

Systematic Review: Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers for Treating Essential Hypertension

David B. Matchar, MD; Douglas C. McCrory, MD, MHS; Lori A. Orlando, MD, MHS; Manesh R. Patel, MD; Uptal D. Patel, MD; Meenal B. Patwardhan, MD, MHSA; Benjamin Powers, MD; Gregory P. Samsa, PhD; and Rebecca N. Gray, DPhil

Background: The relative effectiveness of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) for lowering blood pressure is unknown.

Purpose: To compare the benefits and harms of ACE inhibitors versus ARBs for treating essential hypertension in adults.

Data Sources: MEDLINE (1966 to May 2006), the Cochrane Central Register of Controlled Trials (Issue 2, 2006), and selected reference lists were searched for relevant English-language trials. The MEDLINE search was updated to August 2007 to identify head-to-head trials that reported blood pressure outcomes and major cardiovascular events.

Study Selection: 61 clinical studies that directly compared ACE inhibitors versus ARBs in adult patients with essential hypertension, reported an outcome of interest, lasted at least 12 weeks, and included at least 20 patients.

Data Extraction: A standardized protocol with predefined criteria was used to extract data on study design, interventions, population characteristics, and outcomes; evaluate study quality and applicability; and assess the strength of the body of evidence for key outcomes.

Data Synthesis: ACE inhibitors and ARBs had similar long-term effects on blood pressure (50 studies; strength of evidence, high).

No consistent differential effects were observed for other outcomes (few studies reported long-term outcomes), including death, cardiovascular events, quality of life, rate of single antihypertensive agent use, lipid levels, progression to diabetes, left ventricular mass or function, and kidney disease. Consistent fair- to good-quality evidence showed that ACE inhibitors were associated with a greater risk for cough. There were fewer withdrawals due to adverse events and greater persistence with therapy for ARBs than for ACE inhibitors, although this evidence was not definitive. Patient subgroups for whom ACE inhibitors or ARBs were more effective, associated with fewer adverse events, or better tolerated were not identified.

Limitations: Few studies involved a representative sample treated in a typical clinical setting over a long duration, treatment protocols had marked heterogeneity, and substantive amounts of data about important outcomes and patient subgroups were missing.

Conclusion: Available evidence shows that ACE inhibitors and ARBs have similar effects on blood pressure control, and that ACE inhibitors have higher rates of cough than ARBs. Data regarding other outcomes are limited.

Ann Intern Med. 2008;148:16-29.

For author affiliations, see end of text.

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More than 65 million U.S. adults—approximately one third—have hypertension. In addition to being the leading attributable risk factor for death throughout the world (1), hypertension results in substantial illness due to its effect on several target organs, including the brain, eyes, heart, arteries, and kidneys.

Despite the high rate of morbidity and mortality attributable to hypertension, control remains suboptimal (2). In addition to several effective nonpharmacologic interventions, many individuals require antihypertensive medication to lower blood pressure and often require several med-

ications together (2). Among the most common of the many choices in antihypertensive therapy are those aimed at inhibiting the renin-angiotensin-aldosterone (renin) system. Currently, renin system inhibitors include angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Although clinicians regard ACE inhibitors and ARBs as effectively equivalent, it is not clear whether this is appropriate. For example, ACE inhibitors do not entirely block production of angiotensin II because of other, unaffected converting enzymes. Also, ACE inhibitors are associated with well-known adverse events not shared by ARBs, including cough (estimated incidence, 5% to 20%) and the possibly related phenomenon of angioedema (estimated incidence, 0.1% to 0.2%) (3). Although both ACE inhibitors and ARBs are highly effective in lowering blood pressure among patients with essential hypertension (4, 5), their comparative effectiveness and the relative advantages and disadvantages of ACE inhibitors versus ARBs are unknown.

This review summarizes the evidence on the comparative long-term benefits and harms of ACE inhibitors versus ARBs for treating essential hypertension in adults. The full technical report was commissioned by the Agency for Healthcare Research and Quality (6).

See also:

Print

Editors' Notes	17
Editorial comment	76
Related article	30

Web-Only

Appendixes
CME quiz
Conversion of graphics into slides

METHODS

We developed and followed a standardized protocol for all steps of the review.

Data Sources and Searches

We searched MEDLINE (1966 to week 3 of May 2006) and the Cochrane Central Register of Controlled Trials (Issue 2, 2006) for studies published in English after 1988, using terms for drug interventions, hypertension, and study design. We also reviewed bibliographies submitted by pharmaceutical companies to the Scientific Resource Center for the Agency for Healthcare Research and Quality's Effective Health Care Program, reference lists of relevant review articles, and citations identified by reviewers of the draft report. For the current review, we updated our MEDLINE search to August 2007 to identify new head-to-head trials that reported blood pressure outcomes and major cardiovascular events. Results from the newly identified studies (7–21) were consistent with the evidence described in the full technical report and are not presented here.

Study Selection

We included comparative clinical studies of any design (including randomized, controlled trials and nonrandomized, controlled trials; cohort studies; and case-control studies) that provided direct comparisons of ACE inhibitors versus ARBs at 12 weeks or more after the initial intervention. In addition to simple comparisons of a single ACE inhibitor versus a single ARB, we included studies with “grouped” comparisons (such as a specific ARB versus “ACE inhibitors” or unspecified “ARBs” versus unspecified “ACE inhibitors”) and comparisons in which the same drug was administered with an ACE inhibitor versus that drug with an ARB (for example, losartan and hydrochlorothiazide vs. enalapril and hydrochlorothiazide). We excluded studies with comparisons in which the drugs administered with an ACE inhibitor differed from those administered with an ARB (for example, enalapril and manidipine vs. irbesartan and hydrochlorothiazide). We included studies with treatment protocols that permitted the addition of other antihypertensive medications during the trial, provided that the co-intervention protocols were the same in the ACE inhibitor and ARB treatment groups. Outcomes we considered included blood pressure control, adherence, quality of life, several intermediate outcomes, and harms. We excluded studies with fewer than 20 total patients in the ACE inhibitor and ARB treatment groups and focused on studies of adults (≥ 18 years of age) with essential hypertension, as defined by the study authors.

We also evaluated studies of ARBs versus other (non-ACE inhibitor) comparators and ACE inhibitors versus other (non-ARB) comparators, which were to be considered in case too few direct head-to-head trials were identified for outcomes of interest. **Appendix 1** (available at www.annals.org) contains the details of how we identified and reviewed indirect comparison studies.

Context

Are angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) more effective for treating essential hypertension?

Contribution

This systematic review of trials that directly compared ACE inhibitors and ARBs in adults with essential hypertension found good evidence that the agents had similar long-term effects on blood pressure. There were no consistent differential effects for mortality, cardiovascular events, progression to diabetes, left ventricular function, or kidney disease. Cough was more frequent with ACE inhibitors than ARBs.

Implication

Both ACE inhibitors and ARBs have similar effects on blood pressure and may not have differential effects on other clinical outcomes, although ACE inhibitors do cause cough more often than ARBs.

—The Editors

Data Extraction and Quality, Applicability, and Strength of Evidence Assessments

One author extracted data from each study, which were confirmed by another author. Extracted information included study design; interventions; population characteristics; recruitment setting; inclusion and exclusion criteria; numbers of participants screened, eligible, enrolled, and lost to follow-up; and results for each outcome.

