Annals of Internal Medicine | Review

Systematic Review: Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors or Angiotensin II–Receptor Blockers for Ischemic Heart Disease

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Background: Patients with ischemic heart disease and preserved ventricular function experience considerable morbidity and mortality despite standard medical therapy.

Purpose: To compare benefits and harms of using angiotensin-converting enzyme (ACE) inhibitors, angiotensin II–receptor blockers (ARBs), or combination therapy in adults with stable ischemic heart disease and preserved ventricular function.

Data Sources: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (earliest date, July 2009) were searched without language restrictions.

Study Selection: Two independent investigators screened citations for trials of at least 6 months' duration that compared ACE inhibitors, ARBs, or combination therapy with placebo or active control and reported any of several clinical outcomes.

Data Extraction: Using standardized protocols, 2 independent investigators extracted information about study characteristics and rated the quality and strength of evidence. Disagreement was resolved by consensus.

Data Synthesis: 41 studies met eligibility criteria. Moderate- to high-strength evidence (7 trials; 32 559 participants) showed that ACE inhibitors reduce the relative risk (RR) for total mortality (RR, 0.87 [95% CI, 0.81 to 0.94]) and nonfatal myocardial infarction (RR, 0.83 [CI, 0.73 to 0.94]) but increase the RR for syncope (RR, 1.24 [CI, 1.02 to 1.52]) and cough (RR, 1.67 [CI, 1.22 to 2.29]) compared with placebo. Low-strength evidence (1 trial; 5926 participants) suggested that ARBs reduce the RR for the composite end point of cardiovascular mortality, nonfatal myocardial infarction, or stroke (RR, 0.88 [CI, 0.77 to 1.00]) but not for the individual components. Moderate-strength evidence (1 trial; 25 620 participants) showed similar effects on total mortality (RR, 1.07 [CI, 0.98 to 1.16]) and myocardial infarction (RR, 1.08 [CI, 0.94 to 1.23]) but an increased risk for discontinuations because of hypotension ($P < 0.001$) and syncope ($P = 0.035$) with combination therapy compared with ACE inhibitors alone.

Limitations: Many studies either did not assess or did not report harms in a systematic manner. Many studies did not adequately report benefits or harms by various patient subgroups.

Conclusion: Adding an ACE inhibitor to standard medical therapy improves outcomes, including reduced risk for mortality and myocardial infarctions, in some patients with stable ischemic heart disease and preserved ventricular function. Less evidence supports a benefit of ARB therapy, and combination therapy seems no better than ACE inhibitor therapy alone and increases harms.

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An estimated 16 800 000 adults have ischemic heart disease (1). Standard medical therapy for these patients includes aspirin, β-blockers, and aggressive modification of risk factors (2, 3). Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II–receptor blockers (ARBs) have established benefit in patients with heart failure and those who have had a myocardial infarction with ventricular dysfunction (4–11). Their use, however, in patients with preserved ventricular function is less certain.

Previous systematic reviews (12–17) have not included recent ACE inhibitor trials conducted in this population. In addition, no systematic review has evaluated ARB therapy or the combination of ACE inhibitor and ARB therapy in this population. The Agency for Healthcare Research and Quality commissioned this report (18) to review the evidence for the clinical effects and harms of using ACE inhibitors, ARBs, or combination therapy in adult patients with stable ischemic heart disease and preserved ventricular function receiving standard medical therapy.

Methods

We developed and followed a standard protocol for all steps of this review. A technical report that details methods, including literature search strategies and analysis plans, and includes evidence tables is available at www.effectivehealthcare.ahrq.gov (18). That report also includes information specific to patients who have recently had or will have a coronary revascularization procedure and to patients with an ischemic heart disease risk equivalent.

See also:

Print
Editors' Notes 862

Web-Only
Appendix Table
Appendix Figure
CME quiz
Conversion of graphics into slides

Context

Do patients already receiving standard therapy for ischemic heart disease benefit from additional treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II–receptor blockers (ARBs)?

Contribution

Authors of this systematic review concluded that ACE inhibitors reduce risk for mortality, stroke, and myocardial infarction in patients with stable ischemic heart disease and preserved left ventricular function who already receive standard treatments, such as β-blockers, statins, and aspirin. Evidence about effects of ARBs was scant. Combining ACE inhibitors and ARBs increased risks for hypotension and syncope compared with ACE inhibitor therapy alone.

—The Editors

Key Questions

We refined key questions on the effectiveness of ACE inhibitors and ARBs in adults with stable ischemic heart disease and preserved ventricular function receiving standard medical therapy. We wrote these questions with input from a technical expert panel that included cardiologists, pharmacists, an internist, and a managed care organization representative. The following key questions were formulated.

1. In patients with stable ischemic heart disease who have preserved ventricular function, what are the benefits and harms of adding ACE inhibitors or ARBs to standard medical therapy compared with standard medical therapy alone?

2. In patients with stable ischemic heart disease who have preserved ventricular function and are receiving standard medical therapy, what are the benefits and harms of combining ACE inhibitors and ARBs compared with either an ACE inhibitor or an ARB alone?

3. What is the evidence that benefits or harms differ in prespecified subpopulations?

Data Sources and Searches

We searched MEDLINE (1966 to July 2009), EMBASE (1990 to July 2009) (19), and Cochrane Central Register of Controlled Trials (second quarter of 2009) (20) for both randomized, controlled trials (RCTs) and observational studies. We searched for systematic reviews in MEDLINE (1966 to July 2009) and the Cochrane Database of Systematic Reviews (second quarter of 2009) with no language restrictions. We also manually searched references from trials or reviews and major cardiology meeting abstracts (American Heart Association, American College of Cardiology, and European Society of Cardiology for June 2006 to July 2009). We ultimately did not include any studies that were published only in abstract form. We contacted authors of 11 trials to obtain information on their inclusion and exclusion criteria, including data on mean ejection fraction and inclusion of patients with heart failure, and received responses from 10. We also contacted authors from 4 trials for additional information about various clinical outcomes and were successful in getting additional information about such clinical outcomes as mortality (in 2 RCTs), myocardial infarction (in 3 RCTs), stroke (in 2 RCTs), and the composite of the 3 (in 3 RCTs).

