Comparative Effectiveness Review

Number XXX

Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension – An Update of the 2007 Report

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Preface

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

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

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

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

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

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Contents

Executive Summary 9
Introduction 17
Background 17
Scope and Key Questions 18
Methods 28
Topic Development 28
Search Strategy 28
Study Selection 29
Analytic Framework 31
Data Extraction 33
Quality Assessment 33
Applicability 34
Rating the Body of Evidence 35
Data Synthesis 35
Results 36
Literature Search and Screening 36
Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life and other outcomes? 41
Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence? 60
Key Question 3. Are there subgroups of patients – based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated? 72
Summary and Discussion 76
Future Research 82
References 85
Abbreviations 91

Tables

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report 21
Table 2. Types and sources of gray literature searched 29
Table 3. Sources of citations 36

Table 4. Number of studies (number of publications) that evaluated various treatment comparisons 39
Table 5. Distribution of studies by followup time 40
Table 6. Estimated odds ratios for successful blood pressure control on monotherapy (ARBs vs. ACEIs) 46
Table 7. Meta-analyses of successful blood pressure control on monotherapy by subgroup for ARBs vs. ACEIs 47
Table 8. Studies reporting significant changes in lipid profiles with ACEIs and/orARBs 50
Table 9. Characteristics of studies reporting LV mass/function outcomes 52
Table 10. Estimated standardized mean differences for studies reporting serum creatinine (ARB minus ACEI) 55
Table 11. Meta-analyses of serum creatinine by subgroup for ARB minus ACEI 56
Table 12. Estimated standardized mean differences for studies reporting creatinine clearance (ARB minus ACEI) 57
Table 13. Meta-analyses of creatinine clearance for ARB minus ACEI 57
Table 14. Estimated standardized mean differences for studies reporting GFR (ARB minus ACEI) 58
Table 15. Meta-analyses of GFR for ARB minus ACEI 58
Table 16. Meta-analyses of all flow rate studies for ARB minus ACEI 59
Table 17. Studies reporting angioedema 61
Table 18. Estimated odds ratios for cough (ARBs vs. ACEIs) 62
Table 19. Meta-analyses of cough by subgroup for ARBs versus ACEIs 64
Table 20. Meta-analyses of cough for direct renin inhibitors vs. ACEIs 66
Table 21. Estimated odds ratios for withdrawals due to adverse events (ARBs vs. ACEIs) 66
Table 22. Meta-analyses of withdrawals due to adverse events by subgroup for ARBs vs. ACEIs 68
Table 23. Meta-analyses of withdrawals due to adverse events for direct renin inhibitors vs. ACEIs 69
Table 24. Studies of treatment adherence with ACEIs and ARBs 70
Table 25. Studies of persistence with ACEIs and ARBs 71
Table 26. Predictors of persistence with ACEIs and ARBs 74
Table 27. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for essential hypertension 76
Table 28. GRADE summary table 78
Table 29. GRADE balance sheet 81

Figures

Figure 1. Analytic framework 32
Figure 2. Literature flow diagram 37
Figure 3. Random-effects analysis of RCTs for successful blood pressure control on

monotherapy (ARBs vs. ACEIs) 48
Figure 4. Random-effects analysis of observational studies for successful blood pressure control on monotherapy (ARBs vs. ACEIs) 49
Figure 5. Random-effects analysis of all studies reporting serum creatinine (ARB mean minus ACEI mean) 56
Figure 6. Random-effects analysis of all studies reporting creatinine clearance (ARB mean minus ACEI mean) 57
Figure 7. Random-effects analysis of all studies reporting GFR (ARB mean minus ACEI mean) 58
Figure 8. Random-effects analysis of RCTs for cough (ARBs vs. ACEIs) 65
Figure 9. Random-effects analysis of RCTs for withdrawals due to adverse events (ARBs vs. ACEIs) 68

Appendices

Appendix A. Exact Search Strings
Appendix B. Methods for Reviewing Indirect Comparison Studies
Appendix C. Abstract and Full-Text Screening Criteria
Appendix D. Data Abstraction Form
Appendix E. Evidence Table
Appendix F. Applicability Criteria
Appendix G. List of Excluded Direct Comparator Studies

Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension – An Update of the 2007 Report

Executive Summary

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.

The full report and this summary are available at
www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

Almost 75 million American adults – approximately one third – have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people aged 55 to 74 years and approximately three-fourths of those aged 75 years and older are affected. In addition to being the primary attributable risk factor for death throughout the world, hypertension results in substantial morbidity because of its impact on numerous target organs, including the brain, eyes, heart, arteries, and kidneys.

Despite the high rates of morbidity and mortality attributable to hypertension, control of the condition remains suboptimal. In addition to several effective nonpharmacological interventions – including diet, exercise, and control of body weight – many individuals will require antihypertensive medication to lower blood pressure.