We used predefined criteria adapted from those developed by the U.S. Preventive Services Task Force (22) and the Centre for Reviews and Dissemination in the United Kingdom (23) to assess the quality of individual studies as good, fair, or poor, and we noted important limitations on internal validity for studies rated as fair or poor. The applicability of individual studies was assessed by noting the most important potential limitations (up to 3) in a study's applicability from among the list described by Rothwell (24), as adapted by the Scientific Resource Center (**Appendix 2**, available at www.annals.org). Quality and applicability assessments are detailed for individual studies in the evidence tables included in the full report (6). Finally, we assessed the strength of the body of evidence for each key question as high, moderate, low, or very low by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (25).

Data Synthesis and Analysis

Given that many studies did not have the statistical power to determine equivalence for relevant outcomes, we considered pooling (without regard to the specific drug within the ACE inhibitor or ARB class) to overcome a type II error. In evaluating direct comparison studies for potential data synthesis, we primarily considered clinical homogeneity. In general, we considered groups of studies as suit-

able for quantitative synthesis when we identified at least 4 clinically and relatively similar studies that assessed the same outcome. We used additional and more detailed criteria to determine suitability for pooling of indirect comparisons, as such comparisons are tenuous (Appendix 1, available at www.annals.org). We did not attempt to pool direct and indirect comparison studies in a single analysis, primarily because we did not identify a sufficient number of clinically similar indirect comparison studies to analyze.

When we pooled studies, we used the random-effects model for the primary analysis and the fixed-effect model for sensitivity analysis. We stratified analyses by study design, separating randomized, controlled trials from observational studies. We performed all analyses by using Comprehensive Meta-analysis, version 2 (Biostat, Englewood, New Jersey). For count outcomes, we calculated summaries of the relative effect (odds ratios) and absolute effect (risk difference). We chose the Peto method for analyzing data on cough and withdrawals due to adverse events because event rates were low and treatment groups were not substantially imbalanced, conditions under which this method is the least biased and most powerful (26). This method also allows inclusion of studies with zero events in 1 group with no continuity correction. For data on rates of successful monotherapy, we used risk differences because event rates were high, which makes the assumption of a constant odds ratio unreasonable.

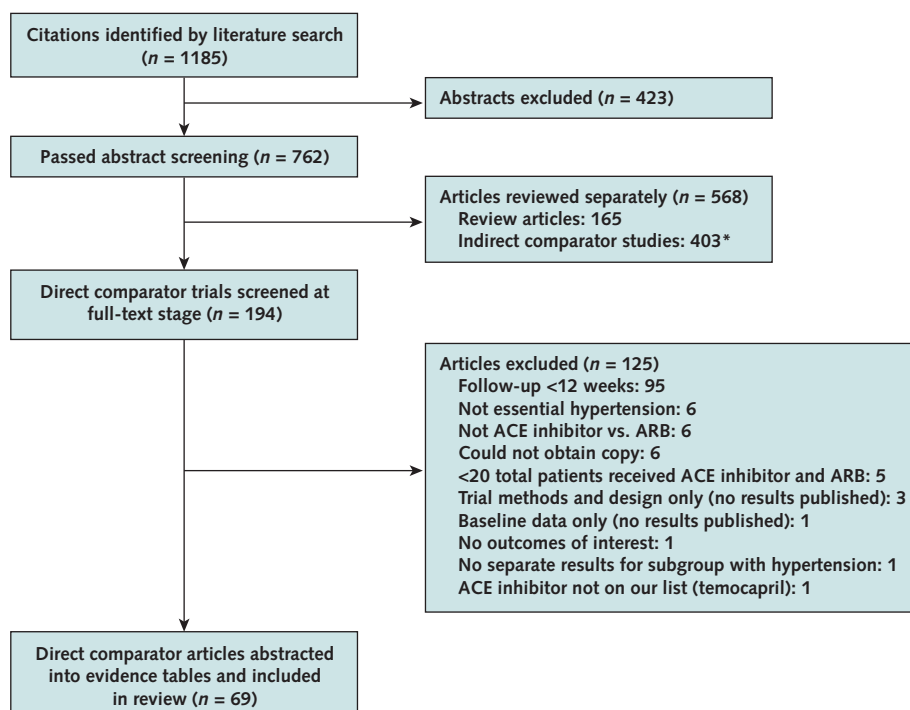
Role of the Funding Source

The Agency for Healthcare Research and Quality formulated the initial study questions and reviewed and commented on planned methods, data analysis, and the draft report. The funding source did not participate in the search of the literature, determination of study eligibility, or evaluation of individual studies.

RESULTS

Of 1185 citations, 69 reports (61 distinct studies) directly compared ACE inhibitors with ARBs (Figure 1). Forty-seven studies were randomized, controlled trials; 1 was a nonrandomized, controlled trial; 9 were retrospective cohort studies; 2 were prospective cohort studies; 1 was a cross-sectional cohort study; and 1 was a case-control study. Table 1 shows the numbers of studies that compared different agents. Enalapril was the most frequently studied ACE inhibitor (24 studies), and losartan the most frequently studied ARB (19 studies). Most studies were relatively short-term; 19 followed patients for 12 weeks, and 21 followed patients between 12 weeks and 6 months. Most studies excluded patients with secondary causes of hypertension, as well as patients with recent acute events, such as myocardial infarction or stroke. Table 2 summarizes the number and quality scores of reviewed studies, by outcome assessed.

Figure 1. Study flow diagram.



*See Appendix 1 (available at www.annals.org). ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

Table 1. Number of Included Studies and Publications Evaluating Various Treatment Comparisons*

ACE Inhibitors	ARBs								
	Unspecified	Candesartan Cilexetil	Eprosartan	Irbesartan	Losartan	Oltmesartan Medoxomil	Telmisartan	Valsartan	Total
Unspecified	9 (11)	1 (1)	0	2 (2)	2 (2)	0	0	0	14 (16)
Benazepril	0	0	0	0	0	0	0	0	0
Captopril	0	0	0	0	2 (2)	0	0	0	2 (2)
Enalapril	0	4 (4)	2 (6)	4 (4)	10 (12)	0	3 (3)	1 (1)	24 (30)
Fosinopril	0	0	0	2 (2)	1 (1)	0	0	0	3 (3)
Lisinopril	0	4 (4)	0	0	0	0	1 (1)	3 (3)	8 (8)
Moexipril	0	0	0	0	0	0	0	0	0
Perindopril	0	1 (1)	0	0	1 (1)	0	2 (2)	0	4 (4)
Quinapril	0	0	0	0	2 (2)	0	0	0	2 (2)
Ramipril	0	0	0	0	0	0	3 (3)	0	3 (3)
Trandolapril	0	0	0	0	1 (1)	0	0	0	1 (1)
Total	9 (11)	10 (10)	2 (6)	8 (8)	19 (21)	0	9 (9)	4 (4)	–

* Data are reported as number of studies (number of publications). ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

Comparative Effectiveness for Controlling Blood Pressure and Improving Cardiovascular Outcomes and Risk

Angiotensin-converting enzyme inhibitors and ARBs seem to have similar long-term effects on blood pressure in individuals with essential hypertension.

Because there were too few deaths or major cardiovascular events in the included studies, we could not discern any differential effect of ACE inhibitors versus ARBs for these critical outcomes. Likewise, ACE inhibitors and ARBs exhibited no consistent differential effects on several potentially important risk factors, including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism or diabetes control, measures of left ventricular mass or function, and progression of renal disease (based on creatinine level, glomerular filtration rate, or proteinuria). Relatively few studies assessed these outcomes over the long term.