Study Selection

Two independent reviewers assessed studies for inclusion in a parallel manner by using a priori–defined criteria. To assess potential benefits, we selected RCTs if they had 1) compared ACE inhibitor or ARB therapy with placebo or active control or compared combination ACE inhibitor and ARB therapy with either agent alone, 2) included patients with stable ischemic heart disease, 3) included patients with preserved left ventricular function (an average ejection fraction in experimental groups >0.40 or no systematic evaluation of left ventricular ejection fraction but exclusion of patients with signs or symptoms of heart failure), 4) included at least 75 patients, 5) followed patients for at least 6 months, and 6) reported data on at least 1 prespecified efficacy outcome (total mortality, cardiovascular mortality, nonfatal myocardial infarction, stroke, or a composite of the latter 3 end points).

We included RCTs in the harms evaluation if they satisfied criteria 1 to 5 above and reported data on a prespecified harm (including withdrawals due to adverse events, hypotension, syncope, or cough). We included observational studies if they met the first 3 criteria above, included at least 1000 patients, followed patients for at least 6 months, and reported data on a prespecified harm (withdrawals due to adverse events, hypotension, syncope, or cough).

Data Extraction and Quality Assessment

Two reviewers used a standardized data abstraction tool to independently extract study data. Data obtained from each study included interventions, study design, inclusion and exclusion criteria, methodological quality criteria, study population, patient baseline characteristics, use of concurrent standard medical therapies, benefits, and harms.

To ascertain the validity of eligible RCTs, 2 independent reviewers assessed the adequacy of randomization, concealment of allocation, blinding of patients, and use of intention-to-treat methodology. We used Evidence-based Practice Center methodology based on Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods, to assess the strength of evidence. We used 4 required domains: risk for bias, consistency, directness, and precision (21). Evidence pertaining to each key question was classified into 3 broad categories: high, moderate, or low. **Table 1** shows the results of this grading. The Assess the Methodological Quality of Systematic Review (AMSTAR) checklist was used to assess methodological quality of systematic reviews (22). We resolved disagreements about abstracted data, quality assessments, and ratings of evidence through discussion.

Table 1. **Outcomes, Strength of Evidence, and Conclusions**

Outcome, by Question	Strength of Evidence*	Conclusions
Question 1†		
Total mortality	High	ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo, but ARB therapy (telmisartan) is similar to placebo.
Cardiovascular mortality	Moderate	ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo, but ARB therapy (telmisartan) is similar to placebo.
Nonfatal MI	High	ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo, but ARB therapy was not evaluated versus placebo.
Stroke	Moderate	ACE inhibitors (enalapril, perindopril, ramipril, trandolapril) are better than placebo, but ARB therapy (telmisartan) is similar to placebo.
Composite‡	High	ACE inhibitors (ramipril, trandolapril) are similar to placebo, and ARB therapy (telmisartan) is better than placebo.
Study withdrawal due to adverse events	Low	The risk for study withdrawal was greater with ACE inhibitors (enalapril, ramipril, trandolapril) versus placebo, but ARB therapy was not evaluated versus placebo.
Hypotension	Low	The risk for hypotension was similar with ACE inhibitors (enalapril, ramipril, zofenopril) versus placebo, but ARB therapy was not evaluated versus placebo.
Syncope	Low	The risk for syncope was greater with ACE inhibitors (ramipril, trandolapril) versus placebo, but ARB therapy was not evaluated versus placebo.
Cough	Low	The risk for cough was greater with ACE inhibitors (enalapril, ramipril, trandolapril) versus placebo, but ARB therapy was not evaluated versus placebo.
Question 2§		
Total mortality	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) is similar to ACE inhibitor (ramipril) alone.
Cardiovascular mortality	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) is similar to ACE inhibitor (ramipril) alone.
Fatal and nonfatal MI	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) is similar to ACE inhibitor (ramipril) alone.
Fatal and nonfatal stroke	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) is similar to ACE inhibitor (ramipril) alone.
Composite‡	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) is similar to ACE inhibitor (ramipril) alone.
Study withdrawal, by event		
Adverse event	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) caused more study withdrawals due to adverse events than did ACE inhibitor (ramipril) alone.
Hypotension	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) caused more study withdrawals due to hypotension than did ACE inhibitor (ramipril) alone.
Syncope	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) caused more study withdrawals due to syncope than did ACE inhibitor (ramipril) alone.
Cough	Moderate	Combination of ACE inhibitor and ARB (ramipril and telmisartan) caused similar numbers of study withdrawals due to cough as did ACE inhibitor (ramipril) alone.
Question 3‖		
Sex	Moderate	ACE inhibitors (perindopril, ramipril) reduce the composite efficacy end point (cardiovascular death, nonfatal MI, or 1 of the following depending on the trial: stroke or nonfatal cardiac arrest) similarly in men and women.
	Low	ARB therapy (telmisartan) may not reduce the composite efficacy end point of cardiovascular death, nonfatal MI, stroke, or heart failure hospitalization in women as much as in men (P value for interaction = 0.084).
LV ejection fraction	Insufficient	The effect of ACE inhibitors, ARBs, and their combination in participants with varying degrees of preserved LV function cannot be determined.
Baseline risk	Low	ACE inhibitors (perindopril, ramipril) reduce composite efficacy end points (cardiovascular death, nonfatal MI, or 1 of the following depending on the trial: stroke or nonfatal cardiac arrest) in low-, medium-, and high-risk baseline categories versus placebo. As the baseline risk is increased, the benefits from ACE inhibitor therapy might be increased.
	Low	ARB therapy (telmisartan) might provide greater efficacy versus placebo in patients with low baseline risk than in those with medium or high baseline risk for the composite end point of cardiovascular death, nonfatal MI, stroke, or heart failure (P value for interaction = 0.462).
Antiplatelet therapy	Moderate	ACE inhibitor therapy (perindopril, ramipril) is significantly better at reducing the composite end point in patients without antiplatelet therapy versus those with antiplatelet therapy (P value for interaction $<$ 0.003).
β-Blocker or lipid-lowering therapy	Moderate	ACE inhibitors (perindopril, ramipril) provided similar ability to reduce the composite end point versus placebo in patients with or without β-blocker (P value for interaction = 0.134) and lipid-lowering (P value for interaction = 0.651) therapy.
History of revascularization	Moderate	ACE inhibitor therapy (perindopril, ramipril) is probably better at reducing the composite end point versus placebo in patients without a history of revascularization than in those with such history (P value for interaction = 0.078).