Among the many choices in antihypertensive therapy, some of the most common are those aimed at affecting the renin-angiotensin-aldosterone (renin) system. The renin system is an important mediator of blood volume, arterial pressure, and cardiac and vascular function. Components of this system can be identified in many tissues, but the primary site of renin release is the kidney. The renin system can be triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Via proteolytic cleavage, renin converts the decapeptide substrate angiotensinogen I into the octapeptide angiotensin II. Angiotensin II acts

directly on the resistance vessels to: increase systemic vascular resistance and arterial pressure; stimulate the adrenal cortex to release aldosterone, which leads to increased sodium and water reabsorption and potassium excretion; promote secretion of antidiuretic hormone, which leads to fluid retention; stimulate thirst; promote adrenergic function; and increase cardiac and vascular hypertrophy.

Therapies aimed at modifying the renin system have been used extensively for treatment of hypertension, heart failure, myocardial infarction, diabetes, and renal disease. Currently, three classes of drugs that interact with this system are used to inhibit the effects of angiotensin II – the angiotensin-converting enzyme inhibitors (ACEIs), the angiotensin II receptor antagonists (ARBs), and the direct renin inhibitors. ACEIs block the conversion of angiotensin I into angiotensin II; ARBs selectively inhibit angiotensin II from activating the angiotensin-specific receptor (AT1); and direct renin inhibitors block the conversion of angiotensinogen into angiotensin I.

Although ACEIs and ARBs both target the renin system and are treated by clinicians as being equivalent, this may not be appropriate. While both drug classes reduce the downstream effects of angiotensin II, it is not clear that these medications are in fact clinically equivalent. ACEIs, for example, do not entirely block production of angiotensin II because of the presence of unaffected converting enzymes. Also, ACEIs have well-known side effects not shared by ARBs, including cough (estimated incidence 5 to 20 percent) and angioedema (estimated incidence 0.1 to 0.2 percent, with a lesser reported risk with ARBs). Additional considerations arise with the newer direct renin inhibitors, because their side-effect profiles and efficacy may be more favorable than those of either ACEIs or ARBs. Given the public health importance and widespread use of these agents, it is important to understand their comparative effects on clinical outcomes.

This review summarizes the evidence on the comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors, focusing on their use for treating essential hypertension in adults. It is an update of a 2007 report that evaluated the scientific literature on ACEIs and ARBs for adults with essential hypertension and adds an evaluation of direct renin inhibitors, which were not covered in the original report. The need for this updated report was determined on the basis of an analysis conducted by the Southern California EPC. In that analysis, investigators assessed the conclusions from the original comparative effectiveness review, performed a limited literature search of potentially new evidence, and solicited expert opinions concerning the state of the evidence and validity of the original report.

Key questions addressed are:

Key Question 1. For adult patients[a] with essential hypertension, how do ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin II receptor antagonists), and direct renin inhibitors[b] differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes[c]?

(a) "Adult patients" are defined as adults, age 18 years or older.

(b) ACEIs evaluated are: Benazepril (Lotensin®), captopril (Capoten®), enalapril (Vasotec®), fosinopril (Monopril®), lisinopril (Prinivil®, Zestril®), moexipril (Univasc®), perindopril (Aceon®), quinapril (Accupril®), ramipril (Altace®), and trandolapril (Mavik®). ARBs considered are: Candesartan cilexetil (Atacand®), eprosartan (Teveten®), irbesartan (Avapro®), losartan (Cozaar®), olmesartan medoxomil (Benicar®), telmisartan (Micardis®), and valsartan (Diovan®). Direct renin inhibitors considered are: Aliskiren (Tekturna®).

(c) Outcomes considered include:

Primary outcomes:

1. Blood pressure control (we will prefer seated trough blood pressure, where reported).
2. Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific).
3. Morbidity (especially major cardiovascular events [myocardial infarction (MI), stroke] and measures of quality of life).
4. Safety (focusing on serious adverse event rates, overall adverse event rates, and withdrawals due to adverse events, withdrawal rates, and switch rates).
5. Specific adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia).
6. Persistence/adherence.
7. Rate of use of a single antihypertensive medication for blood pressure control.

Secondary outcomes:

1. Lipid levels (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglycerides).
2. Rates of progression to type 2 diabetes.
3. Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, or aggregated measures of serial glucose measurements).
4. Measures of left ventricular mass/function (left ventricular mass index and ejection fraction).
5. Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria)

Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety,[d] adverse events,[e] tolerability, persistence with drug therapy, and treatment adherence?

(d) Safety outcomes considered include: Overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, and switch rates. (For practical reasons, we separate safety/adverse events and tolerability/persistence

[including switch rates], as the latter may or may not be due to identifiable adverse events.)

(e) Specific adverse events: These included, but were no limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia.

Key Question 3. Are there subgroups of patients – based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

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 ACEIs, ARBs, and direct renin inhibitors for adults with essential hypertension.

