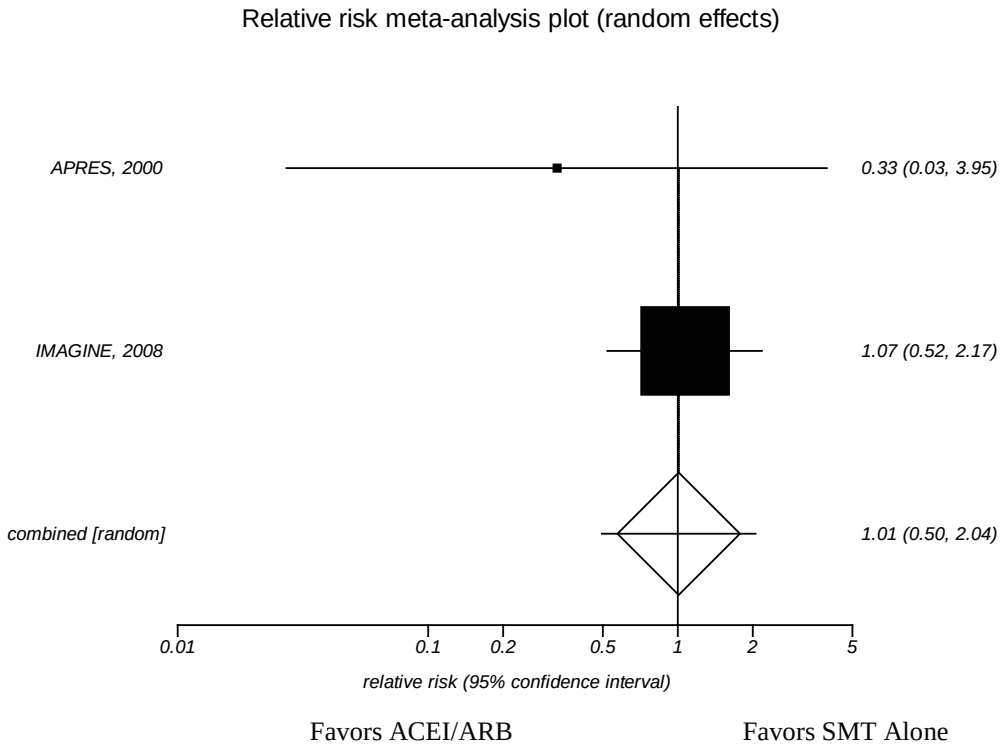
Figure 24. KQ3 Nonfatal myocardial infarction base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease who have recently undergone, or are set to undergo, a coronary revascularization procedure



Test for heterogeneity: Cochran Q=1.46284 (df=4) p=0.8332; I^2 statistic=0%

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

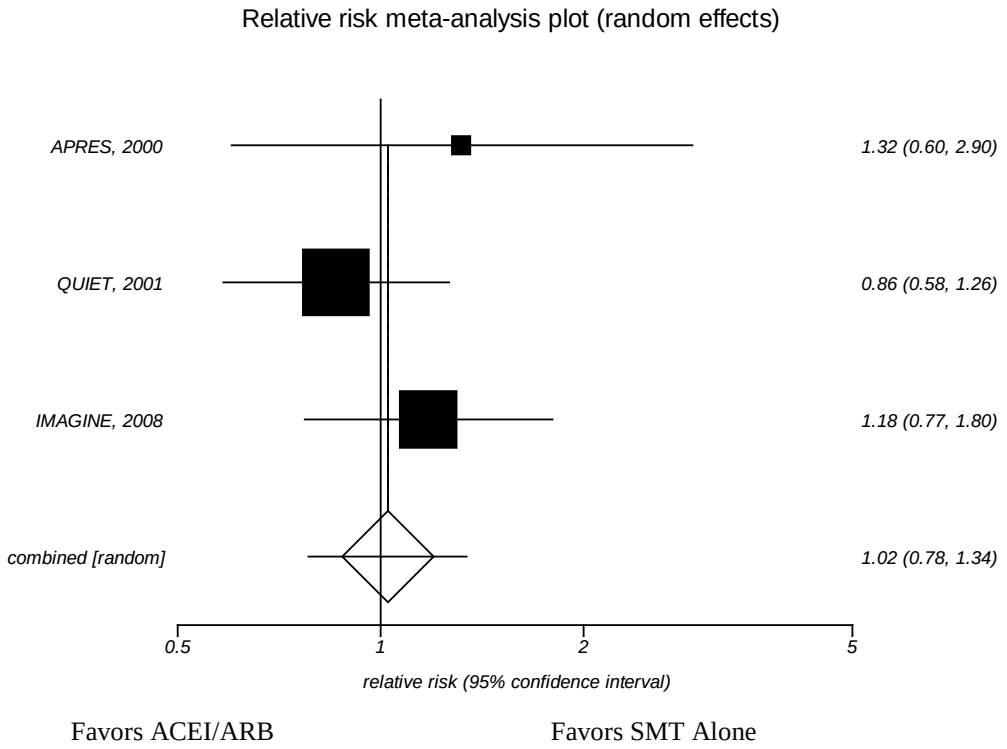
Figure 25. KQ3 Stroke base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease who have recently undergone, or are set to undergo, a coronary revascularization procedure



Test for heterogeneity: Cochran Q=0.497689 (df=1) p=0.4805; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 26. KQ3 Hospitalization for angina base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease who have recently undergone, or are set to undergo, a coronary revascularization procedure

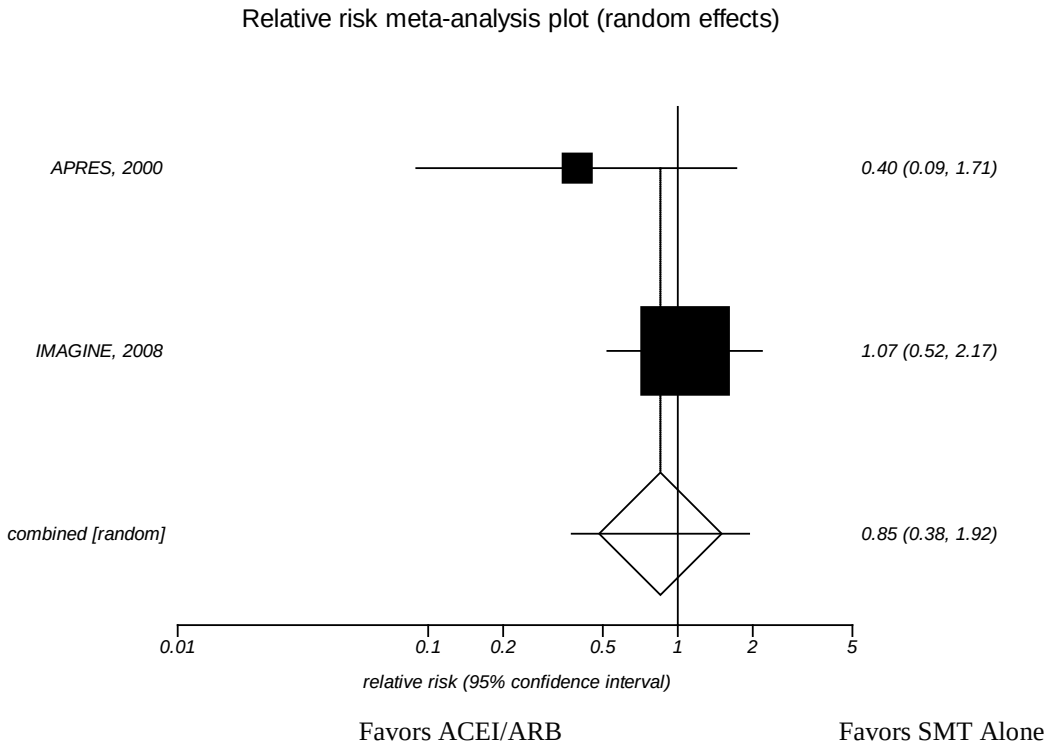


Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=1.573147 (df=2) p=0.4554; I^2 statistic=0%

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

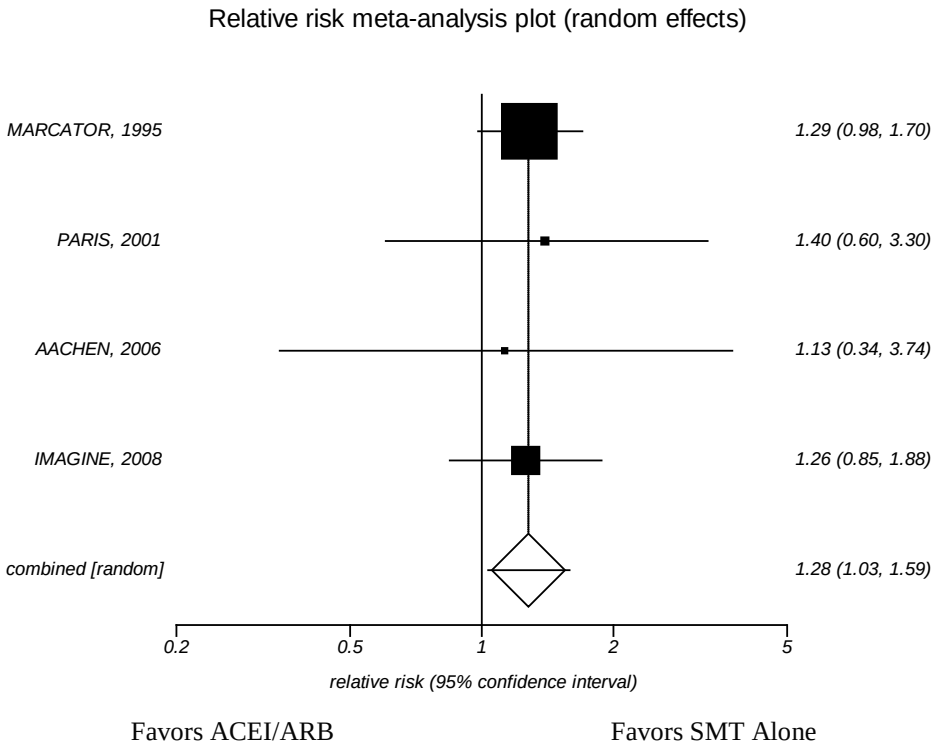
Figure 27. KQ3 Hospitalization for heart failure base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease who have recently undergone, or are set to undergo, a coronary revascularization procedure



Test for heterogeneity: Cochran Q=1.21564 (df=1) p=0.2702; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 28. KQ3 Need for subsequent revascularization base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease who have recently undergone, or are set to undergo, a coronary revascularization procedure



Test for heterogeneity: Cochran Q=0.082314 (df=3) p=0.9939; I^2 statistic=0%

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

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 Points

- The same 12 studies evaluated for efficacy in Key Question 1 were assessed for harms in this key question as well.
- Between 10 and 17 percent of patients receiving ACE inhibitor (ramipril, perindopril) or ARB (telmisartan) therapy withdrew in the run-in period.
- ACE inhibitor and ARB therapy significantly increased the risk of withdrawing due to adverse events (ramipril, enalapril, trandolapril, candesartan) and experiencing syncope

(ramipril, trandolapril), cough (ramipril, enalapril, trandolapril) and hyperkalemia (ramipril, telmisartan) versus placebo in patients with stable ischemic heart disease.

- ACE inhibitor did not significantly impact the risk for hypotension (ramipril, enalapril, zofenopril) or angioedema (ramipril, trandolapril) versus placebo in patients with stable ischemic heart disease.
- ACE inhibitor (enalapril) therapy significantly increased the risk of hypotension and cough versus calcium channel blockers in patients with stable ischemic heart disease.
- ACE inhibitor (enalapril, imidapril, lisinopril) therapy did not significantly impact the risk for withdrawals due to adverse events versus calcium channel blockers in patients with stable ischemic heart disease.
- No trials were available comparing ACE inhibitor or ARB therapy with either placebo or active therapy in patients with stable ischemic heart disease risk equivalents.

Detailed Analysis

The same 12 studies evaluated for efficacy in Key Question 1 were assessed for harms in this Key Question as well.[38-51] While we sought to evaluate for a variety of adverse effects, limited data was available for which to make quantitative comparisons.

Outcome Evidence Evaluations

Run-In Period Withdrawals

Eight of the 12 available trials included a run-in period within their study (Appendix Table 21).[38-43,45,47,48,51] A few of the studies used dose-escalating protocols for ACE inhibitors, ranging from 14-28 days duration.[38-41,43] The SCAT[42] and CAMELOT[45] trials used a placebo run-in period of 1 month and 14 days duration (respectively). The FOSIDIAL trial[48] provided daily placebo for 14 days followed by a single ACE inhibitor dose as part of its run-in protocol. The TRANSCEND[51] trial differed in design from the others in this regard as it included only patients who had proven intolerance to an ACE inhibitor. Placebo was given for 7 days followed by an ARB for 14 days.

Three ACE inhibitor trials with a run-in period (HOPE, PART-2, EUROPA) provided data on the reasons for exclusion.[38-41,43] The percent excluded during the run-in period ranged from 9.8 percent in HOPE (ramipril 2.5mg/days X 7 to 10 days then placebo/day X 10 to 14 days)[38] to 17 percent in PART-2 (ramipril 5mg/day X 7 days then 10mg/day X 7 days).[41] Given the higher doses of ACE inhibitor used in PART-2,[41] the higher rate of exclusion during the run-in period was not surprising. The most common reasons for exclusion in the HOPE trial[38] included non-compliance, adverse-events, abnormal serum creatinine or potassium levels, and withdrawal of consent; although the numbers for each were not provided. The PART-2 trial[41] reported ineligibility (41 percent), suspected adverse events (41 percent) and patient preferences (18 percent) as the reasons for exclusion during the run-in period. The EUROPA trial[43] reported hypotension (20.2 percent), increased serum creatinine or potassium (10.4 percent), other intolerance (23.1 percent) and unspecified reasons (31 percent) as their top reasons for exclusion following run-in.

One trial provided an ARB (telmisartan) during the run-in period (TRANSCEND).[51] The TRANSCEND trial[51] reported an exclusion of 11.1 percent of patients during the following their run-in period. The main reasons for exclusion included poor compliance (42 percent), withdrawn

consent (18.2 percent), symptomatic hypotension (7.2 percent), increased serum creatinine or potassium (7.2 percent) and other reasons (27.2 percent).

Study Withdrawals

Of the 12 trials providing efficacy outcome data, 10 provided data on study withdrawals (Appendix Table 22).[38-41,43-46,48-51] The percentage of patients who withdrew during study followup ranged from 0-38.5 percent. Patients within the ACE inhibitor (ramipril, perindopril, enalapril, imidapril, lisinopril, fosinopril, zofenopril) or ARB (telmisartan, candesartan) groups had 4.4-36.9 percent withdrawal rates, with patients in the control groups having 1.0-38.5 percent withdrawal rates. Amongst the studies evaluating patients with kidney disease (an ischemic heart disease risk equivalent), study withdrawal rates ranged from 0-5 percent.[48,49]

Withdrawals Due to Adverse Events

Withdrawal due to adverse events data was available in four trials (1275 events in 12548 patients; 10.2 percent).[41,45-47] The same base case and subgroup/sensitivity analyses as Key Question 1 were conducted to discern the impact of ACE inhibitor or ARB therapy on withdrawals due to adverse events in this population.

Three trials were included in the base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 23).[41,45,47] Patients receiving ACE inhibitors (ramipril, enalapril, trandolapril) or ARBs (none available) were significantly more likely to withdraw due to adverse events than patients receiving placebo [RR 2.30 (1.34 to 3.95)](Figure 29). A high level of statistical heterogeneity was seen (I^2 = 87.2 percent). Given the high level of statistical heterogeneity, we explored clinical and methodological aspects of the constituent studies. First, all three of the trials included in this analysis showed significantly increased withdrawal risk with ACE inhibitors versus placebo although the magnitude of the effect differed. The PART-2 trial[41] with ramipril showed over a 10-fold increase in the risk of withdrawals [RR 10.37 (3.42 to 31.72)] whereas the PEACE trial[47] with trandolapril showed slightly more than a 2-fold increase [RR 2.21 (1.93 to 2.54)]. Too few studies were included to assess for the presence of publication bias. Two trials were included in the base case analysis evaluating randomized, active controlled trials in patients with stable ischemic heart disease, both of which evaluated ACE inhibitors with CCBs.[45,46] In one trial enalapril was compared with amlodipine where in the other, therapy with enalapril, imidapril, or lisinopril was compared with nifedipine. ACE inhibitor use did not significantly impact withdrawal due to adverse event rates as compared with CCBs [RR 1.40 (0.92 to 2.12)](Figure 30). Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed in this analysis. No trials evaluating the impact of ACE inhibitors or ARBs versus placebo in patients with ischemic heart disease risk equivalents were included, thus their impact could not be assessed.