ACE = angiotensin-converting enzyme; ARB = angiotensin II–receptor blocker; LV = left ventricular; MI = myocardial infarction.
* The strength of the evidence rating was determined for the primary analysis, combining ACE inhibitors and ARBs. The strength of the evidence for ACE inhibitors and ARBs separately was determined on only selected outcomes as requested by the Agency for Healthcare Research and Quality and can be found in the full report (18).
† Question 1: In patients with stable ischemic heart disease who have preserved ventricular function, what are the benefits and harms of adding ACE inhibitors or ARBs to standard medical therapy compared with standard medical therapy alone?
‡ Composite of cardiovascular mortality, nonfatal MI, and stroke.
§ Question 2: In patients with stable ischemic heart disease who have preserved ventricular function and are receiving standard medical therapy, what are the benefits and harms of combining ACE inhibitors and ARBs versus using either an ACE inhibitor or an ARB alone?
‖ Question 3: What is the evidence that benefits or harms differ in prespecified subpopulations?

Data Synthesis and Analysis

We qualitatively examined data from all identified studies. We conducted meta-analyses when 2 or more RCTs adequate for pooling were available. We reported outcomes as pooled relative risks (RRs) with associated 95% CIs by using a random-effects model (23). We assessed statistical heterogeneity by using the I^2 statistic (24). We evaluated the presence of publication bias and related biases by using funnel plots and Egger tests (25, 26), but the small number of studies limited the ability of these methods to detect publication bias (data not shown). We conducted an analysis comparing either an ACE inhibitor or an ARB with a control and then conducted analyses in which ACE inhibitor or ARB trials were evaluated separately.

Role of the Funding Source

This project was prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center, Hartford, Connecticut, with funding from the Agency for Healthcare Research and Quality. The funding source formulated the initial study questions and provided copyright release for this manuscript, but did not participate in the literature search, data analysis, or interpretation of results.

RESULTS

Results of Primary Literature Review

We screened 1531 abstracts and evaluated 366 full-text articles (**Appendix Figure**, available at www.annals.org). A total of 44 articles (27–70), reporting on 9 RCTs (28, 31–33, 35, 37, 40–42) and 2 nonrandomized comparative studies (34, 36), as well as 6 systematic reviews (12–17) met our eligibility criteria.

Evidence of Benefits With ACE Inhibitors or ARBs

Eight RCTs (37 148 participants) met our inclusion criteria (**Appendix Table**, available at www.annals.org) (28, 31–33, 35, 37, 40, 41). All of the RCTs were placebo-controlled (28, 31–33, 35, 37, 40, 41), and 1 also had an active comparator group (amlodipine) (35). All but 1 RCT (33) had adequate randomization, double blinding, and intention-to-treat methods. Seven of the RCTs evaluated ACE inhibitors, with 2 using enalapril (32, 35); 2 using ramipril (28, 31); and 1 each using perindopril (33), trandolapril (37), and zofenopril (40). We identified a single RCT that evaluated the ARB telmisartan (41) in patients with a history of intolerance to ACE inhibitors.

The mean age of the trial participants ranged from 57 to 67 years; 57% to 89% of participants were men. In all, 8% to 39% of participants had diabetes, 27% to 100% had hypertension, 7% to 45% had peripheral vascular disease, and 3% to 22% had a previous stroke or transient ischemic attack. Baseline medical therapy use also varied between trials. β-Blocker, antiplatelet, and lipid-lowering therapies were used in 10% to 79%, 3% to 95%, and 28% to 84% of patients in these studies, respectively. Differences between use of baseline therapy may have been related to the standard of care at the time the study was conducted or to underlying medical conditions of the patient population.

Total and Cardiovascular Mortality

Seven RCTs reported data on total mortality (28, 31–33, 35, 37, 41). Pooled analysis showed that ACE inhibitors reduced the risk for total mortality (RR, 0.87 [95% CI, 0.81 to 0.94]; $I^2 = 0\%$) compared with placebo. A single RCT that included patients intolerant to ACE inhibitors suggested that ARBs did not affect risk for total mortality compared with placebo (RR, 1.05 [CI, 0.91 to 1.20]) (41). The pooled RR that included the ACE inhibitor trials and the single ARB trial was 0.91 (CI, 0.84 to 0.98; $I^2 = 21.5\%$) (**Figure**).