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors essential hypertension

Key question	Strength of evidence	Conclusions
1. Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes:		
a. Blood pressure control?	High	ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence from 75 studies (69 RCTs, four nonrandomized controlled clinical trials, one retrospective cohort study, and one case-control study) in which 24,943 patients receiving an ACEI or an ARB were followed for periods from 12 weeks to 5 years (median 24 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols. Evidence concerning the effect of direct renin inhibitors on blood pressure is very limited and currently based on only three studies. These studies found the direct renin inhibitor to have a greater reduction in blood pressure compared to an ACEI (two studies) and no significant difference compared to an ARB (one study).
b. Mortality and major cardiovascular events?	Low	Due to insufficient numbers of deaths or major cardiovascular events reported, it was not possible to discern any differential effect of ACEIs versus ARBs versus direct renin inhibitors for these critical outcomes. In 21 studies that reported mortality, MI, or clinical stroke as outcomes among 38,504 subjects, there were 346 deaths and 13 strokes reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended

Key question	Strength of evidence	Conclusions
		followup.
c. Quality of life?	Low	No differences were found in measures of general quality of life; this is based on four studies, two of which did not provide quantitative data. No study evaluated the comparative effectiveness of direct renin inhibitors for quality-of-life outcomes.
d. Rate of use of a single antihypertensive medication?	High	There was no statistically evident difference in the rate of treatment success based on use of a single antihypertensive for ARBs compared to ACEIs. The trend toward less frequent addition of a second agent to an ARB was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients, and by RCTs with very loosely defined protocols for medication titration and switching. There were no relevant studies evaluating direct renin inhibitors.
e. Risk factor reduction and other intermediate outcomes?	Moderate (lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease) Low (progression to type 2 diabetes and LV mass/function)	There were no consistent differential effects of ACEIs, ARBs, or direct renin inhibitors on several potentially important clinical outcomes, including lipid levels and markers of carbohydrate metabolism/diabetes control. There appears to be a small difference in change in renal function between ACEIs and ARBs (favoring ACEIs), but this difference is both small and most likely not clinically meaningful or significant. Relatively few studies assessed these outcomes over the long term. There were no included studies evaluating rates of progression to type 2 diabetes mellitus. Although we included 13 studies of LV mass/function, these were dominated by poor-quality studies with small sample sizes.
2. Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?	High (cough, withdrawals due to adverse events) Low (angioedema)	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs (odds ratio 0.212; 95% CI 0.157 to 0.284). For RCTs, this translates to a difference in rates of cough of 7.8 percent; however, for cohort studies with lower rates of cough, this translates to a difference of 1.2 percent. There were only two studies comparing direct renin inhibitors to ACEIs and these gave an estimated odds ratio of 0.333 (95% CI of 0.2241 to 0.4933). The withdrawal rate for ARBs was found to have an estimated odds ratio of 0.565 (95% CI 0.453 to 0.704) compared with ACEIs. For RCTs, this translated to a difference in withdrawals of 2.3 percent. The direct renin inhibitor trials did not find a statistically significant difference (odds ratio 0.886; 95% CI 0.458 to 1.714) when compared with the withdrawal rate associated with ACEIs. There was no evidence of differences across treatments in rates of other commonly reported specific adverse events. Angioedema was not reported in the majority of studies, making it impossible to accurately characterize its frequency and timing in this population. In the studies that did report

Key question	Strength of evidence	Conclusions
	Moderate (persistence with drug therapy/ treatment adherence)	episodes of angioedema, this adverse event was observed only in patients treated with an ACEI (five patients) or a direct renin inhibitor (one patient). ACEIs and ARBs have similar rates of treatment adherence based on pill counts; this result may not be applicable outside the clinical trial setting. Rates of continuation with therapy appear to be somewhat better with ARBs than with ACEIs; however, due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify. The studies evaluating direct renin inhibitors did not find evidence of differences in treatment adherence compared with ACEIs or ARBs.
3. Key Question 3. Are there subgroups of patients – based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – a for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?	Insufficient	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs, ARBs, and direct renin inhibitors for any particular patient subgroup.

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CI = confidence interval; GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; RCTs = randomized controlled trials

Remaining Issues

Despite the relative importance of both ACEIs and ARBs for treatment of essential hypertension, there is a paucity of comparative evidence for long-term benefits and harms of these two classes of agents. In particular, there is a lack of information about death or major cardiovascular events, and inconsistently reported data on adverse events. Only nine studies compared ACEIs and ARBs for periods longer than 1 year. In addition, although direct renin inhibitors have been proposed as a new class with potentially more favorable side-effect profiles and efficacy, the number of studies with comparative evidence for this new drug class versus ACEIs or ARBS is extremely limited. Only three studies focusing on direct renin inhibitors met our inclusion criteria, with the longest followup being 36 weeks.

Future Research

With the exception of rates of cough, the hypothesis that ACEIs, ARBs, and direct renin inhibitors have clinically meaningful differences in long-term outcomes in individuals with essential hypertension is not strongly supported by the available evidence. Given the importance of these issues, it is notable how few large, long-term, head-to-head studies have been published.