Blood Pressure Control

Of the 50 identified studies that reported blood pressure control, 47 were randomized, controlled trials. These studies had substantial protocol differences, including maximal medication dose, whether additional blood pressure medications were permitted, whether adjustments were by algorithm or physician discretion, whether nonresponders were withdrawn, and whether blood pressure was reported as a change or only as final blood pressure. Thirty-seven studies (42 articles) reported no statistically significant differences in blood pressure control (27–68), 2 studies (3 articles) favored ACE inhibitors (69–71), 8 studies favored ARBs (72–79), and 3 studies did not report the comparison between the agents (80–82). Both studies favoring ACE inhibitors compared 50 mg of losartan with 20 mg of enalapril, in contrast to other studies showing no difference between these 2 agents, which compared 100 mg of losartan with 10 or 20 mg of enalapril. For studies that favored ARBs, we found no salient features of the study design that

might explain the difference. Notably, across studies, the modal difference in systolic or diastolic blood pressure was 0 mm Hg and generally did not exceed 4 mm Hg.

Success as a Single Antihypertensive Agent

We identified 22 studies (27, 34, 37, 42–44, 46, 47, 49, 53, 55, 58–60, 66–69, 73, 80, 82, 83) that reported successful monotherapy. The definition of “successful” differed across studies. Definitions included various systolic or diastolic blood pressure cutoffs or lack of additional antihypertensive medication at the end of the study. The rates of successful monotherapy ranged between 6% and 93% (median, 61%). The average proportion of patients who achieved successful monotherapy across all studies was about 55% for both ACE inhibitors and ARBs.

Figure 2 shows estimates for the differences between ACE inhibitors and ARBs in the proportion of patients achieving successful blood pressure control with a single agent. We found no important statistical heterogeneity for these estimates (Q statistic = 25.8; I^2 = 18%; P = 0.22). The summary estimate using a random-effects model was 1.3% (95% CI, –1.0% to 3.5%; P = 0.26). Results based on odds ratios and median incidence were similar.

Because the definition of successful control of blood pressure with a single agent requires that a patient continue the originally prescribed drug regimen and receive no additional antihypertensive agent, successful monotherapy reflects both the efficacy of the medication and tolerability and adherence to the prescribed therapy. The tendency in favoring ARBs for this outcome seemed driven primarily by differences in tolerability and adherence. The observed benefit of ARBs seemed heavily influenced by retrospective cohort studies, in which medication discontinuation rates were higher in ACE inhibitor–treated patients, and by randomized, controlled trials that had loosely defined protocols for medication titration and switching.

Table 2. Summary of Reviewed Studies*

Outcome	Study Design	Studies, n	Study Quality, n			Participants, nt	Publication Years
			Good	Fair	Poor		
Blood pressure control	RCT	47	5	31	11	12 295	1995–2006
	Non-RCT	1	0	0	1	62	2000
	Retrospective cohort	1	0	1	0	1087	2002
	Case-control	1	0	0	1	88	2000
Death and major cardiovascular events	RCT	9	3	5	1	3322	2000–2006
Quality of life	RCT	4	0	4	0	1142	1999–2002
Rate of use of a single antihypertensive	RCT	19	3	13	3	4851	1995–2005
	Retrospective cohort	2	0	2	0	7071	2002–2005
	Case-control	1	0	0	1	88	2000
Lipid levels	RCT	11	2	7	2	1613	1995–2005
	Case-control	1	0	0	1	88	2000
Progression to type 2 diabetes	–	–	–	–	–	–	–
Markers of carbohydrate metabolism or diabetes control	RCT	11	2	7	2	1614	1995–2005
	Non-RCT	1	0	0	1	62	2000
	Case-control	1	0	0	1	88	2000
Measures of left ventricular mass or function	RCT	6	0	3	3	566	2002–2005
	Non-RCT	1	0	0	1	62	2000
	Case-control	1	0	0	1	88	2000
Measures of kidney disease (creatinine level, glomerular filtration rate, proteinuria)	RCT	16	2	11	3	2574	1995–2005
	Non-RCT	1	0	0	1	62	2000
	Cross-sectional cohort	1	0	0	1	49	2003
	Case-control	1	0	0	1	88	2000
Serious adverse events (overall rates)	RCT	7	1	6	0	3829	1997–2006
Adverse events (overall rates)	RCT	29	4	20	5	10 482	1995–2006
Cough	RCT	26	4	20	2	10 070	1995–2006
	Prospective cohort	2	0	0	2	51 859	1999–2001
	Cross-sectional cohort	1	0	0	1	49	2003
Angioedema	RCT	3	0	3	0	1209	1999–2000
Withdrawals due to adverse events	RCT	22	2	18	2	7514	1995–2005
	Non-RCT	1	0	0	1	62	2000
	Case-control	1	0	0	1	88	2000
Adherence or persistence	RCT	8	0	7	1	3366	2000–2006
	Retrospective cohort	9	0	8	1	220 106	1998–2006

* ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; RCT = randomized, controlled trial.
 † Represents number included in ACE inhibitor and ARB treatment groups or, in the case of RCTs, number randomly assigned.

Death and Major Cardiovascular Events

Only 9 studies, described in 13 publications (27, 29, 31, 38, 41, 44, 46, 48, 49, 59, 62, 65, 79), reported how many patients died or had myocardial infarction or stroke (Table 2). Most of these studies excluded patients with clinically significant cardiovascular disease and other comorbid conditions. Of 3322 patients who received an ACE inhibitor or an ARB in these studies, 16 died; 12 of these were from a study by Barnett and colleagues (29). That study provided the most and the longest-term data on cardiovascular events, evaluating telmisartan (n = 120) versus enalapril (n = 130) in patients with type 2 diabetes and early nephropathy over a 5-year treatment period. Event rates were similar in this higher-risk sample, with stroke, congestive heart failure, nonfatal myocardial infarction, or death occurring in 31 patients receiving telmisartan (25.8% [CI, 18.3% to 34.6%]) and 25 patients receiving enalapril (19.2% [CI, 12.9% to 27.1%]). In none of the studies did investigators attribute any observed events directly to therapy.

Lipid Levels and Glucose Control

Eleven randomized, controlled trials (36, 38–40, 42, 44, 46, 58, 62, 67, 70) and 1 observational case-control study (68) reported lipid levels. We rated most of these studies as fair quality. None addressed the use of lipid-lowering agents during the study. Nine studies found no change either between or within groups in total cholesterol, low-density lipoprotein, high-density lipoprotein, or triglyceride levels during the study. The remaining 3 studies detected a small but statistically significant change within the groups in total cholesterol (44, 46), low-density lipoprotein (36), and triglyceride levels (44). The magnitude of these changes was equivalent for the compared medications except for 1 of the total cholesterol studies (44), which favored the ARB, and the low-density lipoprotein study (36), which favored the ACE inhibitor.

Thirteen studies measured glucose or hemoglobin A_{1c}. All but 2 (28, 68) were randomized, controlled trials. We rated 2 as good quality (36, 62), 7 as fair quality (38–40, 46, 53, 67, 70), and 4 as poor quality (28, 42, 44, 68).