When inclusion was restricted to the three randomized, placebo controlled trials evaluating ACE inhibitors (ramipril, enalapril, trandolapril) on withdrawals due to adverse events, the same results as the first base case analysis were seen since all of the trials included in this endpoint analysis evaluated ACE inhibitors (Appendix Figure 42).[41,45,47] As stated, no trials evaluated the impact of ARBs on this endpoint, thus their impact could not be assessed.

Since no trials utilized an open label design and all trials utilized intention-to-treat methodology, the impact of these factors on withdrawals due to adverse events could not be assessed.

Hypotension

Hypotension data was available in three trials (116 events in 11637 patients; 1.0 percent).[38,45,50] The same base case and subgroup/sensitivity analyses as Key Question 1 were conducted to discern the impact of ACE inhibitor or ARB therapy on hypotension in this population.

Three trials were included in the base case analysis evaluating the impact of ACE inhibitors (ramipril, enalapril, zofenopril) or ARBs (none available) on hypotension in randomized, placebo controlled trials in patients with stable ischemic heart disease (Appendix Table 24).[38,45,50] Therapy with ACE inhibitors did not significantly impact the risk of hypotension versus placebo [RR 1.79 (0.68 to 4.71)](Figure 31). Moderate statistical heterogeneity was seen (I^2 = 40.6 percent) mainly resulting from the higher incidence of hypotension in the CAMELOT trial,[45] and publication bias could not be evaluated due to the low number of studies.

A single trial was included in the base case analysis evaluating the impact of ACE inhibitors (enalapril) or ARBs (none available) on hypotension in randomized, active controlled trials in patients with stable ischemic heart disease.[45] In this trial, the ACE inhibitor significantly increased the incidence of hypotension as compared with the CCB amlodipine [RR 2.87 (1.79 to 4.60)]. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed for in this analysis.

When inclusion was restricted to the three randomized, placebo controlled trials evaluating the impact of ACE inhibitors (ramipril, enalapril, zofenopril) on hypotension, the same results as the first base case analysis were seen since all of the trials included in this endpoint analysis evaluated ACE inhibitors (Appendix Figure 43).[38,45,50] No trials evaluated the impact of ARBs on this endpoint.

Since no trials utilized an open label design and all trials utilized intention-to-treat methodology, the impact of these factors on hypotension could not be assessed.

Syncope

Syncope data was available from two trials (365 events in 17587 patients; 2.1 percent).[38,47] Both trials were randomized, double blind, placebo controlled trials of ACE inhibitors (ramipril, trandolapril) in patients with stable ischemic heart disease (Appendix Table 25). Thus no data is available for ACE inhibitors versus active controls in patients with stable ischemic heart disease, or versus placebo in patients with stable ischemic heart disease risk equivalents. No trials assessing the impact of ARBs versus placebo or active control on syncope were available.

In the two trials that evaluated syncope, ACE inhibitors (ramipril, trandolapril) were found to significantly increase the risk of syncope as compared to placebo in patients with stable ischemic heart disease [RR 1.24 (1.02 to 1.52)](Figure 32).[38,47] Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed for this endpoint. However, it should be noted that the incidence of syncope was qualitatively higher in the PEACE trial[47] (4.4 percent) than the HOPE trial (0.04 percent).[38] The disparate incidences reported in these two trials likely reflect difference in outcome reporting within the trials rather than inherent differences between the evaluated therapies.

Since no trials utilized an open label design and all trials utilized intention-to-treat methodology, the impact of these factors on syncope could not be assessed.

Cough

Cough data was available in three trials (2943 events in 19580 patients; 15.0 percent).[38,45,47] The same base case and subgroup/sensitivity analyses as Key Question 1 were conducted to discern the impact of ACE inhibitor (ramipril, enalapril, trandolapril) or ARB (none available) therapy on cough in this population.

Three trials were included in the base case analysis evaluating randomized, placebo controlled trials in patients with stable ischemic heart disease, all of which used ACE inhibitors (Appendix Table 26).[38,45,47] Since only ACE inhibitor trials were available, the impact of ARB use on cough could not be assessed. Patients receiving ACE inhibitors (ramipril, enalapril, trandolapril) were significantly more likely to experience cough than patients receiving placebo [RR 1.67 (1.22 to 2.29)](Figure 33). A moderate level of statistical heterogeneity was seen (I^2 = 60.2 percent), and publication bias could not be evaluated due to the low number of trials. The magnitude of increase in relative risk was similar between the three trials (RR range 1.42 to 2.15). Similar to syncope, patients in the CAMELOT[45] and PEACE trials[47] had higher incidences of cough (9.2 and 33.3 percent respectively) than patients in the HOPE trial (0.3 percent).[38] This difference may be related to lack of outcome reporting within the trials rather than actual differences between therapies.

A single trial was included in the base case analysis evaluating cough in randomized, active controlled trials in patients with stable ischemic heart disease, which compared the ACE inhibitor enalapril with the CCB amlodipine.[45] ACE inhibitor use significantly increased the risk of cough as compared to CCB use [RR 2.43 (1.66 to 3.57)]. Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed for in this analysis.

No trials were available evaluating patients with ischemic heart disease risk equivalents, thus the impact on cough in this population could not be assessed.

Since no trials utilized an open label design and all trials utilized intention-to-treat methodology, the impact of these factors on cough could not be assessed.

Angioedema

Angioedema data was available from two trials (19 events in 17587 patients; 0.1 percent).[38,47] Both were randomized, double blind, placebo controlled trials of ACE inhibitors (ramipril, trandolapril) in patients with stable ischemic heart disease (Appendix Table 27). Thus no endpoint data is available for ACE inhibitors versus active controls in patients with stable ischemic heart disease or ACE inhibitors versus placebo in patients with stable ischemic heart disease risk equivalents. Since only ACE inhibitor trials were available, the impact of ARB use on angioedema could not be assessed.

In the two trials that were included in the analysis, ACE inhibitors (ramipril, trandolapril) did not significantly impact the risk of angioedema as compared to placebo in patients with stable ischemic heart disease [RR 2.03 (0.75 to 5.47)](Figure 34).[38,47] Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed for this endpoint.

Since no trials utilized an open label design and all trials utilized intention-to-treat methodology, the impact of these factors on angioedema could not be assessed.

Hyperkalemia

Hyperkalemia data was available from two trials (852 events in 15,037 patients; 5.7 percent).[51,89] Both trials were randomized, double blind, placebo controlled trials of ACE inhibitor (ramipril) or ARB (telmisartan) therapy in patients with stable ischemic heart disease

(Appendix Table 28). Thus no data for this endpoint is available for ACE inhibitors or ARBs versus active controls or in patients with stable ischemic heart disease risk equivalents. The HOPE trial[89] defined hyperkalemia as a serum potassium concentration >5.0 mmol/L whereas the TRANSCEND trial[51] defined it as a concentration >5.5 mmol/L.

In the two trials that that were included in the analysis, ACE inhibitor (ramipril) or ARB (telmisartan) therapy were found to significantly increase the risk of hyperkalemia as compared to placebo in patients with stable ischemic heart disease [RR 1.71 (1.02 to 2.87)](Figure 35).[51,89] Due to the low number of trials, statistical heterogeneity and publication bias could not be assessed.

In the HOPE trial, patients with stable ischemic heart disease receiving ACE inhibitor therapy with ramipril were at significantly greater risk for hyperkalemia than patients receiving placebo [RR 1.34 (1.16 to 1.55)].[89] Similarly, the TRANSCEND trial showed that patients with ischemic heart disease receiving ARB therapy with telmisartan were at significantly higher risk for hyperkalemia than patients receiving placebo [RR 2.28 (1.63 to 3.18)].[51]

Since no trials utilized an open label design and all trials utilized intention-to-treat methodology, the impact of these factors on hyperkalemia could not be assessed.

Rash and Blood Dyscrasias

None of the included trials reported results on rash or blood dyscrasias (Appendix Tables 29-30).

Discussion

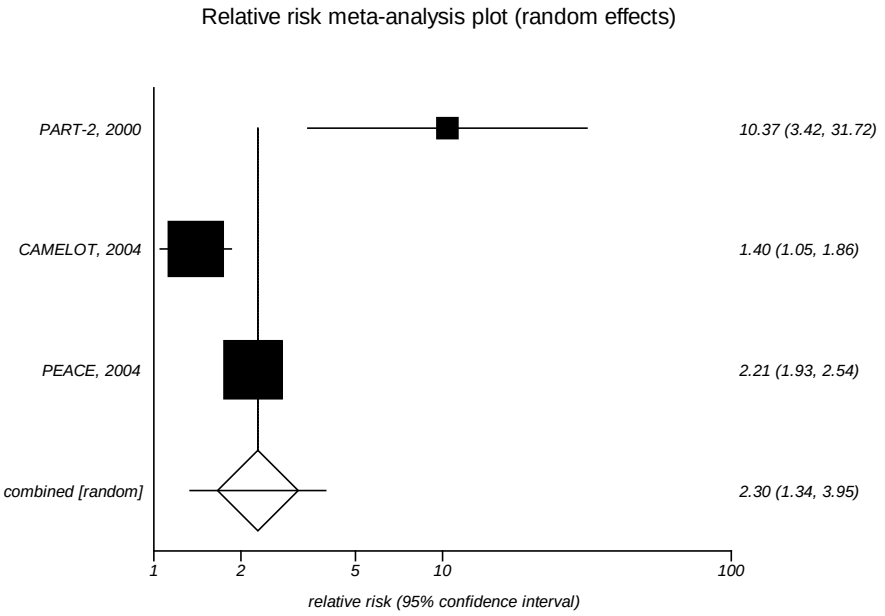
The same 12 studies evaluated for efficacy in Key Question 1 were assessed for harms in this key question.[38-51] Unlike the efficacy endpoints, these trials did not routinely report the pre-specified harms. Thus, their true and comparative incidence may differ from those reported in the trials. However, the trials do show that ACE inhibitors significantly increase the risk of withdrawing due to adverse events, syncope, and cough; in addition ACE inhibitors and ARBs significantly increased the risk of hyperkalemia as compared with placebo in patients with stable ischemic heart disease. There were also nonsignificant increases in risk of hypotension and angioedema with ACE inhibitors as compared with placebo, although these analyses seemed underpowered. It should be noted that some of these adverse events are considered dose-independent (including angioedema, rash and cough), while others are dose-related adverse events (including hypotension and hyperkalemia). As such, higher doses of ACE inhibitors or ARBs would be expected to increase the risk of certain adverse events including hypotension and hyperkalemia. However, since the studies included in the current review did not investigate multiple doses definitive statements cannot be made. When ACE inhibitors were compared with CCBs, an increased risk of cough and hypotension was seen with ACE inhibitor use. It is important to note that the harms data used in this Key Question for the HOPE trial[38] was obtained from the FDA.gov web site where they were listed as serious adverse events. Thus, the actual incidence of various outcomes, not defined as serious, is unknown and may differ from those reported here. In addition, very few data were available for ARBs regarding their impact on these safety endpoints. As such, additional information is required before the balance between their benefit and safety in this population can be assessed.

As mentioned above, a number of the included studies included run-in periods in their study design. As shown in Appendix Table 20, there were a number of patients that were excluded following the run-in period for various adverse events, including some of interest in

this Key Question. Thus, the true incidence of harms with these therapies in environments outside of clinical trials may be higher than those reported here. Unlike the studies reported in Key Question 3, the studies in the current key question used longer followup times (many over 4 years) thus reflecting the overall risk of harms with ACE inhibitors and ARBs when used for extended periods of time. Additionally, factors that could potentially confound the incidence of some of these risks have to be considered. For example, there are many potential causes of hyperkalemia such as use of potassium-sparing diuretics, spironolactone or eplerenone, non-steroidal antiinflamamtory agents, beta-blockers, trimethoprim/sulfamethoxazole, heparin, and acidosis amongst others. While these might be potential confounders, we would anticipate that the process of randomizing such a large number of subjects would lead to a relatively equal distribution between experimental groups and would not account for the effects we observed. However, adequate data from each trial does not exist to prove that this is the case, although similar numbers of patients in both HOPE[89] and TRANSCEND[51] utilized agents such as beta-blockers and diuretics.

The unique design of the TRANSCEND study deserves discussion within the topic of harms.[51] All of the patients included in this study were shown to be intolerant of ACE inhibitors at baseline, and were then randomized to the ARB telmisartan or placebo. The most common reasons reported for ACE intolerance included cough (88.2 percent), symptomatic hypotension (4.1 percent), angioedema (1.3 percent), renal dysfunction (1.0 percent), and other reasons (8.3 percent). In terms of harms, following a median followup of 56 months, the ARB was relatively well tolerated with only a statistically higher risk of hypotension symptoms as compared with placebo (p=0.049).[51] Thus it appears that in patients with stable ischemic heart disease who cannot tolerate ACE inhibitors or are at an increased risk for harms, that ARBs may be a relatively safe alternative.

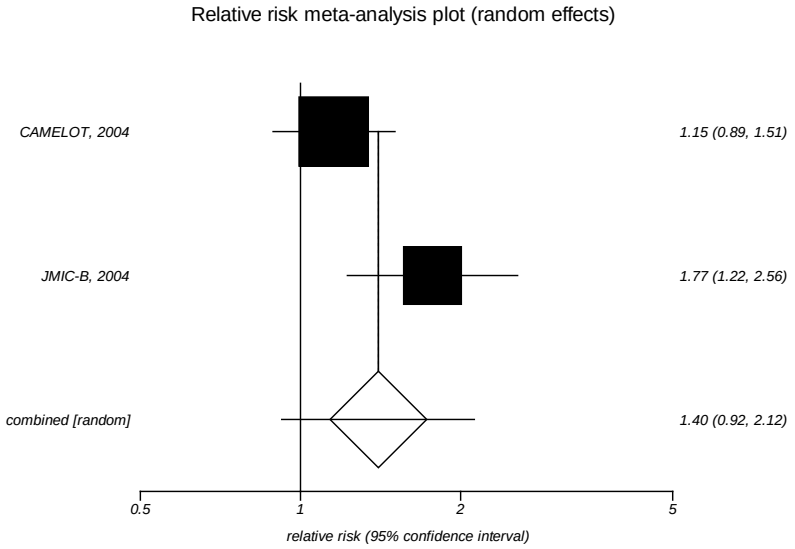
Figure 29. KQ4 Withdrawal due to adverse events base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=15.650446 (df=2) p=0.0004; I^2 statistic=87.2%

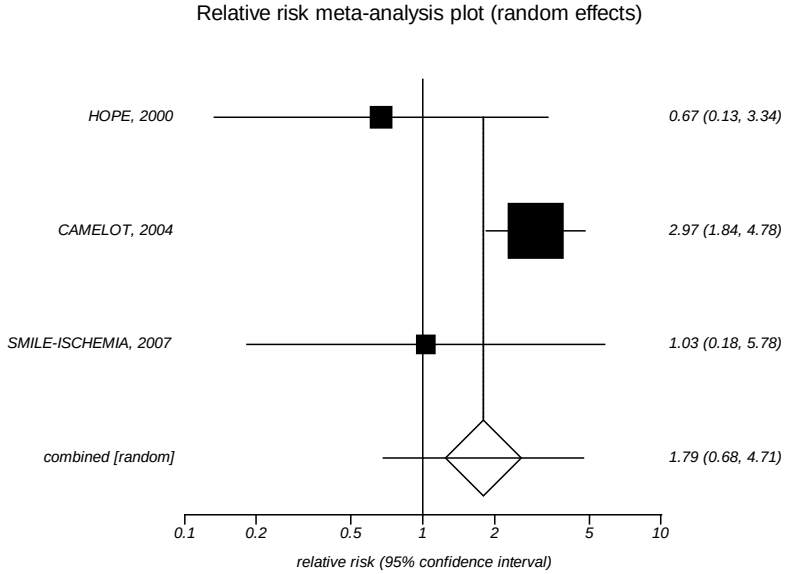
Figure 30. KQ4 Withdrawal due to adverse events base case analysis—Meta-analysis of randomized placebo-controlled trials comparing ACEI or ARB with CCB in patients with stable ischemic heart disease