Further comparative studies in this area should emphasize:

- Subgroups of special importance such as individuals with essential hypertension and diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia.
- 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.
- Outcomes over several years.
- Outcomes measured according to current clinical standards.
- Broader representation of groups such as the elderly and ethnic and racial minorities.
- Evaluation of specific pairs of ACEIs and ARBs to allow differentiation within class. (Only one direct renin inhibitor, aliskiren, is currently available.)
- Long-term comparisons of direct renin inhibitors with ACEIs and ARBs.

In addition, we think that research aimed at generating additional evidence regarding four specific areas should be prioritized. These areas include:

(1) The incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or direct renin inhibitors.

Comment: Angioedema is a well known adverse reaction to ACEIs and ARBs; however, due to its infrequent occurrence, we lacked sufficient evidence to directly compare the incidence, timing, and clinical consequences of this reaction among patients treated with ACEIs, ARBs, or direct renin inhibitors. Others have estimated that angioedema is experienced by 1 in every 1000 patients treated with an ACEI, and 1 to 5 of every 10,000 of those treated with an ARB. Furthermore, others have reported a 3- to 4-fold increased risk of angioedema in African-American patients. Future research should utilize large databases with sufficient sample sizes to obtain more precise estimates of this rare but serious event. Assessment of study designs or analyses that could explore the impact of angioedema should be prioritized.

(2) Relative persistence with drug therapy across the different classes of drugs.

Comment: Although we report with moderate confidence that persistence with drug therapy is greater with ARB treatment than with ACEI treatment, medication discontinuation rates varied significantly across studies. Because medication discontinuation often requires followup visits and initiation of alternative medications, it has important health economic implications. Future studies that more precisely estimate discontinuation rates in usual clinic settings, the additional health care utilization following discontinuation, and the conditional tolerability of an ACEI or ARB following prior intolerance to one of these agents would be valuable in understanding the consequences of differential medication discontinuation.

(3) The impact of cough on patients' quality of life.

Comment: Given the demonstrated higher incidence of cough with ACEIs, it would also be valuable to gain more precise understanding of the impact of cough on quality of life, care patterns (e.g., use of therapeutic agents for cough symptoms or conditions

associated with cough), and health outcomes, particularly for individuals who continue to use ACEIs.

(4) The potential to gain insight on the comparative benefits and harms of ACEIs, ARBs, and direct renin inhibitors based on findings from studies evaluating patients with other, related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease.

Comment: While our review is restricted to patients with essential hypertension, the agents studied here have been compared in large studies for related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease. Trials comparing ACEIs, ARBs, and direct renin inhibitors in these target conditions often report the outcomes of interest in this review. For evaluation of rarer events (e.g., mortality or angioedema) it may be worth combining data across target conditions. Future research should consider this strategy and evaluate the extent to which results differ across target condition.

Introduction

Background

Almost 75 million American adults – approximately one third – have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people aged 55 to 74 years and approximately three-fourths of those aged 75 years and older are affected.[1] In addition to being the primary attributable risk factor for death throughout the world,[2] hypertension results in substantial morbidity because of its impact on numerous target organs, including the brain, eyes, heart, arteries, and kidneys.

Despite the high morbidity and mortality attributable to hypertension, control of the condition remains suboptimal. Approximately one-third of adults remain unaware of their hypertension, over 40 percent of individuals with hypertension are not on treatment, and two-thirds of hypertensive patients continue to have blood pressures above even modest treatment goals (< 140/90 mmHg).[3-4] Several nonpharmacological interventions – including diet, exercise, and control of body weight – are effective in lowering blood pressure; however, such therapies are often insufficient or not sustained, resulting in reliance on pharmacotherapy. Various classes of antihypertensive drug treatments are available, but determining their comparative effectiveness is complicated. Therapeutic choices may be influenced by patient characteristics – including comorbidities and race – that also affect the risk of certain clinical end points. Multi-drug therapy is often required to achieve satisfactory control, leading to greater variables to consider in treatment choices.[3] Finally, adverse events that are characteristic of the individual agents or drug classes further complicate therapeutic decisionmaking.

Among the many choices in antihypertensive therapy, some of the most common are those aimed at affecting the renin-angiotensin-aldosterone (renin) system. The renin system is an important mediator of blood volume, arterial pressure, and cardiac and vascular function. Components of this system can be identified in many tissues, but the primary site of renin release is the kidney. The renin system can be triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to the distal tubule. Via proteolytic cleavage, renin acts on the oligopeptide substrate angiotensinogen to produce the decapeptide angiotensin I. In turn, two terminal peptide residues of angiotensin I are removed by the angiotensin-converting enzyme (ACE) to form the octapeptide angiotensin II. Angiotensin II acts directly on the resistance vessels to: increase systemic vascular resistance and arterial pressure; stimulate the adrenal cortex to release aldosterone, which leads to increased sodium and water reabsorption and potassium excretion; promote secretion of antidiuretic hormone, which leads to fluid retention; stimulate thirst; promote adrenergic function; and increase cardiac and vascular hypertrophy.