None addressed hypoglycemic therapy during the study. No change occurred in hemoglobin A_{1c} either between or within groups in 11 studies. One reported a small decrease in glucose that was statistically greater in the ACE inhibitor group (36), and 1 reported a statistically significant but clinically unimportant increase in hemoglobin A_{1c} for both groups (46). Results were similar between the 6 studies that specifically included diabetic patients and the studies that did not.

Left Ventricular Mass or Function

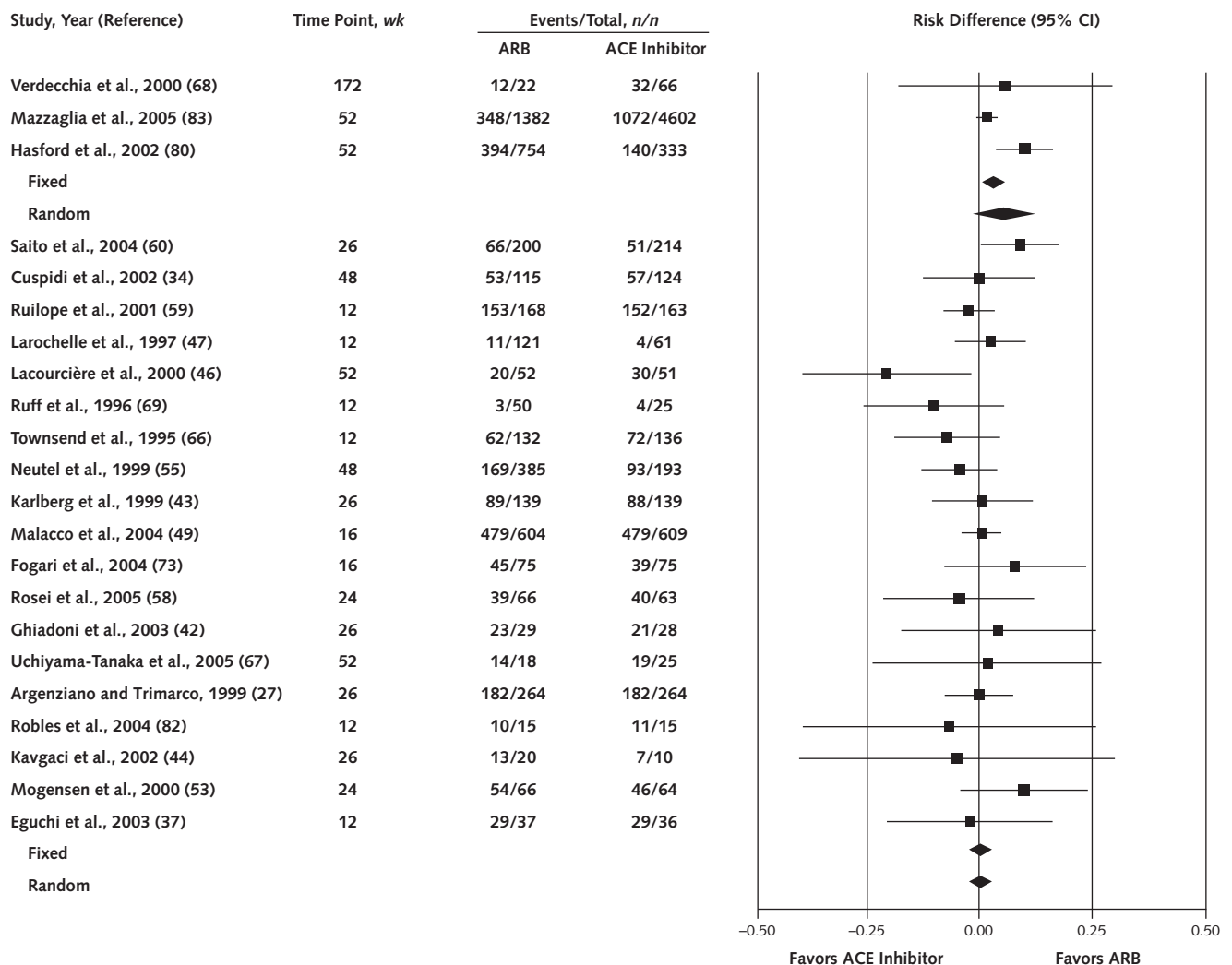
Eight studies presented results on left ventricular mass or function assessed by left ventricular mass index (28, 35, 68), left ventricular ejection fraction (32, 61), or both (34, 57, 65). Half of these studies had fewer than 50 patients (28, 35, 61, 65), whereas the other half had 100 or more patients (32, 34, 57, 68). All but 2 (28, 68) were randomized, controlled trials. Two had relatively long-term fol-

low-up (≥ 3 years) (35, 68), 5 had between 6 and 12 months of follow-up (28, 32, 34, 57, 65), and 1 had only 3 months of follow-up (61). Despite differences in sample size, study design, length of follow-up, study quality, therapeutic agents, and outcome measure, most of the studies demonstrated either similar differences in improvements in left ventricular mass or function, with an approximately 2% difference between the ACE inhibitor and ARB groups (28, 34, 65, 68), or no change in these measures for either group (35, 57).

Serum Creatinine Level, Glomerular Filtration Rate, and Proteinuria

Twenty studies identified renal outcomes. We excluded 1 of these studies (65) from our analysis because no changes would be expected in the outcome assessed (serum creatinine) in the sample studied (patients with end-stage renal disease who had been receiving maintenance hemo-

Figure 2. Successful monotherapy: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs).



The first group is observational studies and the second group is randomized, controlled trials.

dialysis for ≥ 1 month). Of the remaining 19 studies, 9 assessed either serum creatinine or glomerular filtration rate (28, 35, 38, 39, 52, 63, 67, 68, 78), 4 assessed proteinuria (36, 53, 62, 84), and 6 assessed both (29, 44, 46, 50, 58, 70).

The 15 studies that described changes in creatinine level or glomerular filtration rate did not consistently demonstrate differential effects related to renal function with the use of ACE inhibitors versus ARBs. Among the 9 studies that reported data on renal function, none was rated as good quality, 4 were of poor quality (28, 44, 63, 68), 2 were not randomized, controlled trials (28, 68), and only 2 had more than 100 patients (29, 52). All but 2 (29, 52) compared losartan with a specific ACE inhibitor. The most frequently studied ACE inhibitor was enalapril (28, 29, 35, 63, 68). The 10 studies that described changes in urine albumin level or protein excretion consistently were of fair quality and demonstrated no differential effects between ACE inhibitors and ARBs related to the reduction of urinary protein or albumin excretion among patients with essential hypertension.

Quality of Life, Adverse Events, Persistence, and Adherence

On the basis of 4 studies, 2 of which did not provide quantitative data, we found no differences in measures of general quality of life. Angiotensin-converting enzyme inhibitors have been consistently shown to be associated with a greater risk for cough than ARBs (Peto pooled odds ratio, 0.32). For randomized, controlled trials, this translates to a difference in rates of cough of 6.7%; however, for cohort studies with lower rates of cough, this translates to a difference of 1.1%. We found no evidence of differences in rates of other commonly reported specific adverse events. Angioedema was reported only in patients treated with ACE inhibitors; however, because angioedema was rarely explicitly reported in the included studies, we could not estimate its frequency in this population. Pill counts indicated that rates of adherence to ACE inhibitors and ARBs were similar; this result may not be applicable outside the clinical trial setting. Rates of continuation with therapy seem to be somewhat better with ARBs than with ACE inhibitors; however, the precise magnitude of this effect is difficult to quantify.