Six RCTs reported data on cardiovascular mortality (28–31, 33, 35, 37, 41). Pooled analysis showed that ACE inhibitors compared with placebo reduced the risk for cardiovascular mortality (RR, 0.83 [CI, 0.70 to 0.98]; $I^2 = 45.5\%$). A single RCT suggested that ARBs did not affect risk for cardiovascular mortality compared with placebo (RR, 1.02 [CI, 0.86 to 1.22]). The pooled RR that included the ACE inhibitor trials and the single ARB trial was 0.87 (CI, 0.75 to 1.02; $I^2 = 57.9\%$) (**Figure**). The pooled result and CI are suggestive of and compatible with a reduced risk for cardiovascular mortality. The heterogeneity is caused, in part, by the inclusion of the ARB trial and 1 ACE inhibitor trial (35), which suggested an increased risk for events with ACE inhibitor use. The increased baseline use of antiplatelet agents, shorter follow-up, and decreased intensity of ACE inhibition in that trial versus other ACE inhibitor trials may explain the findings.

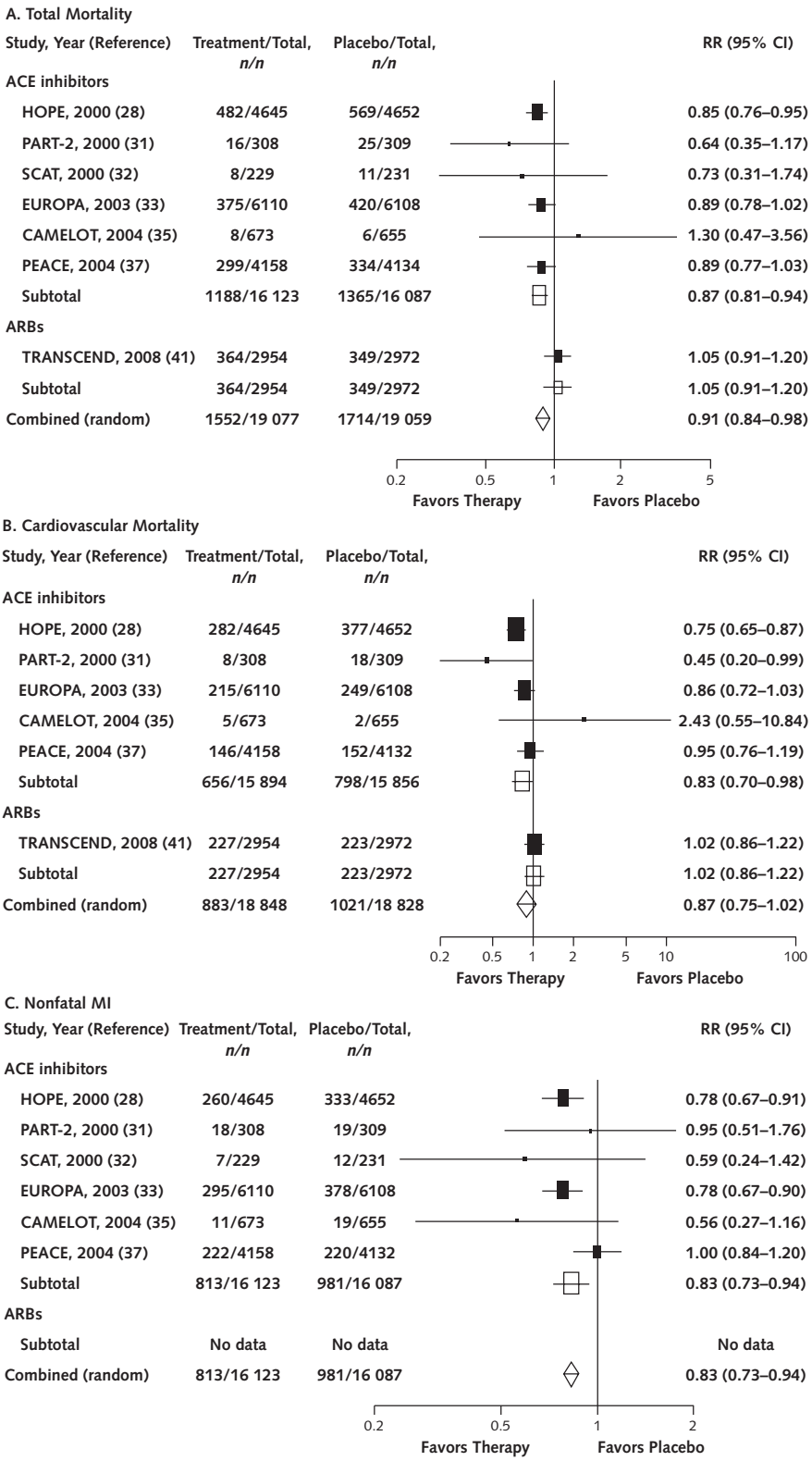
Nonfatal Myocardial Infarction

Six RCTs evaluating ACE inhibitors reported data on nonfatal myocardial infarction (28–33, 35, 37). All but 1 RCT (33) had adequate randomization, double blinding, and intention-to-treat methods. Pooled analysis demonstrated that ACE inhibitors reduced the risk for nonfatal myocardial infarction (RR, 0.83 [CI, 0.73 to 0.94]; $I^2 = 30.5\%$) compared with placebo (**Figure**). Two of the RCTs (33, 35) with small sample sizes and low event rates showed more dramatic reductions in the risk for nonfatal myocardial infarction than the others, but the CIs were very large and overlapped with the pooled estimate.