Therapies aimed at modifying the renin system have been used extensively for treatment of hypertension, heart failure, myocardial infarction (MI), diabetes, and renal disease.[5-6] Currently, three classes of drugs that interact with this system are used to inhibit the effects of angiotensin II: the angiotensin-converting enzyme inhibitors (ACEIs); the angiotensin II receptor antagonists (ARBs); and the direct renin inhibitors. ACEIs block the conversion of angiotensin I into angiotensin II; ARBs selectively inhibit angiotensin II from activating the angiotensin

specific receptor (AT_1); and direct renin inhibitors block the conversion of angiotensinogen into angiotensin I.

Although ACEIs and ARBs both target the renin system and are often treated by clinicians as being equivalent, this may not be appropriate. While both drug classes reduce the downstream effects of angiotensin II, there are differences that may distinguish them. ACEIs, for example, do not entirely block production of angiotensin II because of the presence of unaffected converting enzymes. Treatment with an ACEI, but not an ARB results in increased levels of bradykinin, and this mechanism may mediate differences in clinical efficacy or side effects such as cough or angioedema. ACEIs have well-known side effects not shared by ARBs, including cough (estimated incidence 5 to 20 percent) and angioedema (estimated incidence 0.1 to 0.2 percent, with a lesser reported risk with ARBs)[7] Further, distinguishing effectiveness between these two groups of commonly used angiotensin antagonists is particularly problematic. Although ACEIs, ARBs and direct renin inhibitors are highly effective in lowering blood pressure among patients with essential hypertension,[5-6] the comparative effectiveness of these medication classes is not known. ACEIs and ARBs are the 1st and 4th most commonly prescribed medications for hypertension, respectively, and the use of direct renin inhibitors has been rising since their introduction.[8] Although ACEIs and ARBs are occasionally used in combination, such combinations provide little blood pressure lowering over each agent used alone,[9] and most providers choose to use either an ACEI or an ARB for hypertension. It is therefore important to understand the comparative effectiveness of these agents for providers making this choice.

In this comparative effectiveness review, which updates the 2007 report on *Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension,*[10] we examine the scientific literature on ACEIs, ARBs, and direct renin inhibitors for individuals with hypertension. The outcomes analyzed in this comparison are the relative benefits (i.e., blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes), as well as safety (i.e., adverse events, tolerability, persistence with drug therapy, and treatment adherence). Moreover, we examine the clinical determinants of these outcomes, such as age, race, ethnicity, sex, comorbidities, and concurrent use of other medications. The focus is on long-term outcomes and impact.

The need for this updated report was determined on the basis of an analysis conducted by the Southern California EPC.[11] In that analysis, investigators assessed the conclusions from the original comparative effectiveness review, performed a limited literature search of potentially new evidence, and solicited expert opinions concerning the state of the evidence and validity of the original report.

Scope and Key Questions

This review summarizes the evidence on the comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for treating essential hypertension in adults. Key questions addressed are:

Key Question 1. For adult patients[a] with essential hypertension, how do ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin II receptor antagonists), and direct renin inhibitors[b] differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes[c]?

(a) Adult patients" are defined as adults, age 18 years or older.

(b) Table 1 lists the specific ACEIs, ARBs, and direct renin inhibitors evaluated in this review and describes their characteristics and current indications.

(c) Outcomes considered include:

Primary outcomes:

1. Blood pressure control (we will prefer seated trough blood pressure, where reported).
2. Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific).
3. Morbidity (especially major cardiovascular events [myocardial infarction (MI), stroke] and measures of quality of life).
4. Safety (focusing on serious adverse event rates, overall adverse event rates, and withdrawals due to adverse events, withdrawal rates, and switch rates).
5. Specific adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia).
6. Persistence/adherence.
7. Rate of use of a single antihypertensive medication for blood pressure control.

Secondary outcomes:

1. Lipid levels (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglycerides).
2. Rates of progression to type 2 diabetes.
3. Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, or aggregated measures of serial glucose measurements).
4. Measures of left ventricular mass/function (left ventricular mass index and ejection fraction).
5. Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria).

Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety,[d] adverse events,[e] tolerability, persistence with drug therapy, and treatment adherence?

(d) Safety outcomes considered include: Overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, and switch rates. (For practical reasons, we separate safety/adverse events and tolerability/persistence [including switch rates], as the latter may or may not be due to identifiable adverse events.)

(e) Specific adverse events: These included, but were no limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia.