Quality of Life

Four fair-quality studies described in 8 papers reported quality-of-life outcomes (27, 31, 35, 38, 41, 43, 48, 76). They used a variety of quality-of-life scales. None demonstrated a differential effect on quality of life between ACE inhibitors and ARBs.

Serious and Overall Adverse Events

Seven studies of either fair or good quality (43, 49, 52, 58, 74, 78, 79) reported overall rates of serious adverse events. The biggest issues in evaluating these studies were inconsistent reporting and a low rate of serious adverse

events (0% to 6%). A potentially salient and serious adverse event, angioedema, was reported in only 3 of the 61 included studies (43, 51, 55). All reported cases occurred in patients treated with an ACE inhibitor. Because angioedema was rarely explicitly reported in the included studies, we could not estimate its frequency.

Of the 29 studies that reported overall adverse event rates (29, 30, 33, 34, 36–38, 43, 45, 47, 49, 51, 52, 55, 58, 59, 63, 66, 69, 70, 72–79, 81), 20 were assessed as being fair quality and 5 as poor quality. The manner in which adverse events were reported substantially varied. Depending on the definition used, adverse event rates ranged from 0% to 100% (median, 32%) for ACE inhibitors and 0% to 96% (median, 28%) for ARBs.

Specific Adverse Events

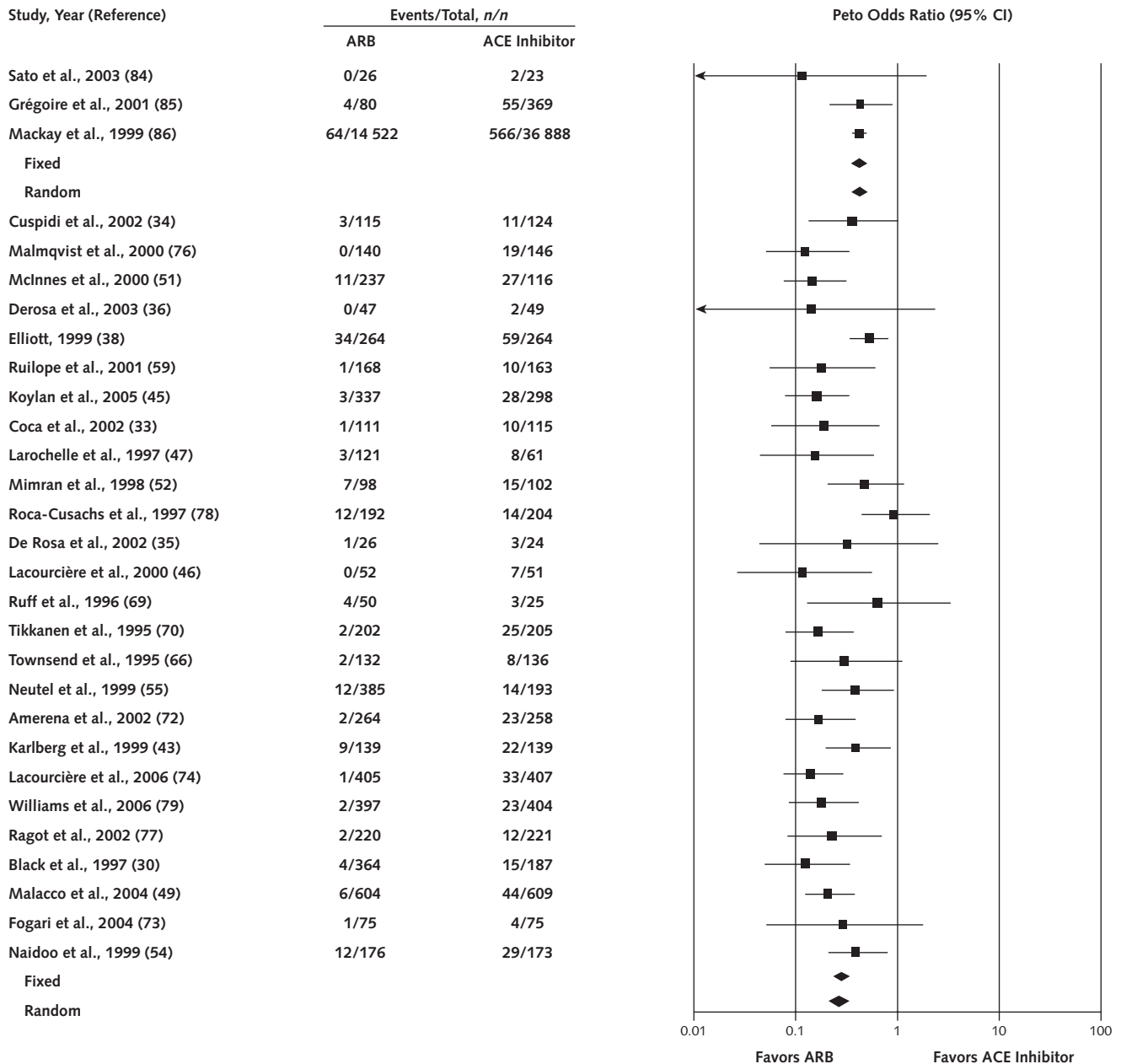
Thirty studies reported rates of 1 or more specific adverse events (30, 33–36, 38, 43, 45–47, 49, 51, 52, 54, 55, 59, 66, 69, 70, 72–79, 84–86), including cough (29 studies); headache (21 studies); dizziness (18 studies); fatigue (10 studies); upper respiratory infection (6 studies); nausea (6 studies); viral infection, ankle edema, and back pain (3 studies each); and palpitations, myalgia, diarrhea, malaise, and hypotension (2 studies each). Several other adverse events were reported in 1 study, including pharyngitis, rhinitis, dyspnea, abdominal pain, urinary tract infection, constipation, dry mouth, feeling sick, pyrosis, insomnia, musculoskeletal pain, flatulence, epigastric discomfort, increased sweating, and erythematous rash.

Given the large number of commonly reported specific adverse events, we focused on 3 that had the largest difference in absolute rates across studies: headache, dizziness, and cough.

Headache. Twenty-one studies compared headache in patients treated with ACE inhibitors and ARBs. Rates of headache ranged from 1% to 22% for ARB-treated groups (overall rate, 6.3%) and from 0% to 34% in ACE inhibitor-treated groups (overall rate, 7.9%). Meta-analyses did not reveal evidence of a differential effect of ACE inhibitors and ARBs on headache.

Dizziness. Eighteen studies compared dizziness in patients treated with ACE inhibitors and ARBs. Rates of dizziness ranged from 1% to 20% for ARB-treated groups (overall rate, 4.3%) and from 0% to 18% in ACE inhibitor-treated groups (overall rate, 5.4%). Meta-analyses did not reveal evidence of a differential effect of ACE inhibitors and ARBs on dizziness.

Cough. Twenty-nine studies compared cough in patients treated with ACE inhibitors and ARBs (30, 33–36, 38, 43, 45–47, 49, 51, 52, 54, 55, 59, 66, 69, 70, 72–74, 76–79, 84–86). We rated 4 of these studies as good, 20 as fair, and 5 as poor in quality. Rates of cough ranged from 0% to 13% for ARB-treated groups (mean, 3%; median, 1%) and from 0% to 23% in ACE inhibitor-treated groups (mean, 10%, median, 9%). All 29 studies demon-

Figure 3. Cough as an adverse event: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs).