Stroke

Seven RCTs reported data on stroke (28–33, 35, 37, 41). Pooled analysis showed that ACE inhibitors reduced the risk for stroke (RR, 0.78 [CI, 0.63 to 0.97]; $I^2 = 37.7\%$) compared with placebo. The pooled RR in the single ARB trial was 0.83 (CI, 0.65 to 1.06), which suggests and is compatible with a reduced risk for stroke. The

Figure. **Meta-analysis of randomized, placebo-controlled trials of ACE inhibitors or ARBs in patients with stable ischemic heart disease and preserved left ventricular systolic function.**



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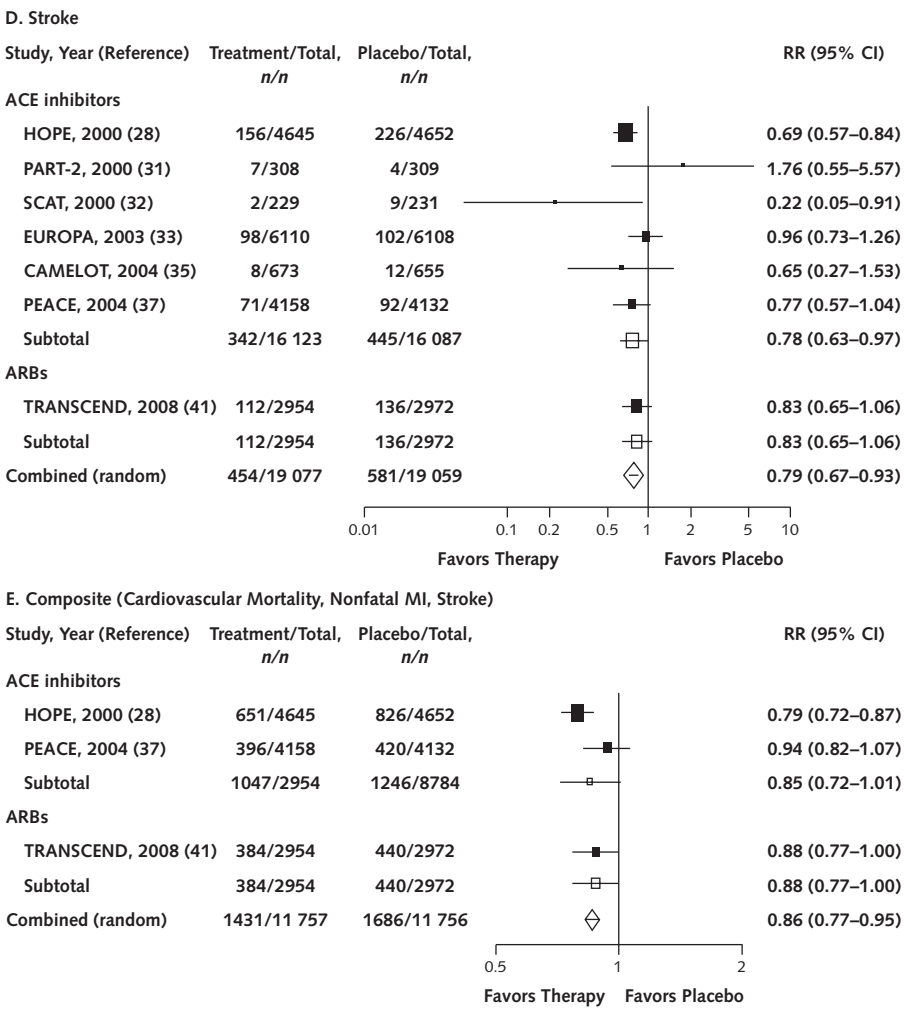

ACE = angiotensin-converting enzyme; ARB = angiotensin II–receptor blocker; CAMELOT = Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis; EUROPA = European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; HOPE = Heart Outcomes Prevention Evaluation; MI = myocardial infarction; PART-2 = Prevention of Atherosclerosis with Ramipril 2; PEACE = Prevention of Events with Angiotensin Converting Enzyme Inhibition; RR = relative risk; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; TRANSCEND = Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease.

pooled RR estimate that included the ACE inhibitor trials and the single ARB trial was 0.79 (CI, 0.67 to 0.93; I^2 = 27.6%) (**Figure**). One RCT (31), which used a different event definition (nonfatal stroke requiring hospital admission), suggested that patients receiving ACE inhibitors had an increased risk for stroke compared with those receiving placebo. Another RCT (32) showed that ACE inhibitors compared with placebo decreased risk for stroke more than that reported in other trials. Both trials had a small sample size and event rate, which resulted in CIs that overlapped with the pooled estimate.

Composite End Point

Three RCTs (28, 37, 41) reported data on the composite end point (cardiovascular mortality, nonfatal myocardial infarction, or stroke). Pooled analysis of 2 RCTs (28, 37) suggested that ACE inhibitors reduced the risk for the composite end point (RR, 0.85 [CI, 0.72 to 1.01]) compared with placebo. The single ARB trial also suggested a reduced risk (RR, 0.88 [CI, 0.77 to 1.00]). The pooled RR that included the ACE inhibitor trials and the single ARB trial was 0.86 (CI, 0.77 to 0.95; I^2 = 58.0%), probably due to increased power (**Figure**).

Evidence of Harms With ACE Inhibitors or ARBs

Withdrawals Due to Adverse Events

Three of 8 RCTs (31, 35, 37) reported data on withdrawals due to adverse events, all evaluating ACE inhibitors (**Table 2**). Pooled analysis of these selected reports suggested that patients receiving ACE inhibitors

were more likely than those receiving placebo to withdraw because of adverse events (RR, 2.30 [CI, 1.34 to 3.95]; $I^2 = 87.2\%$). One study (31) showed a more than 10-fold increase in the risk for withdrawals (RR, 10.37 [CI, 3.42 to 31.72]), whereas another study (37) showed a slightly more than 2-fold increase (RR, 2.21 [CI, 1.93 to 2.54]).