Key Question 3. Are there subgroups of patients – based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
ACEIs				
Benazepril (Lotensin®)	- After oral administration, peak plasma concentrations reached within 0.5-1 hr. - Effective half-life in adults following multiple dosing 10-12 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	Treatment of hypertension. May be used alone or in combination with thiazide diuretics.	Initial dose for adults not receiving a diuretic is 10 mg once daily. Usual maintenance range is 20-40 mg per day in a single or two equal doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - In patients with renal insufficiency (creatinine clearance ≤30 mL/min/1.73 m²) peak levels and initial half-life increase, time to steady state may be delayed. Recommended initial dose in such patients is 5 mg once daily. Dosage may be titrated upward until BP is controlled or to a maximum total daily dose of 40 mg.
Captopril (Capoten®)	- After oral administration, peak plasma concentrations reached in 1 hr. Presence of food reduces absorption by 30-40%. - In adults, effective half-life < 3 hr (accurate determination of half-life not possible). - In a 24-hr period, 95% of observed dose eliminated in the urine. - Reduction of BP maximum at 60-90 minutes after oral administration, duration of effect dose-related. - Reduction in BP may be progressive.	1. Treatment of hypertension. 2. Treatment of congestive heart failure. 3. To improve survival following MI in clinically stable patients.	Should be taken 1 hr before meals, dosage must be individualized. Initial dose is 25 mg twice per day or three times per day. Dosage may be increased to 50 mg twice per day or three times per day. Usual dose range is 25-150 mg twice per day or three times per day.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration, and minimal effective dose should be calculated.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Enalapril (Vasotec®)	- After oral administration, peak serum concentrations occur within 1 hr. - Primarily renal, 94% of dose is recovered in the urine and feces. - Effective half-life following multiple doses is 11 hr. - With GFR ≤ 30 mL/min, time to peak concentration and steady state delayed.	Treatment of hypertension.	10-40 mg per day in a single or two divided doses. Daily dose should not exceed 50 mg. Dosage reduction and/or discontinuation may be required for some patients who develop increases in blood urea and serum creatinine.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. Enalapril has been detected in human breast milk. - Dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range.
Fosinopril (Monopril®)	- After oral administration, peak concentrations achieved in 3 hr. - Terminal elimination half-life is 12 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with thiazide diuretics. 2. For heart failure as adjunctive therapy when added to conventional therapy, including diuretics with or without digitalis.	Initial dosage is 10 mg once daily, both as monotherapy and when the drug is added to a diuretic.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - In children, doses between 0.1 and 0.6 mg/kg. For children weighing more then 50 kg, dosage is 5-10 mg once daily. - For heart failure patients, an initial dose of 5 mg can be increased over a several-week period but not exceeding 40 mg once daily.
Lisinopril (Prinivil®; Zestril®)	- Reaches peak serum concentrations within 7 hr. - On multiple doses, effective half-life accumulation is 12 hr. - Excreted primarily through the kidneys.	1. Treatment of hypertension. 2. As adjunctive therapy in the management of heart failure not responding to diuretics and digitalis. 3. Acute MI – for the treatment of hemodynamically stable patients, to improve survival.	Initial dose is 10 mg once daily, usual dose range 20-40 mg daily in a single dose. Patients on a diuretic dosage should be adjusted according to BP response, and the diuretic should ideally be discontinued. For patients with creatinine clearance ≤ 10 mL/min, recommended initial dose is 2.5 mg, can be titrated upward up to a maximum of 40 mg daily.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dose selection for elderly patients should start at the low end of dosing range.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Moexipril (Univasc®)	- Bioavailability of oral drug is 13% compared to IV; markedly affected by food. - After oral administration, 7% appears in urine (vs. 40% of IV dose), 52% in feces (vs. 20% of IV dose).	Treatment of hypertension.	Initial dose in patients not receiving diuretics is 7.5 mg 1 hr prior to meals, once daily. Recommended dose range is 7.5-30 mg daily in one or two divided doses. Diuretic therapy should ideally be discontinued or an initial dose of 3.75 mg should be used with medical supervision. For patients with creatinine clearance ≤ 40 mL/min/1.73 m², the recommended initial dose is 3.75 mg once daily, can be titrated to a maximum daily dose of 15 mg.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dosage should be adjusted for populations with decreased renal function, mild to moderate cirrhosis and in elderly patients.
Perindopril (Aceon®)	- After oral administration, peak plasma concentrations occur at approximately 1 hr. - Mean half-life 0.8-1.0 hr. - Clearance almost exclusively renal.	1. Treatment of hypertension. May be used alone or in combination with thiazide diuretics. 2. Stable coronary artery disease: to reduce risk of cardiovascular mortality or nonfatal MI.	Initial dose is 4 mg once daily. May be titrated upward until BP is controlled to a maximum of 16 mg per day. Usual dose range is 4-8 mg as single daily dose. May be given in two divided doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Dose selection for elderly patients should start at the low end of dosing range. - Patients with renal impairment: initial daily dose should be reduced.
Quinapril (Accupril®)	- After oral administration, peak plasma concentrations reached within 1 hr. - After multiple oral dosing, effective half-life within 2 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with thiazide diuretics. 2. Management of heart failure as adjunctive therapy when added to conventional therapy, including diuretics and/or digitalis.	Initial dosage for patients not on diuretics is 10-20 mg once daily. Dosage adjusted according to BP measured at peak and trough.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment and heart failure: initial daily dose should be reduced. - Recommended dosage for elderly patients is 10 mg once daily followed by titration to the optimal response.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Ramipril (Altace®)	- After oral administration, peak plasma concentrations reached within 1 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or in combination with thiazide diuretics. 2. Reduction in risk of MI, stroke, and death from cardiovascular causes for patients 55 years or older at high cardiovascular risk.	Initial dose for patients not receiving a diuretic is 2.5 mg once daily. Dosage adjustment according to BP response. Usual maintenance dosage is 2.5-20 mg once daily in a single dose or divided equally into 2 doses.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration and minimal effective dose should be calculated.