The first group is observational studies and the second group is randomized, controlled trials.

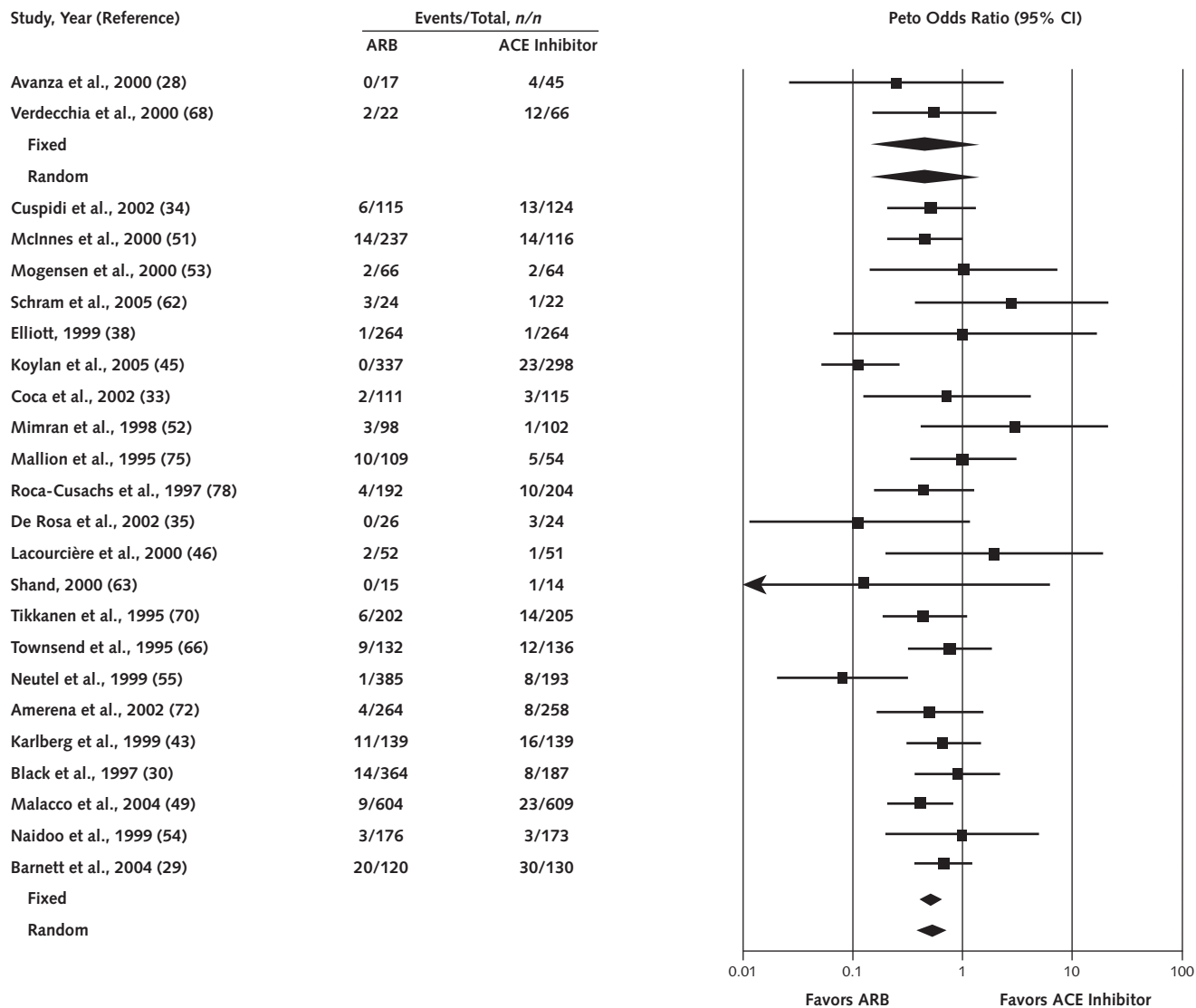
strated higher rates of cough in ACE inhibitor–treated participants. For the meta-analysis of studies reporting cough as an adverse event, we included all 29 studies that reported cough rates (Figure 3). The Cochran Q test and the I^2 between studies demonstrated statistical heterogeneity among the studies (Q statistic = 57.5; I^2 = 51.3%). The observed rates of cough were much higher in randomized, controlled trials, in which patients were queried systematically for the symptom, than those in cohort studies. The rates of cough in randomized,

controlled trials were 9.9% for the ACE inhibitor group and 3.2% for the ARB group (absolute risk difference, 6.7 percentage points), whereas the rates of cough in cohort studies were 1.7% for the ACE inhibitor group and 0.6% for the ARB group (absolute risk difference, 1.1 percentage points).

Withdrawals Due to Adverse Events

Twenty-four studies (28–30, 33–35, 38, 43, 45, 46, 49, 51–55, 62, 63, 66, 68, 70, 72, 75, 78) reported with-

Figure 4. Withdrawals due to adverse events: angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs).



The first group is observational studies and the second group is randomized, controlled trials.

drawals due to adverse events. We rated 2 as good in methodological quality, 18 as fair, and 4 as poor. Rates of withdrawal due to adverse events ranged from 1% to 41% (mean, 10%; median, 3%) for patients who received ARBs and 1% to 41% (mean, 19%; median, 8%) for patients who received ACE inhibitors. Sixteen studies demonstrated higher withdrawal rates in ACE inhibitor–treated participants, 3 demonstrated higher rates in ARB-treated participants, and 5 showed no difference in rates (Figure 4). The differences in rates of adverse events (such as cough) and the duration of the trials probably explain this heterogeneity. We found modest statistical heterogeneity between studies (Q statistic = 36.0; $I^2 = 36.2\%$). The Peto summary odds ratio fa-

vored ARBs (0.51 [CI, 0.38 to 0.70]; random-effects model). Given this odds ratio and a median withdrawal rate of 8% for ACE inhibitors, the expected withdrawal rate for ARBs is 3.7%.

Caveats regarding these data are that only 1 study was of good methodological quality and reporting of withdrawal data varied greatly.

Adherence and Persistence

Seventeen studies described in 19 papers (33, 45, 51, 58, 60, 72, 76, 79, 80, 83, 87–95) reported quantitative information on persistence or adherence. We operationally defined adherence as the consistency with which medica-

tion was taken, measured by such direct evidence as pill counts. Collecting such evidence typically requires an experimental setting; this limits the ability to generalize because patients who participate in trials and are aware that they are being observed will probably demonstrate better adherence than those in usual practice. Adherence for both ACE inhibitors and ARBs was high (>90%).

We operationally defined persistence as the percentage of patients continuing a particular therapy after a certain period (for example, patients continuing ARB therapy 12 months after the initial prescription), where the patient's treatment status was determined by the pattern of filled prescriptions. Thus, persistence could be measured in non-experimental settings (for example, by using administrative databases).

Studies addressing persistence included 2 randomized, controlled trials and 9 longitudinal cohort studies. These studies consistently showed that persistence with ARBs was somewhat better than persistence with ACE inhibitors (Table 3); for example, the median absolute difference in persistence rates for the longitudinal cohort studies was in the range of 6% to 7%.