Favors ACEI/ARB Favors CCB Alone

Test for heterogeneity: Cochran Q=3.367103 (df=1) p=0.0.0665; I^2 statistic=87.2%
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

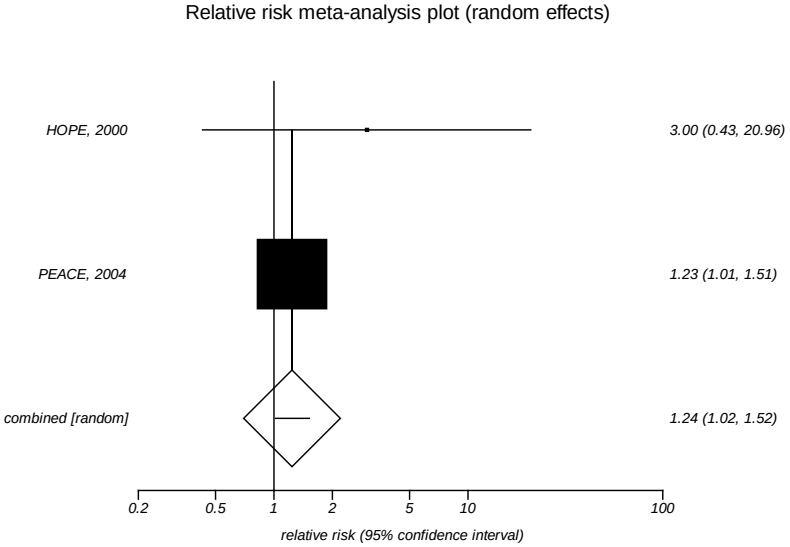
Figure 31. KQ4 Hypotension base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=3.368646 (df=2) p=0.1856; I^2 statistic=40.6%

Figure 32. KQ4 Syncope base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease

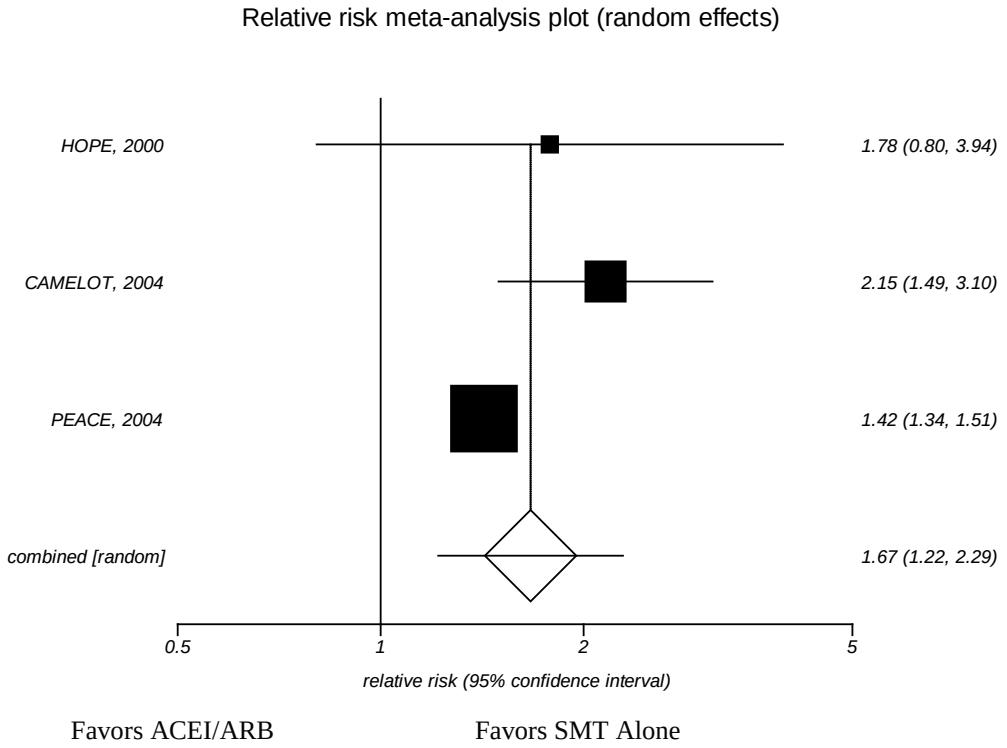


Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=0.589094 (df=1) p=0.4428; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 33. KQ4 Cough base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease

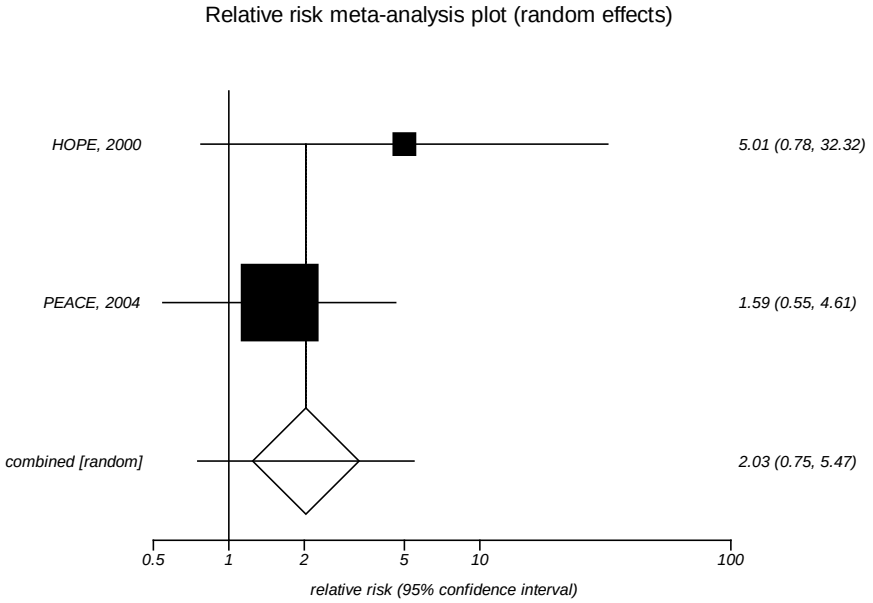


Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=5.0194 (df=2) p=0.0813
I^2 statistic=60.2%

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

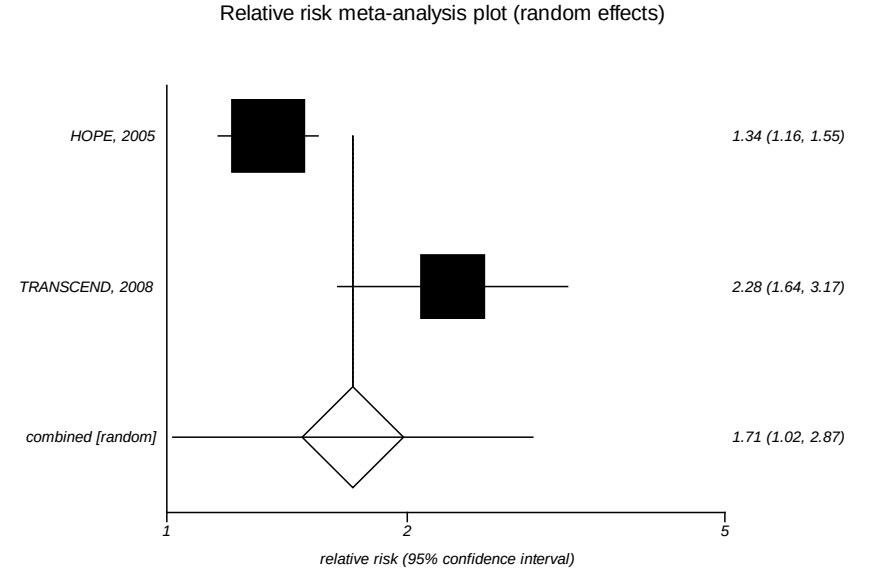
Figure 34. KQ4 Angioedema base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=0.933147 (df=2) p=0.6271; I^2 statistic=0%

Figure 35. KQ4 Hyperkalemia base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=8.277468 (df=1) p=0.004; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

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?

Key Points

- Only the ONTARGET trial provided information to answer this Key Question.
- Twelve percent of patients withdrew in the run-in period before randomization.
- Patients were randomized to the ACE inhibitor ramipril, the ARB telmisartan, or to combination therapy with ramipril + telmisartan.
- Combination therapy (ACE inhibitor + ARB) resulted in more discontinuations than ACE inhibitor therapy alone.
- Combination therapy resulted in more discontinuations due to hypotension, syncope, diarrhea, and renal impairment than ACE inhibitor therapy alone.
- When viewed in light of the efficacy results from Key Question 2, the balance of benefits to harms for combination therapy versus ACE inhibitor therapy alone is not favorable.

Detailed Analysis

The ONTARGET trial provides insight into the comparative harms of combining an ACE inhibitor with an ARB versus using an ACE inhibitor alone. Patients were randomized to the ACE inhibitor ramipril, the ARB telmisartan, or the combination of ramipril plus telmisartan. Key Question 2 provides the efficacy evaluation and provides more details on study characteristics. In the discussion, we evaluate the balance of benefits to harms.

While Key Question 5 does not ask about the comparative harms of ACE inhibitors versus ARBs, the ONTARGET trial is the only direct comparative trial providing this data and we present that data here. It is important to also evaluate the indirect evidence of comparative harms from placebo controlled ACE inhibitor and ARB trials and we refer to these indirect trials in the discussion section.[52]

In ONTARGET, potential participants (n= 29,019) underwent a 21-28 day run-in period.[52] Run-in periods eliminate patients with the greatest risk of harms from being randomized into the trial. As such, an analysis of harms occurring during the run-in period, as well as those occurring post-randomization, may be more applicable to general populations. Patients started on ramipril 2.5mg daily and progressed to ramipril 5mg plus telmisartan 40mg daily by the end of the run-in period. Since patients were receiving combination ramipril + telmisartan therapy after the first 3 days of the run-in period, harms were most likely a result of combination therapy rather than ACE inhibitor monotherapy. Patients (11.7 percent of the total) were excluded following the run-in period for the following reasons: 3.9 percent had poor compliance, 3.0 percent were excluded for unspecified reasons, 2.1 percent withdrew for unspecified reasons, 1.7 percent had symptomatic hypotension, 0.8 percent had elevated serum potassium concentrations, 0.2 percent had elevated serum creatinine concentrations, and 0.1 percent of patients died. We cannot discern whether the proportion of patients with poor compliance, or those excluded or withdrawing for unspecified reasons, also experienced harms.[52]

The discontinuation rate during the trial was significantly lower in the ramipril group than the combination therapy group (24.5 percent vs. 29.3 percent, p<0.001) but was higher than the telmisartan group (24.5 percent vs. 23.0 percent, p=0.02). The telmisartan group experienced more discontinuations for hypotension but fewer discontinuations for cough and angioedema as compared with the ramipril group. In contrast, the combination therapy group experienced more discontinuations due to hypotension, syncope, renal impairment, and diarrhea than the ramipril group. Table 14 delineates the percentage of patients in each group that discontinued therapy during the trial for various reasons.[52]

The percentage of patients receiving the full dose of ramipril at 2 years was 81.7 percent in the ramipril alone group and 75.3 percent in the combination therapy group.[52] The percentage of patients receiving the full dose of telmisartan at 2 years was 88.6 percent in the telmisartan alone group and 84.3 percent in the combination therapy group. Importantly, the use of combination therapy resulted in a greater risk of renal impairment versus ramipril [RR 1.33 (1.22 to 1.44)], although no significant difference in renal failure requiring dialysis was seen [RR 1.37 (0.94 to 1.98)]. No differences were noted between the telmisartan and ramipril groups for either of these endpoints.[52]

Discussion

The benefits in Key Question 2 need to be evaluated in relation to the harms in Key Question 5 in order to discern the comparative balance of benefits and harms. ACE inhibitor therapy, represented by ramipril, provides similar efficacy as the combination of an ACE inhibitor plus an ARB, represented by ramipril and telmisartan, with a lower risk of patient harm.

In Key Question 4, only the TRANSCEND trial provides information on harms associated with the ARB telmisartan and this was only for the hyperkalemia endpoint. Like ACE inhibitors, ARB therapy increased the risk of hyperkalemia versus placebo. The other pooled harms analyses were comprised of only placebo controlled ACE inhibitor trials. As such, the ONTARGET trial is very important in determining the comparative harms of ACE inhibitor and ARB therapy. The ACE inhibitor ramipril and the ARB telmisartan have similar efficacy, similar risks of harms, and therefore a similar balance of benefits to harms. It should be noted that some of these adverse events are considered dose-independent (including angioedema, rash, or cough), while others are dose-related adverse events (including hypotension and hyperkalemia). As such, higher doses of ramipril or telmisartan would be expected to increase the risk of certain adverse events. However, since the studies included in the current review did not investigate multiple doses definitive statements cannot be made.

In patients with angioedema on an ACE inhibitor, caution should be exercised when substituting an ARB due to the risk of cross reactivity. In a retrospective study of patients experiencing angioedema while on an ACE inhibitor, 8 percent of patients who were consequently placed on an ARB had a continuation of their symptoms.[102]

Table 14. KQ5—Discontinuations due to harms in the ONTARGET Trial[52]

Variable	Ramipril (n=8576)	Combination Therapy (n=8502)	Telmisartan (n=8542)	Combination vs. Ramipril	Telmisartan vs. Ramipril
	N (%)			P-Value	
Total Number of Discontinuations	2099 (24.5)	2495 (29.3)	1962 (23.0)	<0.001	0.02
Hypotension	149 (1.7)	406 (4.8)	229 (2.7)	<0.001	<0.001
Syncope	15 (0.2)	29 (0.3)	19 (0.2)	0.03	0.49
Cough	360 (4.2)	392 (4.6)	93 (1.1)	0.19	<0.001
Angioedema	25 (0.3)	18 (0.2)	10 (0.1)	0.30	0.01
Renal Impairment	60 (0.7)	94 (1.1)	68 (0.8)	<0.001	0.46
Rash	NR	NR	NR	NR	NR
Blood Dyscrasias	NR	NR	NR	NR	NR
Diarrhea	12 (0.1)	39 (0.5)	19 (0.2)	<0.001	0.20

Abbreviation: N=number; NR=not reported

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 Points

- For trials to be included, ACE inhibitors or ARBs needed to be started in close proximity to a revascularization procedure.
- The same seven studies evaluated for efficacy in Key Question 3 were assessed for harms in this key question as well.
- Only ACE inhibitor trials were available to answer this Key Question.
- ACE inhibitors (ramipril, quinapril) increased the risk of withdrawals due to adverse events versus placebo and/or control therapy.
- ACE inhibitor (quinapril) therapy increased the risk of hypotension and nonsignificantly increased the risk of cough versus placebo and/or control therapy.
- Hyperkalemia was only assessed in one trial comparing the ACE inhibitor ramipril to placebo with no events in either group.
- Data was unavailable for other adverse events of interest.
- When viewed in light of the efficacy expected from Key Question 3, the balance of benefits to harms associated with ACE inhibitor or ARB therapy as compared to placebo or control therapy is not favorable in this population.

Detailed Analysis

Study Design and Population Characteristics

The same seven studies evaluated for efficacy in Key Question 3 were assessed for harms in this key question as well.[53-59] While we sought to evaluate for a wide variety of adverse effects, only a paucity of data was available from which to make comparisons.

Outcome Evidence Evaluations

Run-In Period Withdrawals

Of the seven trials providing efficacy outcome data, only one required patients to tolerate an ACE inhibitor or ARB before randomization (Appendix Table 31).[54] In the APRES trial, a single test dose of ramipril 2.5mg was given.[54] While only 159 of the 213 eligible patients were randomized, it is unclear how many were not randomized because of adverse effects in this run-in period.[54]

Withdrawals for Any Reason/Withdrawals for Adverse Effects

Aside from the sole ARB (candesartan) trial,[58] which did not provide any withdrawal data, the six ACE inhibitor trials (cilazapril, ramipril, quinapril) all reported study withdrawals for any reason. (Appendix Table 32).[53-57,59] Four of the trials reported withdrawals due to adverse events,[53-55,59] two of the trials[55,59] used quinapril as their ACE inhibitor while the rest used other ACE inhibitors (cilazapril, ramipril).[53,54] Three of the four trials were placebo controlled.[53,54,59] Withdrawals for adverse events was experienced by a number of subjects in the four included trials (336 withdrawals due to adverse events in 2902 subjects; 11.6 percent)(Appendix Table 33).[54-56,59] We conducted seven different analyses to discern the impact of ACE inhibitor or ARB therapy on withdrawals due to adverse events in this population.