Hypotension

Three of 8 trials (28, 35, 40) reported data on hypotension, all evaluating ACE inhibitors (**Table 2**). One study (28) reported only serious adverse events and therefore reported a decreased rate, whereas another study (35) reported a higher rate of hypotension (9.5% in the ACE inhibitor group) than other studies (0.04% to 1.2% in the ACE inhibitor group) (28, 40). Pooled analysis showed no overall effect of ACE inhibitors on hypotension risk (RR, 1.79 [CI, 0.68 to 4.71]; $I^2 = 40.6\%$), although the CI was wide and the analysis was probably underpowered.

Syncope

Two of 8 trials (28, 37) reported data on syncope, both evaluating ACE inhibitors (**Table 2**). One trial (28) reported syncope as a serious adverse event, resulting in a low risk for syncope (0.04%) compared with the other trial (4.4%) (37). Pooled analysis showed that ACE inhibitors increased the risk for syncope (RR, 1.24 [CI, 1.02 to 1.52]) compared with placebo.

Cough

Three of 8 trials (28, 35, 37) reported data on cough, all evaluating ACE inhibitors (**Table 2**). The overall incidence of cough varied widely between trials, with 1 trial (27) reporting only serious events and thus a decreased overall rate (0.3%). The other 2 trials (35, 37) reported rates of cough of 9.2% and 33.3%. Pooled analysis showed an increased risk for cough with ACE inhibitors (RR, 1.67 [CI, 1.22 to 2.29]; $I^2 = 60.2\%$) compared with placebo.

Evidence of Benefits and Harms With a Combination of ACE Inhibitors and ARBs

We found 1 trial (42) of combination therapy in this population. The ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) investigators randomly assigned 25 620 patients with vascular disease or high-risk diabetes to 1 of 3 therapies (ramipril, telmisartan, or combination of the 2 drugs) for a mean of 4.5 years (42). Total mortality (RR, 1.07 [CI, 0.98 to 1.16]), cardiovascular mortality (RR, 1.04 [CI, 0.93 to 1.17]), total myocardial infarctions (RR, 1.08 [CI, 0.94 to 1.23]), stroke (RR, 0.93 [CI, 0.81 to 1.07]), or the composite of the latter 3 end points (RR, 1.00 [CI, 0.93 to 1.09]) did not significantly differ between combination therapy and ramipril alone. Combination therapy, however, was associated with more study discontinuations ($P < 0.001$), as well as discontinuations due to hypotension ($P < 0.001$) and syncope ($P = 0.03$), compared with ramipril alone.

The ONTARGET investigators also evaluated the comparative effectiveness of an ACE inhibitor with that of an ARB. No differences were found in any aforementioned end points when ACE inhibitor and ARB therapy were directly compared. However, ARB therapy did result in fewer study discontinuations ($P = 0.02$) and discontinuations due to hypotension ($P < 0.001$) and cough ($P < 0.001$) than did ACE inhibitor therapy (42).

Evidence of Benefits and Harms, by Subpopulation

We found few trials that evaluated the comparative benefits or harms of ACE inhibitors, ARBs, or their combination in various patient subgroups. A pooled analysis of 2 trials (28, 33) demonstrated that ACE inhibitors reduced event rates more in patients who did not receive antiplatelet therapy than in those who did receive it (P value for interaction < 0.003) (13). Angiotensin-converting enzyme inhibitors reduced event rates more in patients without previous coronary revascularization than in those with revascularization (P value for interaction $= 0.078$). No differential benefits resulting from ACE inhibitors were noted for those receiving or not receiving β-blockers (P value for interaction $= 0.139$) or lipid-lowering agents (P value for interaction $= 0.651$). A single RCT (41) found no difference in outcomes resulting from ARB therapy in patients either receiving or not receiving statins (P value for interaction $= 0.287$). Of the 4 RCTs (28, 35, 41, 42) that assessed the effect of baseline risk on treatment effects, only 1 (28) found a positive relationship on the risk for the composite end point.

Table 2. **Harms Event Rates for ACE Inhibitors**

Outcomes	Events/Total Participants, *n/n (%)*	Range in Rates, %*
Withdrawals due to adverse events†		
ACE inhibitors	732/5139 (14.2)	10.1–15.2
Placebo	343/5096 (6.7)	1.0–10.8
Hypotension‡		
ACE inhibitors	38/5490 (0.7)	0.04–9.5
Placebo	26/5484 (0.5)	0.06–3.2
Syncope§		
ACE inhibitors	203/8803 (2.3)	0.06–4.8
Placebo	162/8784 (1.8)	0.02–3.9
Cough‖		
ACE inhibitors	1726/9476 (18.2)	0.3–39.1
Placebo	1183/9439 (12.5)	0.2–27.5

ACE = angiotensin-converting enzyme.
* Absolute event rates of each outcome.
† 3 studies (references 25, 29, and 31).
‡ 3 studies (references 22, 29, and 34).
§ 2 studies (references 22 and 31).
‖ 3 studies (references 22, 29, and 31).

DISCUSSION

Moderate- to high-strength evidence demonstrates that ACE inhibitors reduce the RR for total mortality, cardiovascular mortality, nonfatal myocardial infarction, and stroke in adults with stable ischemic heart disease and preserved ventricular function (**Table 1**). This includes patients with a history of coronary artery, peripheral vascular, or cerebrovascular disease, as well as patients with diabetes and evidence of end-organ damage. Data are insufficient to adequately assess the benefits of ARBs, because only 1 high-quality RCT (41) was identified, and the population was limited to patients who could not tolerate ACE inhibitors. A single study with moderate-strength evidence showed similar effects on total mortality, cardiovascular mortality, myocardial infarction, and stroke with combination ACE inhibitor and ARB therapy compared with an ACE inhibitor alone but showed a greater risk for study discontinuations and discontinuations due to hypotension and syncope (42).