Certain caveats apply to these results. The longitudinal cohort studies typically used administrative databases. Although investigators in these studies often presented analyses that statistically controlled for differences in characteristics between patients receiving ACE inhibitors and those receiving ARBs, the absence of randomization means that similarity in unmeasured patient characteristics within the groups cannot be guaranteed. Consequently, the consistency

of results reported in Table 3 (across experimental vs. nonexperimental studies, among the various longitudinal cohort studies, and over time within a study) is crucial. In addition, several longitudinal cohort studies, such as those by Marentette and colleagues (93), Bourgault and colleagues (88), Burke and colleagues (95), Wogen and colleagues (94), and Degli Esposti and colleagues (90, 91), corresponded in time to the introduction of ARBs and thus have relatively small sample sizes for this medication class. Persistence estimates are less precise in these studies than might be desired.

Effects in Subgroups of Patients

We found inadequate evidence regarding comparative effectiveness, adverse events, or tolerability of ACE inhibitors and ARBs for any particular patient subgroup (6).

DISCUSSION

With the exception of rates of cough, the available evidence does not strongly support the hypothesis that ACE inhibitors and ARBs have clinically meaningful differences in benefits or harms for individuals with essential hypertension. In particular, both classes of therapy provide similar levels of blood pressure control and seem to have an equivalent effect on death and cardiovascular events; major adverse events; quality of life; and risk factors, such as lipid levels, diabetes mellitus, and left ventricular mass and function. Evidence suggests that ARBs are associated with higher rates of persistence with initial therapy than are

Table 3. Studies of Persistence*

Study	Duration of Therapy	ACE Inhibitors, %			ARBs, %		
		Continued	Switched	Discontinued	Continued	Switched	Discontinued
Randomized trials							
Saito et al., 2004 (60)	6 mo	71	28	2	89	9	2
Koylan et al., 2005 (45)	6 mo	≈82	–	–	≈89	–	–
Longitudinal cohort studies							
Hasford et al., 2002 (80)	1 y	42	–	–	44.7–60.8	–	–
Mazzaglia et al., 2005 (83)	1 y	≈50	≈8	≈42	≈50	≈10	≈40
Bloom, 1998 (87)†	1 y	58	9	33	64	7	29
Conlin et al., 2001 (89)†	4 y	46.5	18.9	34.6	50.8	16.5	32.7
Erkens et al., 2005 (92)	1 y	59.7	–	–	62.0	–	–
Marentette et al., 2002 (93)	1 y	–	–	≈35	–	–	≈15
Bourgault et al., 2005 (88)	1 y	–	–	41	–	–	34
	2 y	–	–	53	–	–	44
	3 y	–	–	60	–	–	47
Burke et al., 2006 (95)	1 y	–	–	37.8	–	–	29.4
	2 y	–	–	48.0	–	–	41.3
	3 y	–	–	54.8	–	–	50.3
	4 y	–	–	60.4	–	–	57.8
Wogen et al., 2003 (94)	1 y	50	–	–	63	–	–
Degli Esposti et al., 2002 (90, 91)	1 y	30.7	9.4	59.9	33.4	24.6	42.0

* The ideal outcome would disaggregate patients into 4 mutually exclusive and exhaustive categories: continued initial medication without change, continued initial medication but added another medication from a different class, changed to another medication from a different class, and discontinued medication entirely. Almost all of the reports aggregated the first 2 categories, which we have combined throughout. Within each category, definitions are not entirely consistent but are close enough for comparison purposes. ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker.

† These studies are from the same research team and report on the same study population at 1 year (Bloom) and 4 years (Conlin et al.).

ACE inhibitors, although the magnitude of this difference is difficult to quantify.

The literature had important limitations. Assessment of the long-term effect of treatment is restricted by the dearth of truly long-term studies; follow-up exceeded 6 months in only one third of head-to-head studies. Many of the studies reported limited data on patient characteristics, did not report results by subpopulation, and underrepresented black patients. Study protocols had substantial differences, including maximal medication dose, whether additional blood pressure medications were permitted, whether adjustments were by algorithm or physician discretion, and whether nonresponders were withdrawn at some point in the study.

Assessment of outcomes was not uniform. Blood pressure was reported in some studies only as final blood pressure and in other studies as change in blood pressure. Important outcomes, such as death, vascular events, and angioedema, were often not mentioned.

This review highlights several issues that should be addressed by further research. In addition to examining the effect of therapy over several years, studies should incorporate pragmatic designs, such as clinical trials in which treatment is consistent with typical clinical practice, or randomization by organizationally meaningful clusters, such as practice organizations or health plans. Assessments should consider subgroups of special importance, such as individuals with essential hypertension and diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia, and should have broader representation of such groups as elderly persons and ethnic and racial minorities. Given the demonstrated higher incidence of cough with ACE inhibitors, it would also be valuable to gain a more precise understanding of the effect of cough on quality of life, care patterns (for example, use of therapeutic agents for cough symptoms or conditions associated with cough), and health outcomes, particularly for individuals who continue to use ACE inhibitors.

Although a strong clinical motivation exists to differentiate among therapies to achieve optimal outcomes and to tailor treatment to the individual patient, this review indicates that, for the relatively low-risk individual with essential hypertension, any differences between ACE inhibitors and ARBs in major events or changes in risk factors are likely to be small. Identifying such small differences is a substantial challenge requiring large, prolonged studies in generalizable populations and settings. However, in the face of the considerable effect of marginal differences in treatment efficacy for common conditions, such an effort may well be justified.

From Duke Center for Clinical Health Policy Research, Duke Clinical Research Institute, Duke University, and the Center for Health Services Research in Primary Care, Durham U.S. Department of Veterans Affairs Medical Center, Durham, North Carolina.

Disclaimer: The authors of this report are responsible for its content. Statements in the report should not be construed as endorsements by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Grant Support: This project was funded under contract no. 290-02-0025 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services.

Potential Financial Conflicts of Interest: *Honoraria:* D.C. McCrory (AstraZeneca). *Stock ownership or options (other than mutual funds):* G.P. Samsa (Pfizer).

Requests for Single Reprints: David B. Matchar, MD, Duke Center for Clinical Health Policy Research, 2200 West Main Street, Suite 220, Durham, NC 27705; e-mail, david.matchar@duke.edu.

Current author addresses are available at www.annals.org.

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Current Author Addresses: Drs. Matchar, McCrory, Orlando, Patwardhan, Samsa, and Gray: Duke Center for Clinical Health Policy Research, 2200 West Main Street, Suite 220, Durham, NC 27705. Dr. M.R. Patel: Duke Clinical Research Institute, North Pavilion, 2400 Pratt Street, Room 0311, Durham, NC 27705. Dr. U.D. Patel: Department of Nephrology, Duke University Medical Center, DUMC Box 3646, Durham, NC 27710. Dr. Powers: Duke University and Durham Veterans Affairs Medical Center, 2424 Erwin Road, Suite 1105, Durham, NC 27705.

APPENDIX 1: METHODS FOR REVIEWING INDIRECT COMPARISON STUDIES

Our review of the literature on the comparative long-term benefits and harms of angiotensin-converting enzyme (ACE) inhibitors versus angiotensin II receptor blockers (ARBs) for treating hypertension focused, in the first instance, on direct head-to-head comparisons of drugs in the 2 classes. Because we were uncertain that these direct comparisons would adequately address all aspects of the key questions, we also sought to identify and screen potentially relevant indirect comparison studies—studies in which ACE inhibitors and ARBs were compared, in distinct trials, with a common comparator. This Appendix describes the methods we used to identify and review indirect comparison studies.