The three trials included into our base case analysis were randomized, placebo-controlled trials evaluating the impact of ACE inhibitors (ramipril, quinapril) or ARBs (none available) on withdrawals due to adverse events in patients who initiated their therapy in close proximity to a revascularization procedure.[54,56,59] Therapy with ACE inhibitors increased the risk of withdrawals due to adverse events versus placebo [RR 2.17 (1.75 to 2.70)](Figure 36). Statistical heterogeneity was low (I^2 = 0 percent), and publication bias could not be assessed for due to the low number of studies.

No randomized, placebo-controlled trials evaluating the impact of ARBs on withdrawals due to adverse events were available.

In order to assess the impact of study quality on results, inclusion was broadened to include a combined total of four open label or placebo-controlled trials evaluating the impact of ACE inhibitors (rampril, quinapril) or ARBs (none available) on withdrawals due to adverse events in patients who initiated their therapy in close proximity to a revascularization procedure.[54-56,59] As in the base case, ACE inhibitors increased the risk of withdrawals due to adverse events versus placebo [RR 2.18 (1.75 to 2.71)](Appendix Figure 44). In order to assess the impact of utilizing ITT methodologies on results, inclusion was restricted to only the studies that reported this method. Since all the studies in the base case utilized ITT methodologies, the results did not change.[54,56,59]

When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) or ARB (none available) therapy on withdrawals due to adverse events in patients who initiated their therapy in close proximity to coronary artery bypass grafting surgery, risk of withdrawals was significantly increased versus placebo [RR 2.20 (1.77 to 2.74)].[59] The single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) or ARB (none available) therapy in patients who initiated their therapy in close proximity to a percutaneous coronary intervention reported no withdrawals due to adverse events in either group.[56]

Hypotension and Syncope

Only the IMAGINE trial specifically reported the impact of ACE inhibitor therapy on hypotension (Appendix Table 34).[59] In this trial, quinapril increased the risk of hypotension [RR 2.19 (1.67 to 2.87)].[59] No data was available for ARB therapy. None of the potential trials specifically reported the impact of ACE inhibitor or ARB therapy on syncope (Appendix Table 35).

Cough and Angioedema

Three trials reported on the impact of ACE inhibitor (quinapril) or ARB (none available) therapy on cough.[55,57,59] Cough (either severe or regular) was experienced by a number of subjects in the three included trials (446 subjects with cough in 4402 subjects; 10.1 percent) but occurred in only 1 of 99 subjects (1.0 percent) in the trial assessing severe cough. We conducted seven different analyses to discern the impact of ACE inhibitor or ARB therapy on cough in this population.

The two trials included into our base case analysis were randomized, placebo-controlled trials evaluating the impact of ACE inhibitor (quinapril) or ARB (none available) therapy on cough in patients who initiated their therapy in close proximity to a revascularization procedure.[57,59] Therapy with ACE inhibitors did not statistically significantly the risk of cough versus placebo [RR 4.97 (0.58 to 42.95)](Appendix Table 36 and Figure 37), although few trials had data available. Due to the low number of studies in this analysis, statistical heterogeneity and publication bias could not be assessed.

No randomized, placebo-controlled trials evaluating the impact of ARBs on cough were available.

In order to assess the impact of study quality on results, inclusion was broadened to include a combined total of three open label or placebo-controlled trials evaluating the impact of ACE inhibitors (quinapril) or ARBs (none available) on cough in patients who initiated their therapy in close proximity to a revascularization procedure.[55,57,59] As in the base case, ACE inhibitors did not statistically significantly impact the risk of cough versus placebo [RR 4.43 (0.81 to 24.37)](Appendix Figure 45). Statistical heterogeneity was high (I^2 = 78.2 percent), and publication bias could not be determined. The open label Kondo trial found that ACE inhibitor therapy with quinapril did not significantly impact the risk of cough versus placebo [RR 3.06 (0.26 to 36.89)], although few events occurred in this single trial.[55] In order to assess the impact of utilizing ITT methodologies on results, inclusion was restricted to only the studies that reported this method. Since all the studies in the base case utilized ITT methodologies, the results did not change.[57,59]

When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) therapy on cough in patients who initiated

their therapy in close proximity to coronary artery bypass grafting surgery, risk of cough was significantly increased versus placebo [RR 1.90 (1.57 to 2.29)].[59] When inclusion was restricted to the single randomized, placebo-controlled trial evaluating the impact of ACE inhibitor (quinapril) therapy on cough in patients who initiated their therapy in close proximity to a percutaneous coronary intervention, risk of cough was significantly increased versus placebo [RR 16.4 (3.94 to 68.08)].[57]

Given the high level of statistical heterogeneity in these analyses, we explored clinical and methodological aspects of the constituent trials. First, it should be mentioned that two of the three constituent trials found a significant increase in the risk of cough individually [QUIET[57] RR 16.4 (3.94 to 68.08) and IMAGINE[59] RR 1.90 (1.57 to 2.29)] and the third trial[59] found a nonsignificant increase in the risk of cough [RR 3.06 (0.26 to 36.89)] versus placebo. As such, all of the studies agree on the direction of effect with the QUIET trial showing an accentuated magnitude of effect. We cannot readily discern a clinical reason why the QUIET trial[57] would have shown a much greater magnitude of risk associated with ACE inhibitor therapy. Quinapril was the ACE inhibitor used in these trials and the dose administered was the same, 10-20mg per day. The QUIET[57] and IMAGINE[59] trials were both double-blinded and had followup periods of 27 months or 33 months, respectively. The Kondo trial[55] was open label and had six months of followup. It was the IMAGINE[59] trial that had the highest incidence of cough (21 percent vs. 11 percent) followed by the QUIET[57] trial (3.8 percent vs. 0.2 percent) and then the Kondo trial (2.0 percent vs. 0.0 percent). The QUIET[57] and IMAGINE[59] trials reported cough and Kondo reported severe cough, but what constituted a cough or severe cough were not defined. For both the base case analysis [RR 2.10 (1.75 to 2.53)] and the analysis allowing open label trials [RR 2.10 (1.75 to 2.53)], the fixed effect model showed significant increases in the risk of cough with ACE inhibitors as the IMAGINE[59] trial became a driver of the pooled effect.

None of the trials reported results for the angioedema endpoint (Appendix Table 37).

Renal Impairment and Hyperkalemia

None of the trials reported results on renal impairment or hyperkalemia (Appendix Table 38).

Rash and Blood Dyscrasias

None of the trials reported results on rash or blood dyscrasias (Appendix Tables 39-40).

Discussion

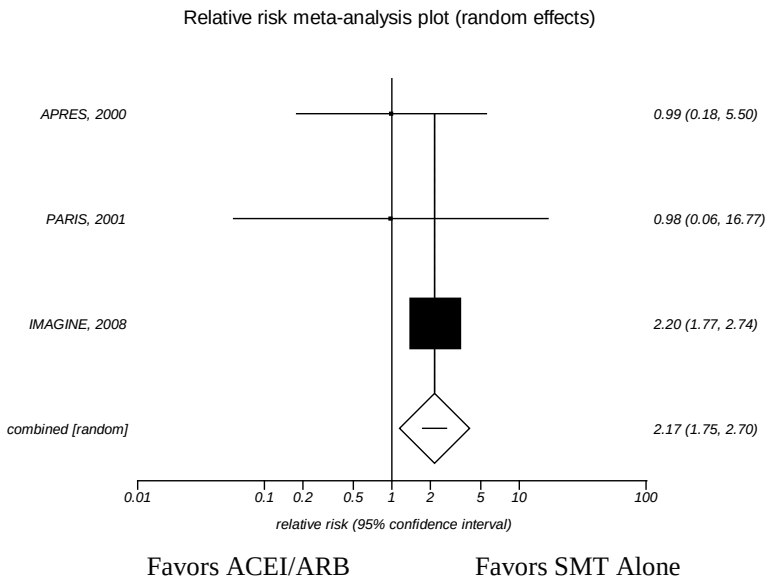
Unlike the trials in Key Questions 1 and 4, trials in Key Questions 3 and 5 did not utilize a lengthy run-in period. Only the APRES[54] trial used a run-in period and this was comprised of a single test dose of ramipril before randomization. As such, the adverse events noted over the followup period likely represent the population of people initiating ACE inhibitor therapy in close proximity to a randomization procedure. Since the only trial[58] evaluating an ARB (candesartan) did not report adverse event results, our results cannot be applied to ARBs. It is unfortunate that adverse events were not more readily reported in the trial publications.

The use of ACE inhibitors (quinapril) was associated with hypotension. While ACE inhibitors (quinapril) did not statistically significantly increased the risk of cough, only three trials[55,57,59] provided information, all three trials agreed on the direction of effect, and two[57,59] of the three trials individually found ACE inhibitors to increase the occurrence of cough versus

placebo. It should be noted that some of these adverse events are considered dose-independent (including angioedema, rash and cough), while others are dose-related adverse events (including hypotension and hyperkalemia). As such, higher doses of ACE inhibitors or ARBs would be expected to increase the risk of certain adverse events. However, since the studies included in the current review did not investigate multiple doses; definitive statements cannot be made.

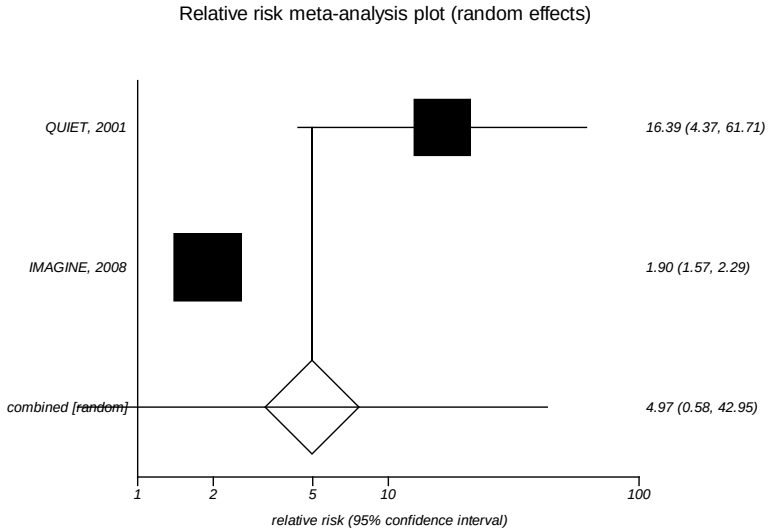
Given the lack of significant benefits found in Key Question 3, the balance of benefits to harms for the initiation of these therapies in close proximity to a revascularization procedure is not favorable.

Figure 36. KQ6 Withdrawals due to adverse events base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Test for heterogeneity: Cochran Q=0.812526 (df=2) p=0.6661; I^2 statistic=0%

Figure 37. KQ6 Cough base case analysis—Meta-analysis of randomized placebo-controlled trials in patients with stable ischemic heart disease



Favors ACEI/ARB Favors SMT Alone

Test for heterogeneity: Cochran Q=9.109545 (df=1) p=0.0025; I^2 statistic=N/A

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95% confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

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, co-morbidities (diabetes, renal dysfunction, hypertension), and other medications (vitamins, lipid lowering drugs, beta-blockers, anti-platelet agents)?

Key Points

- It is not possible to evaluate the risk of harms in this Key Question's specified subgroups.
- Many of the subgroups of interest have efficacy data that can be assessed qualitatively but the impact of ethnicity/genetic polymorphisms, degree and pattern of symptoms, location of lesions, and dose of ACE inhibitor or ARB used cannot be determined at this time.
- Females derive at least as much benefit as males from ACE inhibitor (ramipril, perindopril) therapy in a population with stable ischemic heart disease and preserved left ventricular function.

- While we cannot state with certainty that ARBs do not work as well in females as in males, the results of the TRANSCEND trial (telmisartan versus placebo) and the ACE inhibitor (ramipril) versus ARB (telmisartan) comparison from the ONTARGET trial suggests that this may be a possibility.
- ACE inhibitors (enalapril, imidapril, lisinopril) provide similar benefits as the calcium channel blocker nifedipine in either males or females with stable ischemic heart disease and preserved left ventricular function.
- It is difficult to determine the impact of age giving the different age categories assessed in the trials. However, ACE inhibitors (ramipril, perindopril) and ARBs (telmisartan) seem to provide similar effects regardless of age.
- ACE inhibitors (enalapril, imidapril, lisinopril) provide similar benefits as the calcium channel blocker nifedipine in either younger or older subjects with stable ischemic heart disease and preserved left ventricular function.
- While we cannot evaluate the impact of differing degrees of preserved left ventricular function on ACE inhibitor or ARB efficacy, a meta-analysis found similar reductions in the odds of total mortality and nonfatal myocardial infarction for ACE inhibitors versus placebo when comparing trials in preserved and compromised left ventricular function. As such, it is possible that similar benefits are derived across the spectrum of preserved left ventricular function as well.
- Subjects with diabetes mellitus will benefit as much from ACE inhibitor (ramipril, perindopril) or ARB (telmisartan) therapy as those without diabetes.
- It is possible that combination therapy with an ACE inhibitor (ramipril) plus ARB (telmisartan) might be better than ACE inhibitor (ramipril) therapy alone in patients with diabetes mellitus.
- ACE inhibitors (trandolapril, perindopril, ramipril) work at least as well in patients with renal dysfunction as those without renal dysfunction.
- Given the available results, ACE inhibitor (ramipril, perindopril) and ARB (telmisartan) therapy have similar effects in hypertensive and normotensive populations.
- ACE inhibitors (ramipril, perindopril) provide benefits regardless of the baseline risk.
- ARBs (telmisartan) may provide greater benefits in those at lowest baseline risk but ACE inhibitors (ramipril) may provide greater reductions in those at higher baseline risk.
- Subjects with a history of a revascularization procedure may have fewer benefits from ACE inhibitor (ramipril, perindopril) therapy than those without such a history.
- The impact of recent revascularization on the benefits and harms associated with ACE inhibitor or ARB therapy is answered in Key Questions 3 and 6.
- Subjects not receiving concomitant antiplatelet therapy may benefit more from ACE inhibitor (ramipril, perindopril) therapy than those receiving antiplatelet therapy.
- Beta-blocker (ramipril, perindopril), lipid lowering (ramipril, perindopril), and vitamin E (ramipril) therapy does not impact the benefits derived from ACE inhibitor therapy.

Detailed Analysis

Many of the major trials included in Key Question 1, base case analysis 1, performed subgroup analyses to assess the impact of baseline characteristics on the benefits seen with ACE inhibitors or ARBs. However, only the HOPE[38] trial and the TRANSCEND[51] trial used the composite endpoint of interest in this CER for subgroup analyses and for TRANSCEND,[51] this was not the primary subgroup analysis. In a meta-analysis, the endpoints of total mortality and nonfatal myocardial infarction were used for subgroup comparisons rather than a composite endpoint. As such, we are explicit in defining which endpoint is being used in each trial. It should be noted, however, that many of these analyses are underpowered and should be considered hypothesis generating and not necessarily used to make clinical decisions until they are verified in subsequent trials.

Sex

Two placebo controlled ACE inhibitor trials, HOPE[38] (ramipril) and EUROPA,[43] (perindopril) provide subgroup analysis based on gender. In the HOPE trial[38] (n=9,297), 2480 subjects (26.7 percent) were female. Upon subgroup analysis, ACE inhibitor therapy significantly reduced the risk of the composite endpoint (cardiovascular death, nonfatal myocardial infarction, or stroke) versus placebo in males and females. Qualitatively, slightly greater relative risk reductions occurred among females receiving ACE inhibitors than their male counterparts. In the EUROPA trial[43] (n=12,218), 1,779 subjects (14.6 percent) were female. Upon subgroup analysis, ACE inhibitors significant reduced the risk of the composite endpoint (cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) versus placebo in males (8.2 percent vs. 10.1 percent, $p<0.05$) but not in females (6.9 percent vs. 8.8 percent, $p>0.05$). Qualitatively, slightly greater relative risk reductions occurred among females receiving ACE inhibitors than their male counterparts. No statistical tests for interaction between the genders were undertaken in HOPE[38] or EUROPA[43] but the 95 percent confidence intervals had substantial overlap in both trials.