Trandolapril (Mavik®)	- After oral administration under fasting conditions, peak concentrations occur within 1 hr. - Effective half-life approximately 6 hr. - Cleared predominantly by renal excretion in subjects with normal renal function.	1. Treatment of hypertension. May be used alone or with other antihypertensive medication. 2. Heart failure post-MI or LV dysfunction post-MI. Used to decrease risk of death and heart failure-related hospitalization.	Initial dosage in patients not receiving a diuretic is 1 mg once daily in patients who are not black and 2 mg in black patients. Dosage adjusted according to BP.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Patients with renal impairment: initial daily dose should be reduced, smaller increments should be utilized for titration and minimal effective dose should be calculated.
ARBs				
Candesartan cilexetil (Atacand®)	After oral administration, peak serum concentrations reached after 3-4 hr. - Elimination of half-life occurs within 9 hr. - Excreted in urine and feces.	1. Treatment of hypertension. May be used alone or in combination with other antihypertensive agents. 2. Heart failure: used in patients with LV systolic dysfunction to reduce risk of death and heart failure.	Initial dose is 16 mg once daily. Can be given once or twice daily with doses ranging from 8-32 mg. Effect is usually present within 2 weeks, and maximal BP reduction occurs within 4-6 weeks.	- When used in pregnancy during the second and third trimesters, ACEIs can cause injury and even death to the developing fetus. - Lower dose for patients with moderate hepatic impairment or depletion of intravascular volume.
Eprosartan (Teveten®)	- After oral administration, plasma concentrations peak around 1-2 hr in the fasted state. - Mean terminal elimination half-life following multiple doses of 600 mg was 20 hr. - Eliminated primarily by biliary and renal excretion.	Treatment of hypertension. May be used alone or in combination with other antihypertensives, such as diuretics and calcium channel blockers.	Initial dose is 600 mg once daily. Can be given once or twice daily with doses ranging 400 mg to 800 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Elderly, hepatically impaired, or renally impaired patients should not exceed 600 mg daily.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Irbesartan (Avapro®)	- After oral administration, peak plasma concentrations reached at 1.5-2 hr. - Average terminal elimination of half-life is 11-15 hr. - Eliminated primarily by biliary and renal excretion.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents. 2. Nephropathy in type 2 diabetic patients. Indicated for treatment of patients with an elevated serum creatinine and proteinuria > 300 mg/day). Reduces rate of progression of nephropathy.	Initial dose is 150 mg once daily. Patients who require more reduction in BP should be titrated to 300 mg once daily.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Nephropathy in type 2 diabetic patients: maintenance dose is 300 mg once daily. - Children (6-12 years): initial dose of 75 mg, up to 150 mg once daily. Ages 13-16: initial 150 mg once daily, can be titrated to 300 mg once daily, higher doses not recommended. - Lower initial dose for patients with depletion of intravascular volume or salt.
Losartan (Cozaar®)	- After oral administration, mean peak concentrations reached in 1 hr. - Terminal half-life is 2 hr. - Eliminated primarily by biliary and renal excretion.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents, including diuretics. 2. Hypertensive patients with LV hypertrophy: reduces risk of stroke, though some evidence that this does not apply to black patients. 3. Nephropathy in type 2 diabetic patients: reduces rate of progression of nephropathy as measured by doubling of serum creatinine or end-stage renal disease.	Initial dose is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume and patients with history of hepatic impairment. May be given twice daily with total doses from 25 mg to 100 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Pediatric hypertensive patients (6 years and greater): starting dose is 0.7 mg/kg once daily (up to 50 mg total) given as tablet or a suspension. - Hypertensive patients with LV hypertrophy: starting dose is 50 mg once daily. Based on BP response, hydrochlorothiazide 12.5 mg daily should be added and/or dose of losartan should be increased to 100 mg once daily followed by an increase of hydrochlorothiazide to 25 mg once daily.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Olmesartan medoxomil (Benicar®)	- After oral administration, peak plasma concentrations reached after 1-2 hr. - Terminal elimination of half-life is 13 hr. - Eliminated primarily by biliary and renal excretion.	Treatment of hypertension. May be used alone or with other antihypertensive agents.	Initial dose is 20 mg once daily. For patients requiring further reduction in BP, dose may be increased to 40 mg.	When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - In patients with impaired renal failure, a lower starting dose should be considered.
Telmisartan (Micardis®)	- After oral administration, peak concentrations reached within 0.5-1 hr. - Terminal elimination of half-life is 24 hr. - Eliminated mostly through feces.	Treatment of hypertension. May be used alone or with other antihypertensive agents.	Starting dose is 40 mg once daily. BP response is dose-related over range of 20-80 mg.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Patients with depletion of intravascular volume, biliary obstructive disorders, or hepatic insufficiency should start treatment under close medical supervision.
Valsartan (Diovan®)	- After oral administration, peak plasma concentrations reached within 2-4 hr. - Average elimination half-life about 6 hr. - Primarily eliminated in feces and urine.	1. Treatment of hypertension. May be used alone or with other antihypertensive agents. 2. Heart failure: used in treatment of heart failure, reduces hospitalizations. 3. Post-MI: used to reduce cardiovascular mortality.	Initial dose is 80 mg or 160 mg once daily in patients who are not volume depleted. May be used over a dose range of 80 mg to 320 mg once daily.	- When used in pregnancy during the second and third trimesters, drugs that act directly on the rennin-angiotensin system can cause injury and even death to the developing fetus. - Care should be given when dosing patients with hepatic or severe renal impairment.