Search and Abstract Screening

We began by searching MEDLINE for studies of ARBs versus other (non-ACE inhibitor) comparators, including placebo. We screened these abstracts along with the head-to-head trials. For indirect comparisons, we considered only randomized, controlled trials. We coded each included abstract for duration of treatment or follow-up (for example, “12 weeks” or “1 year”).

Because a primary objective for evaluating non-head-to-head studies was to expand the pool of evidence regarding long-term results, we restricted the pool of abstracts for further evaluation to those with a duration of treatment or follow-up of at least 24 weeks. Further, because the credibility of any meta-analysis—particularly for non-head-to-head trials—depends on consistency among studies, we considered only comparators studied in at least 3 trials. The comparators thus identified were atenolol, amlodipine, and placebo.

Next, we searched MEDLINE for studies of ACE inhibitors versus atenolol or amlodipine. To identify potentially relevant trials of ACE inhibitor versus placebo, we began by searching the references of the June 2005 Drug Class Review on ACE inhibitors (4) and supplemented this with a search of MEDLINE for articles published after that review. Finally, the abstracts for all ACE inhibitor versus other studies of treatments were screened for inclusion and evaluated further to identify trials with the right treatment duration or length of follow-up (≥ 24 weeks) and the right comparators (atenolol, amlodipine, or placebo).

From this process, we identified 76 randomized, controlled trial publications comparing ARBs with atenolol, amlodipine, or placebo over at least 24 weeks, and 136 randomized, controlled trial publications comparing ACE inhibitors with the same group of comparators over the same period. We could not obtain 4 articles (2 each for ACE inhibitors and ARBs), so the final counts

were 74 potentially relevant ARB articles and 134 potentially relevant ACE inhibitor articles.

Identifying Publications Reporting Outcomes of Interest

Once data from the direct comparator trials had been abstracted, we identified 3 categories of outcomes that we thought were underreported in these trials: death and major events (myocardial infarction, stroke), measures of carbohydrate metabolism or diabetes control (progression to type 2 diabetes, hemoglobin A_{1c}, insulin or other diabetes medication dosage, fasting plasma glucose, or aggregated measures of serial glucose measurements), and measures of kidney disease (creatinine level, glomerular filtration rate, and proteinuria). We then screened the indirect comparison literature identified through the process described above in full-text form to identify publications that reported on 1 or more of these outcomes. Thirty-two articles on ARBs versus other therapies and 42 articles on ACE inhibitors versus other therapies reported 1 or more of the outcomes of interest and were evaluated further.

Analysis of Comparability of Trials

Because of the challenges of using indirect (non-head-to-head) comparison studies to infer relative efficacy regarding any particular health outcome, we established minimal criteria before considering any indirect comparison. Our goal was to achieve a reasonable degree of clinical homogeneity without being excessively restrictive at this stage.

We defined 3 criteria for considering performing an indirect comparison. The first criterion was that the studies must have a common comparator (amlodipine, atenolol, or placebo), because comparators cannot be considered equivalent with regard to any particular health outcome. The second criterion was that study populations must be generally comparable, at least with regard to key characteristics relevant to the outcome being assessed. For studies examining event rates (mortality, stroke, or myocardial infarction), the key characteristic was the mean age of the population. For studies of laboratory measures (hemoglobin A_{1c}, glucose, or creatinine level; glomerular filtration rate; or proteinuria), the key characteristic was the mean of the corresponding laboratory measure at baseline. The value for the key characteristic could be different by as much as 10% and still be considered comparable (for example, comparable studies for mortality rates in which the study with the highest mean age for patients was 70 years could have mean patient ages as low as 63 years). The third criterion was that among studies satisfying the preceding criteria, there must be more than 1 study of an ACE inhibitor versus the comparator and more than 1 study of an ARB versus the comparator. That is, indirect comparisons for a particular outcome were considered only if we could find at least 4 comparable studies to evaluate, 2 for an ACE inhibitor and 2 for an ARB. Notably, we did not restrict studies to the same ACE inhibitor or ARB, or any other protocol characteristics.

Despite these relatively liberal criteria for considering indirect comparisons between ACE inhibitors and ARBs, we did not identify any appropriate candidate studies related to an outcome of special interest, and thus we did not attempt to use indirect evidence to infer relative effect of ACE inhibitors versus ARBs.

APPENDIX 2: APPLICABILITY CRITERIA

We did not provide a global rating of applicability (such as “high” or “low”) because applicability may differ substantially depending on the user of the review. However, applicability of research studies was assessed by noting the most important *potential* limitations in a study’s applicability from among the list described by Rothwell (24). These criteria, slightly adapted by the Scientific Resource Center, are reproduced below. Assessors were instructed to list the most important (up to 3) limitations affecting applicability, if any, on the basis of this list.

Instructions to abstractors/assessors: Do not assign an overall applicability score. Instead, list the most important (up to 3) limitations affecting applicability, if any, based on the following list.

Setting of the Study

1. In which country (or countries) was the study conducted?
2. In what health care system (or systems) was the study conducted?
3. Were patients recruited from the primary, secondary, or tertiary care settings?
4. How were study centers selected for participation?
5. How were study clinicians selected for participation?

Selection of Participants

6. How were participants diagnosed and identified for eligibility screening before random allocation?
7. What were the study eligibility criteria?
8. What were the study exclusion criteria?
9. Did the study require a run-in period with the control or placebo intervention?
10. Did the study require a run-in period with the active intervention?
11. Did the study selectively recruit participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition?
12. Did the study report the ratio of randomly allocated participants to nonallocated participants (who were eligible)?
13. Did the study report the proportion of eligible participants who declined random allocation?

Characteristics of Study Participants

14. Did the study report participants’ baseline characteristics?
15. Did the study report participants’ race?
16. Did the study report participants’ underlying pathology?

17. Did the study report participants’ stage in the natural history of the disease?

18. Did the study report participants’ severity of disease?

19. Did the study report participants’ comorbid conditions?

20. Did the study report participants’ absolute risk of a poor outcome in the control arm?

Differences between the Study Protocol and Routine Clinical Practice

21. Were the study interventions (active arm) similar to interventions used in routine clinical practice?

22. Was the timing of the intervention similar to the timing in routine clinical practice?

23. Was the study’s control arm appropriate and relevant in relation to routine clinical practice?

24. Were the study’s co-interventions—which were not randomly allocated—adequate to reflect routine clinical practice?

25. Were any interventions prohibited by the study that are routinely used in clinical practice?

26. Have there been diagnostic or therapeutic advances used in routine practice since the study was conducted?

Outcome Measures and Follow-up

27. If applicable, did the study use a clinically relevant surrogate outcome?

28. If applicable, did the study use a scale that is clinically relevant, valid, and reproducible?

29. If applicable, was the intervention beneficial on the most relevant components of the composite outcome?

30. Which clinician measured the outcome (e.g., treating physician or surgeon)?

31. Did the study use patient-centered outcomes?

32. How frequently were participants followed in the study?

33. Was the duration of participant follow-up adequate?

Adverse Effects of Treatment

34. How completely did the study report the occurrence of relevant adverse effects?

35. Did the study report the rates of treatment discontinuations?

36. Were the study centers and/or clinicians selected on the basis of their skill or experience?

37. Did the study exclude participants at elevated risk of intervention complications?

38. Did the study exclude participants who suffered adverse effects during the run-in period?

39. Did the study monitor participants intensively for early signs of adverse effects?