TRANSCEND[51] is the only placebo controlled ARB trial providing subgroup analysis based on gender. In TRANSCEND[51] (n=5,926), 2,547 subjects (43.0 percent) were female. ARB therapy with telmisartan significant reduced the hazard ratio of the composite endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure) versus placebo in males but not in females. There was a nonsignificant increase in risk among females receiving ARB therapy versus placebo. While a differential impact of ARB therapy on the composite endpoint was suggested between genders, the difference was not statistically significant (p-value for interaction = 0.08). When the composite endpoint assessed in the HOPE trial was used, the differential impact of ARB therapy between genders was less pronounced (p-value for interaction 0.16) but females still did not qualitatively benefit as much as males when given ARB therapy.[51]

ONTARGET[52] is the only direct comparative trial of an ACE inhibitor (ramipril), an ARB (telmisartan), and their combination. In the direct comparison between ACE inhibitor and ARB therapy from the ONTARGET trial (n=17,118), 4,581 subjects (26.8 percent) were female.[52] Upon subgroup analysis, ACE inhibitor and ARB therapy provided similar effect on the composite endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure), regardless of sex (p value for interaction 0.68). In fact, no significant impact on the composite endpoint between ACE inhibitor and ARB was seen in males (relative risk of approximately 1.0). Among females, ACE inhibitor therapy was slightly and

nonsignificantly better than ARB therapy. In the comparison between the ACE inhibitor and the combination of ACE inhibitor plus ARB (n=17,078), 4581 subjects (26.8 percent) were female. ACE inhibitor and combination therapy provided a similar effect on the composite endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure) in males (relative risk close to 1.0). Among females, combination therapy was slightly and nonsignificantly better than ACE inhibitor therapy.[52]

In a post-hoc analysis of the JMIC-B trial (n=1,650),[77] the effect of calcium channel blocker (nifedipine) or ACE inhibitor (enalapril, imidapril, lisinopril) on cardiac events (cardiac or sudden death, nonfatal myocardial infarction, angina or heart failure resulting in hospitalization, serious arrhythmia, or performance of coronary revascularization procedure) was investigated in 1,135 male (68.8 percent) and 515 female subjects (31.2 percent). The nifedipine and ACE inhibitor groups similarly impacted the incidence of cardiac events in males [RR 0.98 (0.72 to 1.34)] and females [RR 1.28 (0.76 to 2.14)].[77]

Age

In the HOPE trial[38] (n=9,297), subjects were evaluated in subgroups based on either a baseline age less than 65 years (4,169 subjects, 44.8 percent) or 65 years or older (5,128 subjects, 55.2 percent). Upon subgroup analysis, ACE inhibitor therapy with ramipril significantly reduced the relative risk of experiencing the composite endpoint (cardiovascular death, nonfatal myocardial infarction, or stroke) versus placebo in both younger and older subjects. The reductions in risk between younger and older subjects receiving ACE inhibitors were qualitatively similar with slightly greater reductions in the relative risk among those 65 years or older.[38] In the EUROPA trial[43] (n=12,218), three age subgroups were evaluated: 55 years or younger (n=3,948, 32.3 percent), 55 to 65 years (n=4,439, 36.3 percent), and greater than 65 years (n=3,831, 31.4 percent). Upon subgroup analysis, ACE inhibitor therapy with perindopril significantly reduced the relative risk of the composite endpoint (cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) versus placebo in subjects 55 years or younger and in subjects over 65 years of age.[43] However, the reductions in risk associated with ACE inhibitor treatment were similar between the three age groups with slightly greater reductions among those 55 years of age or younger. No statistical tests for interaction between the genders were undertaken in HOPE[38] or EUROPA[43] but the 95 percent confidence intervals had substantial overlap in both trials.

In the TRANSCEND trial[51] (n=5,926), three age subgroups were evaluated: under 65 years (n=2,375, 40.1 percent), 65 to 74 years (n=2,576, 43.5 percent), and greater than 74 years (n=975, 16.5 percent). None of the subgroups groups found that ARB therapy with telmisartan was significantly better than placebo at reducing the composite endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure). The youngest and oldest subgroup had hazard ratios below 1.0 and the 65-74 year subgroup was approximately 1.0 but this differential effect was not significant (p-value for interaction = 0.895).[51] When the composite endpoint assessed in the HOPE trial[38] was used, ACE inhibitor therapy did not significantly reduce the composite endpoint versus placebo in any of the three age subgroups but the hazard ratios were all less than 1.0 (p-value for interaction = 0.800).[51]

In the comparison between ACE inhibitor (ramipril) and ARB (telmisartan) therapy from the ONTARGET trial[52] (n=17,118), three age subgroups were evaluated: less than 65 years (n=7,319, 42.8 percent), 65 to 74 years (n=7,310, 42.7 percent), and greater than 74 years (n=2,489, 14.5 percent). ACE inhibitor and ARB therapy provided similar effects on the

composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure (p-value for interaction = 0.65). Qualitatively, ARBs were slightly better in those younger than 65 years of age and ACE inhibitors were slightly better in the two older subgroups. In the comparison between the ACE inhibitor and the combination of ACE inhibitor plus ARB (n=17,078), three age subgroups were evaluated: less than 65 years (n=7,362, 43.1 percent), 65 to 74 years (n=7,177, 42.0 percent), and greater than 74 years (n=2,539, 14.9 percent). ACE inhibitor and combination therapy provided a similar effect on the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure (p-value for interaction = 0.75). Qualitatively, younger patients did slightly better on ACE inhibitor therapy and the older age groups did slightly better on combination therapy.[52]

In a post-hoc analysis of the JMIC-B trial (n=1,650),[46] the effect of a CCB (nifedipine) or an ACE inhibitor (enalapril, imidapril, lisinopril) on cardiac events (cardiac or sudden death, nonfatal myocardial infarction, angina or heart failure resulting in hospitalization, serious arrhythmia, or performance of coronary revascularization procedure) was investigated in subjects younger than 66 years of age and in subjects 66 years of age and older. The CCB and ACE inhibitor groups similarly impacted the incidence of cardiac events in younger [RR 1.02 (0.69 to 1.51)] and older subjects [RR 1.09 (0.76 to 1.57)].[77]

Ethnicity/Genetic Polymorphisms

There is currently insufficient data to evaluate the impact of ethnicity on the benefits or harms that can be derived from ACE inhibitors or ARBs in patients with stable ischemic heart disease or ischemic heart disease risk equivalents, as ethnicity was not routinely reported in trials. For Key Question 1, the CAMELOT[45] and PEACE[47] trials reported that Caucasian subjects constituted 89-93 percent of patients. The TRANSCEND[51] trial reported the following ethnicity breakdown: 61 percent European. 21 percent Asian, 13 percent Native or Aboriginal, 1.7-1.9 percent African, 1.3 percent Arab. The JMIC-B trial[46] as well as Kondo et al (2003)[44] and Takahashi et al[49] were entirely conducted in Japan and likely had a high Asian population. For Key Question 2, the ONTARGET[52] trials' study population was similar to TRANSCEND[51]: 73 percent European, 14 percent Asian, 9 percent Native or aboriginal, 2 percent African, and 1 percent Arab. For Key Question 3, ethnicity was only reported in the QUIET[57] and IMAGINE[59] trials, with Caucasian subjects accounting for 94 percent and 96 percent of the total, respectively. The Kondo et al (2001)[55] trial was conducted in Japan and likely conducted in an Asian population. None of these trials from Key Questions 1 or 3 evaluated subgroups based on ethnicity.

None of the available studies evaluated benefits or harms of ACE inhibitors or ARBs in patients with stable ischemic heart disease or heart disease risk equivalents based on patients' genotypes.

Left Ventricular Ejection Fraction

No information is directly available to answer this portion of Key Question 7. However, in a previous meta-analysis by Dagenais et al.,[93] the results of the HOPE,[38] EUROPA,[43] and PEACE[47] trials (trials evaluating the impact of ACE inhibitor therapy in patients with preserved left ventricular function) and then the results for five previously conducted trials of patients with heart failure or left ventricular dysfunction were pooled. The reductions in odds associated with ACE inhibitor therapy versus placebo were similar between trials of preserved left ventricular

function [total mortality, OR 0.86 (0.74 –0.94); nonfatal myocardial infarction, OR 0.82 (0.75-0.91)] and those of left ventricular dysfunction [total mortality, OR 0.80 (0.74-0.87); nonfatal myocardial infarction, OR 0.77 (0.67-0.88)]. However, the absolute risk reduction associated with ACE inhibitor therapy is much smaller in the trials of subjects with preserved left ventricular function [total mortality 1.1 percent; nonfatal myocardial infarction 0.9 percent] and those with left ventricular dysfunction [total mortality 3.8 percent; nonfatal myocardial infarction 1.8 percent]. This means that a larger number needed to treat is required in order to prevent total mortality or nonfatal myocardial infarction in patients with preserved left ventricular function as versus those with left ventricular dysfunction.[93]

A systematic overview[103] of data from individual patients was conducted for the Survival and Ventricular Enlargement (SAVE),[104] Acute Infarction Ramipril Efficacy (AIRE),[105] and Trandolapril in patients with reduced left-ventricular function after acute myocardial infarction (TRACE)[106] trials by and Flather and colleagues.[103] In these trials, patients were post-myocardial infarction with left ventricular dysfunction. While not meeting the inclusion criteria for our review, they did evaluate the impact of ACE inhibitors versus placebo over 4 strata of LVEF (<23 percent, 23-27 percent, 28-35 percent, >35 percent). Qualitatively, the strata with the lowest LVEF (<23 percent) had a larger reduction in the odds of total mortality from ACE inhibitor therapy [OR 0.60 (0.43 to 0.85)] than the other strata [OR 0.82 (0.61 to 1.11), OR 0.68 (0.55 to 0.84), OR 0.87 (0.66 to 1.14), respectively] (p-value for interaction = 0.26). Similarly, the two strata of lowest LVEF (<23 percent, 23-27 percent) had qualitatively greater reductions in the odds for myocardial infarction [OR 0.62 (0.37 to 1.03) and OR 0.66 (0.42 to 1.03), respectively] with ACE inhibitor therapy than the two strata of higher LVEF [OR 0.86 (0.67 to 1.12) and OR 0.79 (0.57 to 1.09), respectively] (p-value for interaction = 0.31).[103] Additionally, the ORs for the strata with LVEF greater than 35 percent in this overview is similar to that in the preserved left ventricular function group in our review and the Dagenais et al, meta-analysis.[93]

So while we cannot determine the impact of differing left ventricular ejection fractions in a population with preserved left ventricular function, it is possible that the impact on the relative risk of our efficacy endpoints would be the same.

Degree and Location of Lesion

No information is available to answer this portion of Key Question 7.

Presence and Pattern of Symptoms

No information is available to answer this portion of Key Question 7.

Dose of ACE Inhibitor or ARB Used

No information is available to answer this portion of Key Question 7.

Diabetes Mellitus

In the HOPE trial[38] (n=9,297), ACE inhibitor therapy with ramipril significantly reduced the risk of experiencing the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and stroke versus placebo both in patients with (n=3,577, 38.5 percent) and without (n=5,720, 61.5 percent) diabetes mellitus (p<0.05 for both). Qualitatively, the relative risk reductions in patients with and without diabetes mellitus were quite similar and the 95 percent confidence intervals had significant overlap.[38] In the EUROPA trial[43] (n=12,218), ACE inhibitor therapy with perindopril significantly reduced the risk of experiencing the composite endpoint of

cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest versus placebo in the subgroup without diabetes mellitus (n=10,716, 87.7 percent), but not among those with diabetes mellitus (n=1,502, 12.3 percent). Qualitatively, the relative risk reductions in patients with and without diabetes mellitus were quite similar and the 95 percent confidence intervals had significant overlap.[43]

In the TRANSCEND trial[51] (n=5,926), ARB therapy with telmisartan did not significantly reduce the risk of experiencing the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure versus placebo both patients with (n=2,118, 35.7 percent) and without (n=3,805, 64.2 percent) diabetes mellitus; No significant interaction occurred between these subgroups (p-value for interaction = 0.311).[43] Qualitatively, the hazard ratio for experiencing the composite endpoint on ACE inhibitor therapy versus placebo for those with diabetes was approximately 1.0 and less than 1.0 for those without diabetes. When the composite endpoint assessed in the HOPE trial[38] was used, ACE inhibitor therapy did not significantly reduce the risk of experiencing the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure versus placebo in the subgroups with and without diabetes mellitus, both groups had hazard ratios less than 1.0; again, no significant interaction occurred between subgroups (p-value for interaction = 0.609).

In the comparison between ACE inhibitor (ramipril) and ARB (telmisartan) therapy from the ONTARGET trial[52] (n=17,118), ACE inhibitor and ARB therapy provided similar benefits on the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure versus placebo in the subgroups with (n=6,391, 37.3 percent) and without (n=10,722, 62.6 percent) diabetes mellitus and no significant interaction occurred between subgroups (p-value for interaction = 0.97).[52] Qualitatively, the hazard ratio for experiencing a composite endpoint while receiving ACE inhibitor therapy versus placebo for those with and without diabetes mellitus were approximately 1.0. In the comparison between the ACE inhibitor and the combination of ACE inhibitor plus ARB (n=17,078), those with diabetes (n=6,365, 37.3 percent) tended to have more benefit from combination therapy while those without diabetes (n=10,708, 62.7 percent) tended to have more benefit from ACE inhibitor therapy, although this differential effect was not significant (p-value for interaction = 0.15). Neither subgroup demonstrated a significant advantage of ACE inhibitor versus combination therapy or vice versa.[52]

In the MICRO-HOPE[75] substudy of the HOPE trial (n=9,297), the effect of ACE inhibitor ramipril on the risk of overt nephropathy was investigated in 3,577 patients (38.5 percent) with diabetes. The cumulative incidence of the composite endpoint of cardiovascular death, myocardial infarction and stroke was significantly lower with ACE inhibitor therapy than placebo [RR 0.75 (0.64 to 0.88); p=0.0004]. Benefit was noted with ramipril irrespective of whether participants had a history of cardiovascular events (p-value for interaction = 0.91), hypertension (p-value for interaction =0.93), or microalbuminuria (p-value for interaction = 0.34), whether participants had type 1 or type 2 diabetes (p-value for interaction = 0.32), and regardless of current treatment for hyperglycemia (p for interaction = 0.51). Ramipril had the same effect on the primary outcome after adjustment for changes in blood pressure [RR 0.75 (0.64 to 0.88)].[75]

In the PERSUADE[76] substudy of the EUROPA trial (n=12,218), the effect of the ACE inhibitor perindopril in reducing cardiovascular death, MI and other cardiovascular outcomes was investigated in 1,502 patients (12.3 percent) with diabetes. The cumulative incidence of the

composite endpoint of cardiovascular death, myocardial infarction, and cardiac arrest was nonsignificantly lower in the perindopril group than in the placebo group [RR 0.81 (0.62 to 1.07); p=0.131] , which is comparable to patients without diabetes [RR 0.81 (0.71 to 0.92). The combined incidence of total mortality, MI, unstable angina, and cardiac arrest as well as cardiovascular mortality, MI and stroke was nonsignificantly lower in the perindopril group than in the placebo group [RR 0.85 (0.68 to 1.05)] and [RR 0.86 (0.66 to 1.11).[76]

In a post-hoc analysis of the JMIC-B trial,[77] the effect of calcium channel blocker (nifedipine) or ACE inhibitor (enalapril, imidapril, lisinopril) on cardiac events was investigated in 372 patients (22.5 percent) with diabetes. The nifedipine and ACE inhibitor groups similarly impacted the incidence of cardiac events (cardiac or sudden death, nonfatal myocardial infarction, angina or heart failure resulting in hospitalization, serious arrhythmia, or performance of coronary revascularization procedure) in diabetic patients [RR 1.06 (0.61 to 1.84)].[77]

Renal Dysfunction

In a post-hoc analysis from the PEACE trial,[78] those with renal insufficiency (a calculated glomerular filtration rate below 60mg/mL/1.73m^2) were compared to those with normal renal function. Those with renal insufficiency had a higher incidence of total mortality than those with normal renal function in both the ACE inhibitor [HR 1.46 (1.07 to 2.00)] (trandolapril) and the placebo group [HR 1.91 (1.43 to 2.54)]. ACE inhibitor use reduced the incidence of total mortality versus placebo in those with [adjusted HR 0.73 (0.54 to 1.00)] but not without renal insufficiency [adjusted HR 0.94 (0.78 to 1.13)].[78]

In a post-hoc analysis from the EUROPA trial,[79] those with renal insufficiency (a calculated glomerular filtration rate below 75mL/min/1.73m^2) were compared to those without renal insufficiency. Those with renal insufficiency (n=6,295, 52.2 percent) were more likely than those without to experience the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest in the ACE inhibitor [HR 1.09 (1.03 to 1.15)] and the placebo group [HR 1.06 (1.02 to 1.12)]. ACE inhibitor (perindopril) use reduced the incidence of the composite endpoint versus placebo in those with [HR 0.84 (0.72 to 0.98)] and without [HR 0.77 (0.64 to 0.93)] renal insufficiency. Similar benefits were seen with ACE inhibitor therapy when glomerular filtration rate cut offs of 60 and 90 mL/min/1.73m^2 were used.[79]

In a post-hoc analysis of the HOPE trial,[80] the 980 patients (10.5 percent) with mild renal insufficiency (serum creatinine above 1.3mg/dL) were compared to those without renal insufficiency (n=8307, 89.4 percent). The cumulative incidence of the composite endpoint of cardiovascular death, nonfatal myocardial infarction and stroke was higher in patients with renal insufficiency than those without (22.2 percent vs. 15.1 percent, p<0.001). In addition, renal insufficiency was an independent predictor of the composite endpoint [adjusted HR 1.40 (1.16 - 1.69)]. ACE inhibitor therapy reduced the incidence of the composite endpoint in patients without [HR 0.79 (0.70 to 0.88)] and with renal insufficiency [HR 0.80 (0.59 to 1.09)] (p-value for interaction >0.2). ACE inhibitor (ramipril) therapy showed improvements in patients with renal insufficiency than those without renal insufficiency (p-value for interaction = 0.051) and was significantly better at preventing total mortality (p-value for interaction = 0.004) and hospitalization for heart failure (p-value for interaction = 0.019). The impact of ACE inhibitors on the other endpoints (myocardial infarction, stroke, and revascularization was similar (p-value for interaction for all endpoints >0.2).[80]

The EUROPA and PEACE trials excluded those with appreciable renal dysfunction (serum creatinines above 1.7 and 2.0, respectively) while HOPE excluded those with overt nephropathy.[38,43,47] As such, results may not be applicable in these populations.