Most patients in the included trials were receiving concomitant antiplatelet and lipid-lowering therapy, with approximately half receiving β-blockers. We could not find differences in outcomes among patients receiving ACE inhibitors with or without β-blockers or lipid-lowering therapy (13). Some evidence suggests that ACE inhibitors confer more pronounced benefits in patients without concomitant antiplatelet therapy than in those who are receiving antiplatelet therapy (13). Whether this is related to a drug interaction between aspirin and ACE inhibitors (blocking the release of vasodilatory prostaglandins) or also occurs with adenosine diphosphate inhibitors is not known (71–75). The effect of antiplatelet therapy on ARB benefits is not known.

Study factors, including the use of different ACE inhibitors, varying doses of ACE inhibitors, differences in baseline blood pressure, and different degrees of blood pressure reduction, may affect pooled estimates of effect or heterogeneity (12, 14, 76, 77). Angiotensin-converting enzyme inhibitors considered to be tissue-specific (ramipril, quinapril, perindopril, or trandolapril) have not provided better cardioprotection than serum-specific agents (for example, enalapril) (76, 78–80). In addition, ACE inhibitors provide similar benefits regardless of changes in blood pressure or history of hypertension (12, 28, 33). However, using increased doses of ACE inhibitors may improve the ability to slow atherosclerosis (81), which may accentuate clinical benefits.

Our review has several limitations. We could analyze only data from published trials and data provided from trial authors. We could not adequately assess the possibility of publication bias for several outcomes, although selective reporting of both benefits and harms was possible. Subgroup data were inconsistently reported. Most studies evaluated patients between ages 60 and 67 years and predominantly enrolled men (57% to 89%), negatively affecting applicability. Few trials reported average left ventricular ejection fractions, and none of the trials assessed the affect of ventricular function on outcomes. Only 1 trial compared ARBs with placebo, and only 1 trial compared combination therapy with an ACE inhibitor alone. As a result, the ability to formally test for statistical heterogeneity was limited in many analyses, and the resultant strength of evidence reduced. Finally, data reporting on harms were inconsistent and incomplete, compromising our ability to determine the balance of benefits to harms.

In conclusion, adding an ACE inhibitor to standard medical therapy improves clinical outcomes in some patients with stable ischemic heart disease and preserved left ventricular function. Combination therapy seems no better than ACE inhibitor therapy alone and increases harms. Future trials are needed to more clearly define the role of ARBs in this patient population.

From the University of Connecticut/Hartford Hospital Evidence-based Practice Center, Hartford, Connecticut.

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Disclosure of Conflicts of Interest

Annals now requires authors who submit manuscripts for consideration to complete the International Committee of Medical Journal Editors (ICMJE) conflict of interest disclosure form. This form, which is discussed further at www.icmje.org/format.pdf, is intended to facilitate detailed reporting of conflicts of interest and standardize the format of reporting across ICMJE member journals. A sample of the form is available at www.icmje.org/sample_disclosure.pdf; instructions are available at www.icmje.org/coi_disclosure.pdf.

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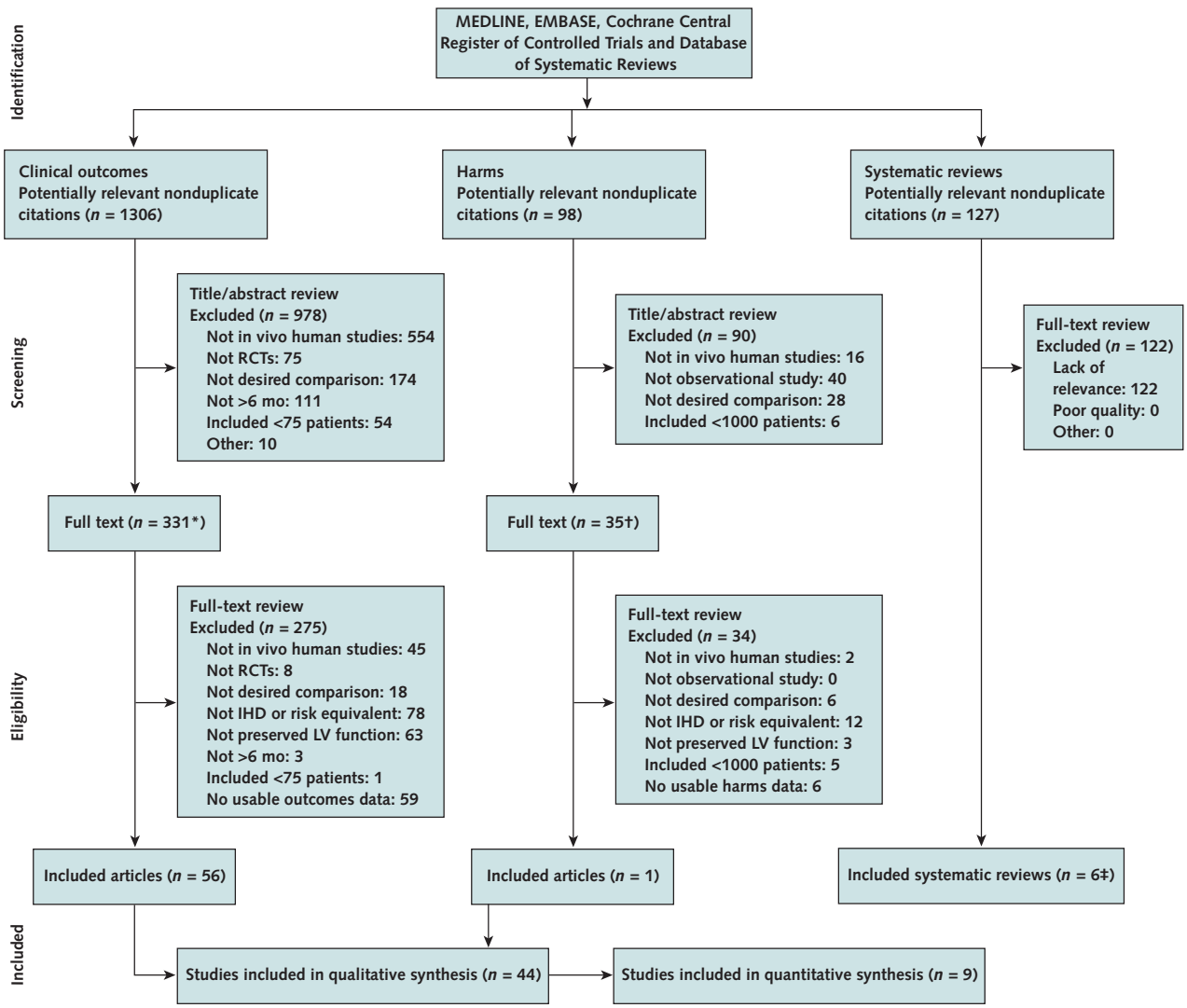
Collection and assembly of data: W.L. Baker, C.I. Coleman, K.M. Reinhart, R. Talati, O.J. Phung.

