Comparative Effectiveness Review
Number 18

Effective Health Care Program

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

Executive Summary

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

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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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 Insuffient	• 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.

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
KQ1b. Cardiovascular mortality (continued)	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.

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
KQ1d. Stroke (continued)	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.

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
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.

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
KQ1j. Hospitalization for heart failure (continued)	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.

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
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.

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
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.

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

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.

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

KQ4b. Hypotension (continued)	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.

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

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.

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
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.

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

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).

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
KQ7a. Sex (continued)	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).

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
KQ7b. Age (continued)	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.

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
KQ7h. Diabetes mellitus (continued)	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.

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
KQ7j. Hypertension (continued)	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).

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
KQ7k. Baseline risk (continued)	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).

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
KQ7n. Beta-blockers (continued)	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 results, 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.

- 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 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.

Full Report

This executive summary is part of the following document: Coleman CI, Baker WL, Kluger J, Reinhart K, Talati R, Quercia R, Mather J, Giovenale S, White CM. Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease. Comparative Effectiveness Review No. 18. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) Rockville, MD: Agency for Healthcare Research and Quality. October 2009. Available at: **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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