Hypertension

In the HOPE trial[38] (n=9,297), subjects were evaluated in subgroups based on their history of hypertension (4,355 subjects, 46.8 percent) or no hypertension (4,942 subjects, 53.2 percent) at baseline. Upon subgroup analysis, ACE inhibitor therapy (ramipril) significantly reduced the relative risk of experiencing the composite endpoint (cardiovascular death, nonfatal myocardial infarction, or stroke) versus placebo in both groups of patients. The reductions in risk between subjects with and without hypertension receiving ACE inhibitors were qualitatively similar with slightly greater reductions in the relative risk among patients with hypertension.[38] In the EUROPA trial[43] (n=12,218), subjects were similarly evaluated in subgroups based on their history hypertension (3312 subjects, 27.1 percent) or no hypertension (8906 subjects, 72.9 percent) at baseline. Upon subgroup analysis, ACE inhibitor therapy (perindopril) significantly reduced the relative risk of the composite endpoint (cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest) versus placebo in subjects both with and without baseline hypertension. Furthermore, the reductions in risk associated with ACE inhibitor treatment were similar between the two groups with slightly greater reductions among those without hypertension.[43]

In the TRANSCEND trial[51] (n=5,926), three systolic blood pressure (SBP) subgroups were evaluated: (1) SBP of 133 or lower (n=1955, 33.0 percent), (2) SBP between 134 and 149 (n=1996, 33.7 percent), and (3) SBP greater than 149 (n=1969, 33.3 percent). None of the subgroups found that ARB therapy (telmisartan) was significantly better than placebo at reducing the composite endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure). The first and third subgroup had hazard ratios below 1.0 and the second subgroup was above 1.0 but this differential effect was not significant (p-value for interaction = 0.796).[51] When the composite endpoint assessed in the HOPE trial[38] was used, ACE inhibitor therapy did not significantly reduce the composite endpoint versus placebo in any of the three SBP subgroups (p-value for interaction = 0.773).[51]

In the comparison between ACE inhibitor (ramipril) and ARB (telmisartan) therapy from the ONTARGET trial[52] (n=17,118), three SBP subgroups were evaluated: SBP of 134 or lower (n=5704, 33.3 percent), SBP 135 to 150 (n=6042, 35.3 percent), and SBP greater than 150 (n=5352, 31.3 percent). ACE inhibitor was found to be better in patients with SBP above 134 while ARB therapy was found to be better in patients with SBP of 134 or below on the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure (p-value for interaction = 0.10). In the comparison between the ACE inhibitor (ramipril) and the combination of ACE inhibitor (ramipril) plus ARB (telmisartan), the same three subgroups were evaluated (n=17,078): SBP of 134 or lower (n=5714, 33.5 percent), SBP 135 to 150 (n=6019, 35.2 percent), and SBP greater than 150 (n=5329, 31.2 percent). ACE inhibitor and combination therapy demonstrated a non-significant effect on the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure (p-value for interaction = 0.15). Qualitatively, middle subgroup did slightly better with ACE inhibitor alone whereas the other two groups did slightly better on combination therapy.[52]

Baseline Risk

In the paper by Dagenais et al,[93] data from the HOPE,[38] EUROPA,[43] and PEACE[47] trials on baseline risk previously unreported elsewhere was made available, and as such, it has unique merit.[93]

The annual rate of experiencing a composite endpoint (cardiovascular death, nonfatal myocardial infarction, or stroke) in the placebo group was 3.95 in HOPE,[38] 2.60 in EUROPA,[43] and 2.13 in PEACE.[47] Through the use of individual patient data from the HOPE[38] and EUROPA[43] trials, the odds of experiencing a composite endpoint were assessed in risk tertiles based upon a baseline characteristic risk model. In HOPE,[38] as the baseline risk increased from low to medium to high, there were greater reductions in the odds of experiencing the composite endpoint associated with ACE inhibitor therapy (ramipril). This occurred in the low and medium risk groups in EUROPA[43] as well but the high-risk group actually had a smaller reduction in the odds of experiencing the composite endpoint. Given the wide 95 percent confidence intervals in these risk subgroups, the impact of baseline risk on the magnitude of ACE inhibitor (ramipril, perindopril) benefits is not well established but is an avenue for future research. However, the difference in baseline risk is unlikely to fully account for the differences between the PEACE[47] trial and the HOPE[38] and EUROPA[43] trials. The lowest risk tertile subgroups in HOPE[38] and EUROPA[43] had baseline risks similar to that in PEACE[47] but the reductions in odds associated with ACE inhibitor therapy (ramipril, perindopril) in these trials was approximately 15 percent as compared to 7 percent in PEACE (trandolapril).[47]

In TRANSCEND[51] (n=5,926), subjects were divided into three subgroups based on HOPE risk score (where a higher score indicates a higher risk of events): less than 3.625 (n=1,978, 33.4 percent), 3.625 to 4.034 (n=1934, 32.6 percent), greater than 4.034 (n=2,014, 34.0 percent). ARB therapy (telmisartan) was not significantly better than placebo therapy for the composite endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in any of the HOPE risk score subgroups. While there was no significant interaction between groups (p-value for interaction = 0.462), qualitatively the smallest hazard ratio occurred in the lowest risk subgroup and the hazard ratio closest to 1.0 occurred in the highest risk subgroup. When the composite endpoint assessed in the HOPE trial was used, the same nonsignificant graded relationship was noted (p-value for interaction = 0.460).[51]

In the comparison between the ACE inhibitor (rampiril) and ARB (telmisartan) from the ONTARGET trial,[52] subjects (n=17,118) were divided in to three subgroups based on HOPE risk score (where a higher score indicates a higher risk of events): less than 3.678 (n=5,751, 33.6 percent), 3.678 to 4.090 (n=5,620, 32.8 percent), greater than 4.090 (n=5,747, 33.6 percent). ACE inhibitor and ARB therapy provided similar effects on the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure among the 3 groups (p-value for interaction = 0.21). Qualitatively, ARBs were slightly better in those at lowest risk and ACE inhibitors were slightly better in the two higher risk subgroups. In the comparison between the ACE inhibitor and the combination of ACE inhibitor plus ARB (n=17,078), subjects were divided in to three subgroups based on HOPE risk score: less than 3.678 (n=5,676, 33.2 percent), 3.678 to 4.090 (n=5,570, 32.6 percent), greater than 4.090 (n=5,832, 34.1 percent). ACE inhibitor and combination therapy provided a similar effect on the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure among the three groups (p-value for interaction = 0.97).[52]

Concurrent Medical Therapy and Revascularization

To determine the impact of standard medical therapy and revascularization on results, a pooled data analysis of the HOPE[38] and EUROPA[43] trials were assessed by Dagenais et al.[93] ACE inhibitor therapy (ramipril, perindopril) was significantly better in patients without antiplatelet therapy [OR 0.60 (0.49 to 0.73)] than in those with antiplatelet therapy [OR 0.83 (0.76 to 0.90)] (p value for interaction < 0.003) and greater benefits occurred in patients without revascularization [OR 0.74 (0.66 to 0.82)] than in those with revascularization [OR 0.85 (0.75 to 0.96)] (p value for interaction = 0.078) for the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and stroke. No differential benefits were noted for those with [OR 0.75 (0.67 to 0.84)] or without beta-blockers [OR 0.82 (0.73 to 0.91)] (p value for interaction = 0.139) or those with [OR 0.80 (0.70 to 0.92)] or without lipid lowering agents [OR 0.77 (0.70 to 0.85)] (p value for interaction = 0.651). Importantly, in all of these subgroups, ACE inhibitors significantly reduced the odds of experiencing the composite endpoint as compared to placebo.

Unfortunately, the TRANSCEND[51] and ONTARGET[52] trials did not conduct subgroup analyses to assess benefits based on history of revascularization. The ONTARGET[52] trial did not conduct subgroup analyses to assess the impact of concurrent medications on benefits and the TRANSCEND[51] trial only evaluated the impact of statin therapy in subgroup analysis. In TRANSCEND (n=5926), 3272 subjects (55.2 percent) were receiving statin therapy.[51] ARB therapy (telmisartan) did not significantly impact the composite endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) versus placebo in those with or without statins. ARB therapy nonsignificantly reduced the hazard ratio among those receiving statins but the hazard ratio for those not receiving statins was approximately 1.0. While a differential impact of ARB therapy on the composite endpoint was suggested between those with and without statin therapy, this was not significant (p-value for interaction = 0.287). When the composite endpoint assessed in the HOPE[38] trial was used, the use of ARB therapy in both subgroups had hazard ratios less than 1.0 (p-value for interaction 0.279) but those receiving statins still benefited more qualitatively than those without statin therapy.

In HOPE[38] and EUROPA[43] (as well as all trials included in Key Questions 1 and 2), subjects could not have had recent revascularization at baseline. Key Questions 3 and 6 provides insight into the impact of starting ACE inhibitors or ARBs in close proximity to a revascularization procedure. As described in detail in those Key Questions, the benefits derived are not worth the risks associated with therapy. This may be because the risk of cardiovascular events is substantially attenuated in the months following revascularization so that the benefits of ACE inhibitor therapy are not as apparent but the harms persist.

The HOPE trial used a two-by-two factorial design where subjects were randomized to ramipril or placebo and then to vitamin E or placebo. Vitamin E had no significant impact on the primary composite outcome of cardiovascular mortality, nonfatal myocardial infarction or stroke either among subjects receiving ACE inhibitor therapy (338 events in vitamin E + ramipril vs. 313 events in ramipril + placebo, RR 1.08) or those not receiving ACE inhibitor therapy (421 vs. 405 events, respectively, RR 1.05).[107]

Discussion

This Key Question provides important information regarding the applicability of the efficacy data from Key Questions 1-3 and identifies several interesting avenues for future

research. Unfortunately, harms data was not evaluated in these subgroups so the balance of benefits to harms in these subgroups cannot be determined with confidence.

In a population with stable ischemic heart disease and preserved left ventricular function, females derived at least as much benefit as males from ACE inhibitor therapy. While we cannot state with certainty that ARBs do not work as well in females as in males, the subgroup analyses of the TRANSCEND[51] and ONTARGET trials,[52] which compared telmisartan to placebo and ramipril, respectively, support the need for more research in this area. ACE inhibitors appear to provide similar benefits as calcium channel blockers in either males or females with stable ischemic heart disease and preserved left ventricular function.

It is difficult to assess the impact of age on benefits given the differing age categories among different trials and the different variables constituting the composite endpoints. However, given the available evidence, the benefits of ACE inhibitor or ARB therapy appear similar regardless of baseline age. Since women with ischemic heart disease are, on average, older than their male counterparts, the similar impact of ARB therapy with telmisartan across age categories support the notion that it's the gender of subjects and not the age which is important but again, further research is needed. ACE inhibitors appear to provide similar benefits to calcium channel blockers in either younger or older subjects with stable ischemic heart disease and preserved left ventricular function.

Research is needed to determine if ethnicity impacts the benefits or harms associated with ACE inhibitors or ARBs in patients with stable ischemic heart disease and preserved left ventricular function. African American and Latino populations were largely underrepresented in the trials specifying the ethnicities of their subjects. In a reanalysis of the combined data from the Studies of Left-Ventricular Dysfunction (SOLVD) prevention and treatment trials comparing the ACE inhibitor enalapril versus placebo that was not included in this review, African American subjects with left ventricular dysfunction appear to derive similar benefits as Caucasians in total mortality (p–value for interaction = 0.68) but inferior benefits for hospitalizations due to heart failure (p-value for interaction = $p<0.01$). African Americans did not experience significant reductions in systolic or diastolic blood pressure from enalapril therapy ($p=0.25$ and $p=0.58$, respectively) while their Caucasian counterparts did ($p<0.01$ and $p<0.01$, respectively).[108] In hypertension trials, not included in this review, ACE inhibitors or ARBs did not lower blood pressure as effectively in African American subjects as they did in Caucasian subjects.[109] In a meta-analysis of 24 studies providing data on ethnicity and adverse events, the risk of angioedema was higher in African American subjects than non-African Americans [RR 3.0 (2.5 to 3.7)] and East Asians had a greater risk of cough than Caucasians [RR 2.7 (1.6 to 4.5)].[110] As such, there may be a different magnitude of response to ACE inhibitor therapy, ARB therapy, or their combination in African Americans. In Latinos, no such subgroup analyses are available to evaluate efficacy or safety in subjects with hypertension or left ventricular dysfunction. In addition, a suggestion can be made for not only evaluating various ethnic populations but also genetic groups. At present, a paucity of data exists regarding the genetic makeup of many ethnic groups. As such, the possibility exists that targeting therapy to a patients genetic background rather than ethnic background may better enhance therapeutic response and could also be the focus of future research in this area.

While none of the available trials evaluated benefits or harms based on patients' genotypes, this is an important area of future research. The ACE gene insertion (I) and deletion (D) polymorphism has been linked with higher plasma activity as well as greater risk of cardiovascular diseases. Subjects with the "DD" genotype have higher ACE activity, lesser

response to ACE inhibitors, and may have more extensive coronary disease compared to subjects with the "II" genotype.[111-113] A single nucleotide polymorphism for the angiotensin II type 1 receptor, the target of angiotensin II, likely impacts the actions of angiotensin II and carriers of a mutant genotype have greater aortic stiffness and pulse-wave velocity.[114] Thus, it is possible that ACE and angiotensin II type 1 receptor gene polymorphism could alter clinical responses to ACE inhibitors and ARBs compared to the populations studied as a whole. Research is needed to determine if these various polymorphisms impact the benefits or harms associated with ACE inhibitors or ARBs in patients with stable ischemic heart disease and preserved left ventricular function.

While we cannot directly evaluate the impact of varying levels of preserved left ventricular function on the efficacy of ACE inhibitors or ARBs, comparing those with preserved left ventricular function versus those with compromised function suggests that the relative reductions are the same but the absolute reductions are lower in those with preserved function. Further evaluation of those specifically with left ventricular dysfunction suggests that it is patients with LVEFs below 27% that may derive greater relative benefits but those with LVEFs above 27% derive a similar magnitude of relative benefit. This may hold true across the spectrum of subjects with normal left ventricular function.