Appendix Figure. **Literature search and selection.**



IHD = ischemic heart disease; LV = left ventricular; RCT = randomized, controlled trial.
* We included 3 citations at this step after a manual reference search.
† We included 27 citations from the outcomes search and evaluated them for harms data.
‡ We included 1 citation at this step after a manual reference search.

Appendix Table. **Description of Included RCTs**

Study, Year (Reference)	Study Design	Duration of Follow-up	Group	Patients, *n*	Mean Age (SD), *y*	Male, %	Mean LVEF (SD)	β-Blocker Therapy, %	Antiplatelet Therapy, %*	Lipid-Lowering Therapy, %†	Randomization Adequate?	Double-Blinding Adequate?	Intention-to-Treat?	Study Funding
HOPE, 2000 (28)	RCT	4.5 y	Ramipril, 10 mg/d	4645	66 (7)	72	NR	39	75	28	Yes	Yes	Yes	Industry, foundation
			Placebo	4652	66 (7)	74		40	77	29				
PART-2, 2000 (31)	RCT	4.7 y	Ramipril, 5–10 mg/d	308	60 (8)	82	NR	42	83	29	Yes	Yes	Yes	Industry, foundation
			Placebo	309	61 (8)	82		43	79	28				
SCAT, 2000 (32)	RCT	4 y	Enalapril, 20 mg/d	229	60 (10)	89	NR	49	91	49	Yes	Yes	Yes	Industry, foundation
			Placebo	231	62 (9)	89		46	89	51				
EUROPA, 2003 (33)	RCT	4.2 y	Perindopril, 8 mg/d	6110	60 (9)	86	NR	62	92	58	NR	Yes	Yes	Industry
			Placebo	6108	60 (9)	85		61	93	57				
CAMELOT, 2004 (35)	RCT	2 y	Enalapril, 20 mg/d	673	59 (10)	72	NR	75	95	82	Yes	Yes	Yes	Industry
			Amlodipine, 10 mg/d	663	57 (10)	76		74	94	83				
			Placebo	655	57 (10)	73		79	95	84				
PEACE, 2004 (37)	RCT	4.8 y	Trandolapril, 4 mg/d	4158	64 (8)	81	0.58 (0.10)	60	90	70	Yes	Yes	Yes	Industry, foundation
			Placebo	4132	64 (8)	83	0.58 (0.9)	60	91	70				
SMILE-ISCHEMIA, 2007 (40)	RCT	6 mo	Zofenopril, 60 mg/d	172	58 (10)	81	0.55 (0.10)	10	3	28	Yes	Yes	Yes	Foundation
			Placebo	177	58 (10)	85	0.53 (0.8)	12	10	32				
TRANSCEND, 2008 (41)	RCT	4.7 y	Telmisartan, 80 mg/d	2954	67 (7)	57	NR	59	80	56	Yes	Yes	Yes	Industry, foundation
			Placebo	2972	67 (7)	57		57	79	55				
ONTARGET, 2008 (42)	RCT	56 mo	Ramipril, 10 mg/d	8576	66 (7)	73	NR	57	81	61	Yes	Yes	Yes	Industry, foundation
			Telmisartan, 80 mg/d	8542	66 (7)	74		57	81	62				
			Ramipril, 10 mg/d, plus telmisartan, 80 mg/d	8502	67 (7)	73		57	81	62				

CAMELOT = Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis; EUROPA = European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; HOPE = Heart Outcomes Prevention Evaluation; LVEF = left ventricular ejection fraction; NR = not reported; ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PART-2 = Prevention of Atherosclerosis with Ramipril Trial 2; PEACE = Prevention of Events with Angiotensin Converting Enzyme Inhibition; RCT = randomized, controlled trial; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; SMILE-ISCHEMIA = Survival of Myocardial Infarction Long-term Evaluation-ISCHEMIA; TRANSCEND = Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease.

* Aspirin, clopidogrel, or ticlopidine use.

† Any lipid-lowering therapy, including statins.