There was no data available to determine if the location of coronary artery lesions impacted the efficacy derived from ACE inhibitor or ARB therapy. In a previous meta-analysis of 4 post-myocardial infarction multicenter trials, the short term use of ACE inhibitors reduced total mortality versus placebo (7.11 percent vs. 7.59 percent, $p<0.004$).[115] Subjects with anterior myocardial infarctions receiving ACE inhibitor therapy did significantly better than those with other types of myocardial infarction (14 percent mortality reduction vs. 2 percent reduction, $p=0.01$). However, this likely reflects the greater myocardial cell loss in anterior infarctions versus lateral and inferior infarctions and the subsequently greater need for left ventricular remodeling.[111] As such, having a stable plaque in the left anterior descending or left main coronary artery may not impact the efficacy derived from ACE inhibitors versus stable plaques in the circumflex or right coronary artery.

Diabetic patients with stable ischemic heart disease and preserved left ventricular function derive benefit from ACE inhibitor and ARB therapy that is similar to that of nondiabetics. There was a suggestion that greater efficacy could be derived from combination therapy with an ACE inhibitor plus ARB versus an ACE inhibitor alone in patients with diabetes mellitus but more research is needed. In trials not meeting the inclusion criteria for this review, the use of combination therapy with an ACE inhibitor, ARB, or renin inhibitor in subjects with diabetes mellitus and evidence of micro- or macroalbuminuria was associated with greater renal protection than using a single renin-angiotensin system blocking agent alone.[116-120] As we found in this review, subjects with renal dysfunction have an elevated risk of developing cardiovascular events as compared to those without renal dysfunction. As such, preventing renal dysfunction with combination renin-angiotensin system blockade in those with diabetes mellitus might impact cardiovascular events. While we could not find differences in cardiovascular events between those subjects with diabetes mellitus receiving ACE inhibitor therapy and those receiving calcium channel blocker therapy, we would be cautious about extrapolating this data to include diabetics with renal dysfunction. The incidence of underlying micro- or macroalbuminuria in the JMIC-B[46] trial population was unknown and direct comparative trials of ARBs versus calcium channel blockers in diabetics with micro- or macroalbuminuria, not eligible for this review, show superior prevention of renal endpoints with ARBs.[120,121]

Patients with renal dysfunction have at least as robust relative reductions in the risk of cardiovascular events when ACE inhibitors are given as compared to placebo. Even in the PEACE[47] trial where the benefits associated with ACE inhibitor therapy was not as robust, no significant benefits were seen in the subgroup with renal dysfunction receiving ACE inhibitors versus those receiving placebo. Hopefully, the TRANSCEND[52] and ONTARGET[51] trials will also evaluate the impact of ARB and combination therapy with an ACE inhibitor plus ARB in those with and without renal dysfunction.

It is difficult to assess the impact of SBP on the results given the differing SBP categories in the different trials and the different variables constituting the composite endpoints. However, given the available evidence, the benefits of ACE inhibitor or ARB therapy appear similar regardless of baseline SBP.

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. These results are far from definitive however and more research is needed. There are no readily apparent pharmacologic differences between the ACE inhibitors and ARBs that would account for this potentially differential response. Perhaps, the lowest risk group was least likely to receive aspirin therapy that may attenuate the benefits of ACE inhibitors.

The use of antiplatelet therapy might attenuate the benefits seen with ACE inhibitors but the impact of antiplatelet therapy on the benefits associated with ARBs is not known.[122-126] Pharmacologically, the use of nonsteroidal anti-inflammatory drugs, such as aspirin, may prevent the ability of ACE inhibitors to release vasodilatory prostaglandins through the preservation of bradykinin.[122-126] Since ARBs do not preserve bradykinin, there may not be the same risk of interaction via this mechanism but more work is needed. Nonsteroidal anti-inflammatory drugs can still cause sodium and water retention, elevate blood pressure, and reduce glomerular filtration rate which can negatively impact patients with stable ischemic disease regardless of ACE inhibitor or ARB therapy. An evaluation of aspirin therapy versus adenosine diphosphate inhibitors on the benefits derived from ACE inhibitor therapy is also warranted, as adenosine diphosphate inhibitors do not impact prostaglandin concentrations.

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. Similarly, vitamin E therapy does not impact the efficacy of ACE inhibitor therapy.

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, on-pump coronary artery bypass grafting, atherectomy) on the benefits associated with ACE inhibitors and ARBs. The benefits derived from initiating ACE inhibitor or ARB therapy along with a revascularization procedure are not worth the risk of harms.

Summary and Discussion

A succinct summary of evidence on comparative long-term benefits and harms of ACE inhibitors and/or ARBs in patients with preserved left ventricular function who have stable ischemic heart disease or heart disease risk equivalents is presented in Table 15. More elaborate discussions are provided at the end of the results for each Key Question. More detailed assessments of strength of evidence for major clinical outcomes and harms are summarized in a EPC grading table of evidence (Appendix Tables 41-47). Major clinical outcomes are those explicitly stated in Key Questions 1-3 and 7 and harms in Key Questions 4-6. Members of the TEP identified these outcomes as important because they are most relevant to patients, clinicians, and policymakers; and have adequate data from studies meeting eligibility criteria for the comparative effectiveness review. Clinical outcomes included total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, a composite of cardiovascular mortality, nonfatal myocardial infarction and stroke, atrial fibrillation, symptom reporting, total hospitalizations, hospitalization for angina, hospitalization for heart failure, revascularization and quality of life. Harms included withdrawals due to adverse events, hypotension, syncope, cough, angioedema, hyperkalemia, rash, and blood dyscrasias.

Table 15. Outcomes, strength of evidence, and conclusions

Key Question	Strength of evidence	Conclusions
KQ1. 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?		
KQ1a. Total mortality	High High Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, imidapril, lisinopril*) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.

	Low Low Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.
KQ1b. Cardiovascular mortality	Moderate Moderate Moderate	▪ ACE inhibitor or ARB therapy is similar to placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, imidapril, lisinopril*) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo in patients with ischemic heart disease risk equivalents. ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.
KQ1c. Nonfatal myocardial infarction	High High Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril) are similar to calcium channel blockers (amlodipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.

	Low Low Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo in patients with ischemic heart disease risk equivalents. ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.
KQ1d. Stroke	Moderate Moderate Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, imidapril, lisinopril*) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Low Low Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo in patients with ischemic heart disease risk equivalents. ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.
KQ1e. Composite of cardiovascular mortality, nonfatal myocardial infarction, or stroke	High Moderate Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (ramipril, trandolapril) are similar placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is better than placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to calcium channel blockers in patients with stable ischemic heart disease.
	Low Low Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo in patients with ischemic heart disease risk equivalents. ▪ ACE inhibitors (fosinopril) are similar to placebo in patients with stable ischemic heart disease risk equivalents. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease risk equivalents.

KQ1f. Atrial fibrillation	High	▪ ACE inhibitor (ramipril) or ARB (telmisartan) therapy is similar to placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1g. Symptom reporting	Moderate	▪ ACE inhibitor (zofenopril) therapy increases the time to onset of ischemic symptoms via treadmill exercise test versus placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1h. Total hospitalization	Moderate	▪ ACE inhibitor (ramipril) or ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1i. Hospitalization for angina	High	▪ ACE inhibitor (enalapril, ramipril) or ARB (telmisartan) therapy is similar to placebo in patients with stable ischemic heart disease.
	Moderate	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, imidapril, lisinopril*) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1j. Hospitalization for heart failure	High High Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.

	Moderate Moderate Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, imidapril, lisinopril*) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1k. Revascularization	High High Moderate	▪ ACE inhibitor or ARB therapy is better than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, perindopril, ramipril) are better than placebo in patients with stable ischemic heart disease. ▪ ARB therapy (telmisartan) is similar to placebo in patients with stable ischemic heart disease.
	Moderate Moderate Insufficient	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, imidapril, lisinopril*) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ1l.Quality of life	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to either placebo or calcium channel blockers in patients with ischemic heart disease or ischemic heart disease risk equivalents.
KQ1 Discussion: 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 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 trial was the only placebo controlled trial available to evaluate major efficacy outcomes for ARB therapy. ARB therapy was associated with similar reductions in the composite endpoint of cardiovascular mortality, nonfatal myocardial infarction, and stroke as the pooled results from the HOPE and PEACE trials comparing ACE inhibitors versus 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 confidence indirect comparisons and direct evidence comparing ACE inhibitors and ARBs (evaluated in KQ2) should be considered.		
KQ2. 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?		

KQ2a. Total mortality	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2b. Cardiovascular mortality	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2c. Fatal + nonfatal myocardial infarction	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2d. Fatal + nonfatal stroke	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2e. Composite of cardiovascular mortality, fatal + nonfatal myocardial infarction, and fatal + nonfatal stroke	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2f. New atrial fibrillation	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2g. Worsening or new angina	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2h. Total hospitalization	Insufficient	▪ No data is available comparing the combination of ACE inhibitor + ARB therapy vs. ACE inhibitor therapy alone in patients with stable ischemic heart disease.
KQ2i. Hospitalization for angina	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2j. Hospitalization for heart failure	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2k. Revascularization	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) is similar to ACE inhibitor (ramipril) alone in patients with stable ischemic heart disease.
KQ2l. Quality of life	Insufficient	▪ No data is available comparing the combination of ACE inhibitor + ARB therapy vs. ACE inhibitor therapy alone in patients with stable ischemic heart disease.
KQ2 Discussion. There is direct comparative evidence from the ONTARGET 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 was 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 KQ1.		

KQ3. 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?		
KQ3a. Total mortality	Moderate	▪ ACE inhibitor (cilazapril, quinapril, ramipril) or ARB (candesartan) therapy is similar to placebo.
KQ3b. Cardiovascular mortality	Low	▪ ACE inhibitor (quinapril, ramipril) or ARB (candesartan) therapy is similar to placebo.
KQ3c. Nonfatal myocardial infarction	Low	▪ ACE inhibitor (cilazapril, quinapril) or ARB (candesartan) therapy is similar to placebo.
KQ3d. Stroke	Low	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo. ▪ ACE inhibitors (quinapril, ramipril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3e. Composite of cardiovascular mortality, nonfatal myocardial infarction, and stroke	Moderate	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo. ▪ ACE inhibitors (quinapril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3f. Atrial fibrillation	Moderate	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo. ▪ ACE inhibitors (quinapril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3g. Symptom reporting	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo.
KQ3h. Total hospitalization	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo.
KQ3i. Hospitalization for angina	Moderate	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo. ▪ ACE inhibitors (quinapril, ramipril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3j. Hospitalization for heart failure	Low	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to placebo. ▪ ACE inhibitors (quinapril, ramipril) are similar to placebo. ▪ ARB therapy was not evaluated vs. placebo.
KQ3k. Revascularization	High	▪ ACE inhibitor or ARB therapy is worse than placebo. ▪ ACE inhibitors (cilazapril, quinapril) are worse than placebo. ▪ ARB (candesartan) therapy is similar to placebo.
KQ3l.Quality of life	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo.

KQ3 Discussion. Trials compared the addition of ACE inhibitors or ARBs to standard medical therapy versus 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, with the exception of the "need for subsequent revascularization" endpoint, 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, 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 a patient with ischemic heart disease derives benefits from these agents? A majority of the trials included in Key Question 1, including HOPE, PEACE, and EUROPA, included patients that 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 thus more concrete interpretations cannot be made until this evidence becomes available.		
KQ4. 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?		
KQ4a. Withdrawals due to adverse events	Low	▪ The risk of withdrawing from a trial was greater with ACE inhibitor or ARB therapy (ARB not evaluated) vs. placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, ramipril, trandolapril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Low	▪ ACE inhibitor or ARB therapy (ARB not evaluated) is similar to calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, imidapril, lisinopril*) are similar to calcium channel blockers (amlodipine, nifedipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4b. Hypotension	Low	▪ The risk of hypotension was similar with ACE inhibitor or ARB therapy (ARB not evaluated) vs. placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, ramipril, zofenopril) are similar to placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.

	Low	▪ The risk of hypotension with ACE inhibitor or ARB therapy (ARB not evaluated) is greater than calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril) are worse than calcium channel blockers (amlodipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4c. Syncope	Low	▪ The risk of syncope with ACE inhibitor or ARB therapy (ARB not evaluated) was greater than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (ramipril, trandolapril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4d. Cough	Low	▪ The risk of cough with ACE inhibitor or ARB therapy (ARB not evaluated) was greater than placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril, ramipril, trandolapril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Low	▪ The risk of cough with ACE inhibitor or ARB therapy (ARB not evaluated) is greater than calcium channel blockers in patients with stable ischemic heart disease. ▪ ACE inhibitors (enalapril) are worse than calcium channel blockers (amlodipine) in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. calcium channel blockers in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.

KQ4e. Angioedema	Low	▪ The risk of angioedema was similar with ACE inhibitor or ARB therapy (ARB not evaluated) vs. placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (ramipril, trandolapril) are similar to placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4f. Hyperkalemia	Low	▪ The risk hyperkalemia with ACE inhibitor (ramipril) or ARB (telmisartan) therapy is greater than placebo therapy in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4g. Rash	Insufficient	▪ No data is available comparing ACE inhibitors or ARBs to placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4h. Blood dyscrasias	Insufficient	▪ No data is available comparing ACE inhibitors or ARBs to placebo in patients with stable ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitors or ARBs to calcium channel blockers in patients with ischemic heart disease.
	Insufficient	▪ No data is available comparing ACE inhibitor or ARB therapy to placebo in patients with ischemic heart disease risk equivalents.
KQ4 Discussion. ACE inhibitors or ARBs significantly increase the risk of withdrawing due to adverse events, syncope, cough and hyperkalemia as compared with placebo. ACE inhibitors or ARBs significantly increased the risk of cough and hypotension as compared with CCBs. A number of the included trials included 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 those 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 as compared with placebo (p=0.049). Thus it appears that in patients with stable ischemic heart disease who cannot tolerate ACE inhibitors or are at an increased risk for harms, that ARBs may be a relatively safe alternative. 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.		

KQ5. 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?		
KQ5a. Study withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) had more discontinuations than ACE inhibitor (ramipril) alone.
KQ5b. Hypotension withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) had more discontinuations due to hypotension than ACE inhibitor (ramipril) alone.
KQ5c. Syncope withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) had more discontinuations due to syncope than ACE inhibitor (ramipril) alone.
KQ5d. Cough withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) had a similar number of discontinuations due to cough as ACE inhibitor (ramipril) alone.
KQ5e. Angioedema withdrawal	Low	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) had a similar number of discontinuations due to angioedema as ACE inhibitor (ramipril) alone.
KQ5f. Renal impairment withdrawal	Moderate	▪ Combination of ACE inhibitor + ARB (ramipril + telmisartan) had more discontinuations due to renal impairment than ACE inhibitor (ramipril) alone.
KQ5g. Rash	Insufficient	▪ No data is available comparing the combination of ACE inhibitor + ARB therapy vs. ACE inhibitor therapy alone in patients with stable ischemic heart disease.
KQ5h. Blood dyscrasias	Insufficient	▪ No data is available comparing the combination of ACE inhibitor + ARB therapy vs. ACE inhibitor therapy alone in patients with stable ischemic heart disease.
KQ5 Discussion. 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 similar efficacy as 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.		
KQ6. 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?		
KQ6a. Study withdrawal	Low	▪ The risk of withdrawals was greater with ACE inhibitor or ARB therapy (ARB not evaluated) vs. placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (quinapril, ramipril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.

KQ6b. Hypotension	Moderate	▪ The risk of hypotension was greater with ACE inhibitor or ARB therapy (ARB not evaluated) vs. placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (quinapril) are worse than placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
KQ6c. Syncope	Insufficient	▪ No data is available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ6d. Cough	Low	▪ The risk of cough with ACE inhibitor or ARB therapy (ARB not evaluated) was similar to placebo in patients with stable ischemic heart disease. ▪ ACE inhibitors (quinapril) are similar to placebo in patients with stable ischemic heart disease. ▪ ARB therapy was not evaluated vs. placebo in patients with stable ischemic heart disease.
KQ6e. Angioedema	Insufficient	▪ No data is available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ6f. Renal impairment or hyperkalemia	Insufficient	▪ No data is available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ6g. Rash	Insufficient	▪ No data is available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ6h. Blood dyscrasias	Insufficient	▪ No data is available evaluating ACE inhibitors or ARBs in patients with stable ischemic heart disease.
KQ6 Discussion. The constituent trials did not utilize a lengthy run-in period. Only the APRES 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, they all agreed on the direction of effect, and two of the three trials individually found ACE inhibitors to increase cough versus 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.		
KQ7. 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, co-morbidities (diabetes, renal dysfunction, hypertension), and other medications (vitamins, lipid lowering drugs, beta-blockers, anti-platelet agents)?		
KQ7a. Sex	Moderate	▪ ACE inhibitors (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or of one of the following depending on the trial: stroke or nonfatal cardiac arrest) similarly in males and females.
	Low	▪ ARB therapy (telmisartan) may not reduce the composite efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure in females as much as in males (p-value for interaction = 0.08).

	Low	▪ When ACE inhibitor (ramipril) and ARB (telmisartan) therapy are directly compared, there is a nonsignificant indication that ACE inhibitor therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in females than ARB therapy with similar efficacy between treatments in males.
	Low	▪ When ACE inhibitor therapy (ramipril) was compared with combination therapy with ACE inhibitors and ARBs (ramipril + telmisartan), there is a nonsignificant indication that combination therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in females than ACE inhibitor therapy with similar efficacy between treatments in males.
	Low	▪ ACE inhibitors (enalapril, imidapril, lisinopril) appear to be similar to calcium channel blockers (nifedipine) in efficacy in either males or females with stable ischemic heart disease and preserved left ventricular function.
	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in males and females cannot be determined at this time.
KQ7b. Age	Low	▪ ACE inhibitors (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or of one of the following depending on the trial: stroke or nonfatal cardiac arrest) versus placebo in both younger and older subjects.
	Low	▪ ARB therapy (telmisartan) impacted the composite efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure similarly versus placebo in those under 65 years, 65 to 74 years, and greater than 74 years of age (p-value for interaction = 0.895). No significant benefits were seen with ARB therapy in any of the age subgroups versus placebo.
	Low	▪ When ACE inhibitor therapy (ramipril) was compared to ARB therapy (telmisartan) or to the combination of ACE inhibitor plus an ARB (ramipril + telmisartan), results were similar in the different age subgroups for the composite efficacy endpoint (cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure).
	Low	▪ ACE inhibitors (enalapril, imidapril, lisinopril*) appear to be similar to calcium channel blockers (nifedipine) in efficacy in either younger or older subjects with stable ischemic heart disease and preserved left ventricular function.
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in subjects of differing ages cannot be determined at this time.
KQ7c. Ethnicity/genetic polymorphisms	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination in subjects of differing ethnicity or genetic polymorphisms cannot be determined at this time.

KQ7d. Left ventricular ejection fraction	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination in subjects with varying degrees of preserved left ventricular function cannot be determined at this time.
KQ7e. Degree and location of lesion	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination in subjects with differing extents and locations of atherosclerotic lesions cannot be determined at this time.
KQ7f. Presence and pattern of symptoms	Insufficient	▪ The impact of the ACE inhibitors, ARBs, and their combination in subjects of different presence and pattern of angina symptoms cannot be determined at this time.
KQ7g. Dose of ACE inhibitor or ARB used	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on efficacy or harms depending on the dose employed cannot be determined at this time.
KQ7h. Diabetes mellitus	Moderate	▪ ACE inhibitors (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or of one of the following depending on the trial: stroke or nonfatal cardiac arrest) similarly in patients with and without diabetes mellitus.
	Low	▪ ARB therapy (telmisartan) impacted the composite efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure similarly versus placebo in those with or without diabetes mellitus (p-value for interaction = 0.311). No significant benefits were seen with ARB therapy in either subgroup versus placebo.
	Low	▪ ACE inhibitor therapy (ramipril) provides similar efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) to ARB therapy (telmisartan) in those with or without diabetes mellitus.
	Low	▪ When ACE inhibitor therapy (ramipril) was compared to combination therapy with ACE inhibitors and ARBs (ramipril + telmisartan), there is a nonsignificant indication that combination therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in those with diabetes mellitus than ACE inhibitor therapy but similar efficacy occurs between treatments in those without diabetes mellitus (p-value for interaction = 0.15).
	Low	▪ ACE inhibitor therapy (enalapril, imidapril, lisinopril*) provided similar efficacy as calcium channel blocker (nifedipine) therapy in those with diabetes mellitus.
	Insufficient	▪ The impact of ACE inhibitors, ARBs, and their combination on harms in patients with or without diabetes mellitus cannot be determined at this time.
KQ7i. Renal dysfunction	Low	▪ ACE inhibitor therapy (perindopril, ramipril, trandolapril) may prevent cardiovascular events and total mortality better in those with mild to moderate renal dysfunction than those without it.

	Insufficient	▪ The impact of ARB therapy on cardiovascular events and total mortality in those with and without renal dysfunction cannot be determined at this time.
	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in patients with or without renal dysfunction cannot be determined at this time.
KQ7j. Hypertension	Moderate	▪ ACE inhibitor therapy (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or of one of the following depending on the trial: stroke or nonfatal cardiac arrest) similarly in those with or without hypertension.
	Low	▪ ARB therapy (telmisartan) impacted the composite efficacy endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure similarly versus placebo in those with systolic blood pressures of <135mmHg, 135-149mmHg, or >149mmHg (p-value for interaction = 0.796).
	Low	▪ When ACE inhibitor (ramipril) and ARB (telmisartan) therapy are directly compared, there is a nonsignificant indication that ACE inhibitor therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in those with baseline systolic blood pressures above 134mmHg while ARBs might provide greater efficacy in those with baseline systolic blood pressures of 134mmHg or below (p-value for interaction = 0.10).
	Low	▪ When ACE inhibitor therapy (ramipril) was compared to combination therapy with ACE inhibitors and ARBs (ramipril + telmisartan), there is a nonsignificant indication that combination therapy may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in those with baseline systolic blood pressures of 134mmHg of less and those with a baseline systolic blood pressure of 150mmHg or more. ACE inhibitor therapy alone tended to provide greater efficacy in the middle blood pressure range (p-value for interaction = 0.15).
	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in patients with or without hypertension cannot be determined at this time.
KQ7k. Baseline Risk	Low	▪ ACE inhibitors (perindopril, ramipril) reduce composite efficacy endpoints (cardiovascular death, nonfatal myocardial infarction, or of one of the following depending on the trial: stroke or nonfatal cardiac arrest) in low, medium, and high baseline risk categories versus placebo. As the baseline risk is increased, the benefits from ACE inhibitor therapy might be accentuated.

	Low	▪ ARB therapy (telmisartan) might provide greater efficacy versus placebo in low baseline risk patients than those with medium or high risk for the composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure (p-value for interaction = 0.462).
	Low	▪ ACE inhibitor therapy (ramipril) may provide greater efficacy (composite endpoint of cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure) in those at medium to high baseline risk while ARB therapy (telmisartan) may provide more efficacy in those at lower baseline risk (p-value for interaction = 0.21).
	Low	▪ Combination therapy with an ACE inhibitor plus an ARB (ramipril + telmisartan) provides similar efficacy as an ACE inhibitor alone regardless of baseline risk (p-value for interaction = 0.97).
	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in patients with different baseline risk cannot be determined at this time.
KQ7l. Antiplatelet therapy	Moderate	▪ ACE inhibitor therapy (perindopril, ramipril) is significantly better at reducing the composite endpoint of cardiovascular death, nonfatal myocardial infarction and stroke than placebo in patients without antiplatelet therapy versus those with antiplatelet therapy (p-value for interaction < 0.003).
	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in patients with antiplatelet therapy cannot be determined at this time.
KQ7m. History of revascularization	Moderate	▪ ACE inhibitor therapy (perindopril, ramipril) is likely better at reducing the composite endpoint of cardiovascular death, nonfatal myocardial infarction and stroke than placebo in patients without a history of revascularization versus those with such as history (p-value for interaction = 0.078).
	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in patients with or without a history of revascularization cannot be determined at this time.
KQ7n. Beta-blockers	Moderate	▪ ACE inhibitors (perindopril, ramipril) provided similar ability to reduce the composite endpoint of cardiovascular death, nonfatal myocardial infarction and stroke versus placebo in patients with or without beta-blockers (p-value for interaction = 0.134)
	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in patients with or without beta-blockers cannot be determined at this time.
KQ7o. Lipid lowering therapy	Moderate	▪ ACE inhibitors (perindopril, ramipril) provided a similar ability to reduce the composite endpoint of cardiovascular death, nonfatal myocardial infarction and stroke versus placebo in patients with or without lipid lowering therapy (p-value for interaction = 0.651)

	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in patients with or without lipid lowering therapy cannot be determined at this time.
KQ7p. Vitamin E therapy	Low	▪ ACE inhibitors (ramipril) provided similar ability to reduce the composite endpoint of cardiovascular death, nonfatal myocardial infarction and stroke versus placebo in patients with or without vitamin E therapy
	Insufficient	▪ The impact of ACE inhibitors, ARBs and their combination on harms in patients with or without vitamin E therapy cannot be determined at this time.
KQ7 Discussion. This KQ 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 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 towards benefits were seen in the subgroup with renal dysfunction receiving ACE inhibitors versus 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 that may subsequently 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.		

Legend: * The JMIC-B trial compared the calcium channel blocker nifedipine to one of three ACE inhibitors (enalapril, imidapril, or lisinopril) while the CAMELOT trial compared calcium channel blocker amlodipine to the ACE inhibitor enalapril.

Future Research

While there are numerous future trials, studies, and evaluations that could be undertaken, and are elucidated throughout the results section of this report; we believe that the following are areas of particular importance to patient care.

- An individual patient data meta-analysis of major placebo-controlled ACE inhibitor or ARB trials or future trials is needed to provide insight into the benefits and harms in minority groups, including Asians, African Americans and Latinos. We cannot determine the comparative benefits and harms associated with the use of these drugs in these populations based on the data provided to date.
- An individual patient data meta-analysis of major placebo-controlled ACE inhibitor or ARB trials or future trials are needed to provide insight into the benefits and harms in patients with single versus multivessel disease and specifically to determine if left anterior descending artery disease is more important than disease in other vessels in predicting efficacy and harms.
- An individual patient data meta-analysis of major placebo-controlled ACE inhibitor or ARB trials is needed to determine if an association exists with a baseline ejection fraction between 40 percent and 70 percent and the benefits or harms associated with therapy.
- An individual patient data meta-analysis is needed to determine if ACE inhibitors provide greater benefits in patients taking adenosine diphosphate drugs than those taking no antiplatelet therapy to tease out if the interaction noted between antiplatelets and ACE inhibitors is applicable to all antiplatelets or just to aspirin. Determining the impact of antiplatelet therapy on ARB therapy efficacy is also needed.
    - There is moderate strength of evidence from the pooled data analysis of the HOPE and EUROPA trials[93] that ACE inhibitors benefit those receiving and not receiving antiplatelet agents as compared to placebo but that those without antiplatelet agents benefit significantly more. However, we cannot be sure that this interaction is between all antiplatelet agents and ACE inhibitors or specifically with aspirin therapy. If it is not attributable to adenosine diphosphate inhibitors then these agents may be substituted for aspirin therapy when ACE inhibitors are used. There is no data on harms in these two subgroups so the balance of benefits to harms cannot be determined in these subgroups. Additionally, no data is available evaluating ARBs in these subgroups. If the benefits derived from ARBs are not impacted by the presence of antiplatelet therapy, this may be a therapeutic alternative to ACE inhibitors.
- An individual patient data meta-analysis is needed to determine if a history of revascularization significantly reduces the benefits associated with ACE inhibitor or ARB therapy and to elucidate the impact on harms associated with these therapies in this population.
    - There is moderate strength of evidence from the pooled data analysis of the HOPE and EUROPA trials[93] that ACE inhibitors benefit those with and without a history of revascularization. However, the benefits versus placebo were nonsignificantly better in those without revascularizations. Performing an individual patient data meta-analysis with the inclusion of more trials can discern

if there are significantly less benefits in those with revascularization. In addition, harms were not evaluated in these subgroups but this is needed to determine the balance of benefits to harms. There is no subgroup data available evaluating benefits or harms with ARBs in patients with or without revascularization either.

- Future trials are needed to discern if adding ACE inhibitors or ARBs to standard medical therapy in patients with stable ischemic heart disease and preserved left ventricular function is superior or inferior to adding other cardiovascular drugs such as calcium channel blockers.
    - There is moderate strength of evidence from two trials that ACE inhibitor or ARB therapy provides similar benefits as calcium channel blockers. The trials were only of modest size and we cannot evaluate the applicability of these results to subjects of different genders, age, comorbidities, and medications. We were unable to determine if other vasoactive drugs such as thiazide diuretics may also provide a similar level of benefit as ACE inhibitors or ARBs.
- Future trials are needed to determine the benefits and harms associated with adding ACE inhibitors or ARBs to standard medical therapy in patients without proven stable ischemic heart disease but with ischemic heart disease risk equivalents.
    - The applicability of these results to subjects of different genders, age, comorbidities, and medications are needed.
- Future studies are needed to determine if the dosing intensity of ACE inhibitor or ARB therapy is related to the extent of efficacy and harms that patients receive.
- Future trials are needed to determine the impact of genetic polymorphisms within the ACE gene or the angiotensin II type 1 receptor and the benefits or harms associated with ACE inhibitors or ARBs in this population.
- Of note, a review of trials registered at www.clinicaltrials.gov [Accessed January 8, 2009] revealed no ongoing trials that would have matched our inclusion criteria or answered any of the remaining clinical questions proposed in this section.

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Abbreviations

Acronym/Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
AHRQ	Agency for Healthcare Research and Quality
AIRE	Acute Infarction Ramipril Efficacy
AMSTAR	Assess the Methodological quality of SysteMAtic Review
APRES	Angiotensin-converting Enzyme inhibition Post Revascularization Study
ARB	Angiotensin Receptor Blocker
CABG	Coronary Artery Bypass Grafting
CAMELOT	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis
CCB	Calcium Channel Blocker
CHARM	Candesartan in Heart failure Assessment of Reduction in Mortality
CI	Confidence Interval
DBP	Diastolic Blood Pressure
EPC	Evidence-based Practice Center
EUROPA	EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease
FOSIDIAL	FOSInopril in DIALysis
GRADE	Grading of Recommendations Assessment, DEvelopment
HDL	High Density Lipoprotein
HOPE	Heart Outcomes Prevention Evaluation
HR	Hazard Ratio
IMAGINE	Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme
ITT	Intention To Treat
JMIC-B	Japan Multicenter Investigation for Cardiovascular Diseases-B
LDL	Low Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
MARCATOR	Multicenter American Research trial with Cilazapril After angioplasty to prevent Transluminal coronary Obstruction and Restenosis
MI	Myocardial Infarction
MICRO-HOPE	Microalbuminuria, Cardiovascular and Renal Outcomes – Heart Outcomes Prevention Evaluation
ONTARGET	ONgoing Telmisartan Alone in combination with Ramipril Global Endpoint Trial
PARIS	Effect of ACE inhibitors on angiographic restenosis after coronary stenting
PART-2	Prevention of Atherosclerosis with Ramipril Trial-2
PEACE	Prevention of Events with Angiotensin Converting Enzyme Inhibition

PICOTS	Population, Intervention, Comparator, Outcomes, Timing of outcomes measurement, Setting
QUIET	Quinapril Ischemic Event Trial
RCT	Randomized Controlled Trial
Ischemic Heart Disease Risk Equivalent	Diabetes mellitus or chronic kidney disease, or mixed vascular atherosclerotic disorders (coronary disease, peripheral artery disease, carotid atherosclerosis)
RR	Relative Risk
SAVE	Survival And Ventricular Enlargement
SBP	Systolic Blood Pressure
SCAT	Simvastatin/enalapril Coronary Atherosclerosis Trial
SMILE-ISCHEMIA	Survival of Myocardial Infarction Long-term Evaluation-ISCHEMIA
TRACE	Trandolapril in patients with reduced left-ventricular function after acute myocardial infarction
TRANSCEND	Telmisartan Ransomized AssessmenNt Study in ACE iNtolerant subjects with cardiovascular Disease
SCR	Scientific Resource Center
VALIANT	VALsartan In Acute myocardial iNfarction Trial
WMD	Weighted Mean Difference