Table 1. Characteristics and labeled indications of ACEIs, ARBs, and direct renin inhibitors evaluated in this report (continued)

Drug (trade name)	Half-life and other relevant pharmacokinetic features	Labeled indications	Dosing for treatment of hypertension	Dose adjustments for special populations
Direct renin inhibitor				
Aliskiren (Tekturna®)	- Poorly absorbed (bioavailability about 2.5%) with an approximate accumulation half life of 24 hours. - Steady state blood levels are reached in about 7-8 days. - Following oral administration, peak plasma concentrations of aliskiren are reached within 1 – 3 hr. - When taken with a high fat meal, mean AUC and Cmax of aliskiren are decreased by 71% and 85% respectively. - One fourth of the absorbed dose appears in the urine as parent drug.	Treatment of hypertension.	- May be used alone or in combination with other antihypertensive agents. - Use with maximal doses of ACEIs has not been adequately studied. - Starting dose: 150 mg once daily. - If blood pressure remains uncontrolled titrate up to 300 mg (available in 150 mg and 300 mg. tablets). - Patients should establish a routine pattern for taking aliskiren with regard to meals. High fat meals decrease absorption substantially.	- No adjustment of the starting dose is required in elderly patients, patients with mild-to-severe renal impairment or mild to- severe hepatic insufficiency. - Care should be taken when dosing aliskiren in patients with severe renal impairment, as clinical experience with such patients is limited. - Pediatric patients: The pharmacokinetics of aliskiren have not been investigated in patients < 18 years of age. - Nursing mothers: It is not known whether aliskiren is excreted in human breast milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. - Race: The pharmacokinetic differences between Blacks, Caucasians, and the Japanese are minimal.

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor antagonist(s); BP = blood pressure; GFR = glomerular filtration rate; hr = hour(s); LV = left ventricular; MI = myocardial infarction

Methods

Topic Development

The topic for the original 2007 report[10] was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program drafted the initial key questions for that report and, after approval from AHRQ, posted them to a public Web site. The public was invited to comment on these questions. After reviewing the public commentary, the SRC drafted final key questions and submitted them to AHRQ for approval.

For the present updated report the same scope and key questions were initially proposed by AHRQ. In response to input from the project's technical expert panel, the key questions were modified to include the comparative risks and benefits of direct renin inhibitors. The revised key questions were then posted to a public Web site for comment and were modified again in response to the comments received.

Search Strategy

We conducted a comprehensive search of the scientific literature to identify systematic reviews, randomized controlled trials, and nonrandomized comparative studies relevant to the key questions. Searches of electronic databases used the National Library of Medicine's Medical Subject Headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. Searches included terms for drug interventions, hypertension, and study design, and were limited to studies published in English after 1988. The texts of the major search strategies are given in Appendix A. We also reviewed selected gray literature received from the SRC, the reference lists of relevant review articles, and citations identified by peer and public reviewers of the draft report. We did not undertake a systematic search for unpublished data.

To identify literature describing direct comparisons of ACEIs, ARBs, or direct renin inhibitors we searched:

- MEDLINE® (1966 to 03 Dec 2009);
- EMBASE® (all years, ending on 03 Feb 2010);
- The Cochrane Central Register of Controlled Trials;
- A register of systematic reviews underway in the Cochrane Hypertension Review Group; and
- Gray literature identified by the SRC.

Table 2 lists the types and sources of gray literature that were searched by the SRC:

Table 2. Types and sources of gray literature searched

Type of source	Specific sources searched
Regulatory information	FDA Health Canada Authorized Medicines for EU
Clinical trial registries	ClinicalTrials.gov Current Controlled Trials Clinical Study Results WHO Clinical Trials
Abstracts and conference papers	Conference Papers Index Scopus
Grants and federally funded research	NIH RePORTER (a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions) HSRPROJ (a database providing access to ongoing grants and contracts in health services research)
Other miscellaneous sources	Hayes, Inc. Health Technology Assessment NY Academy of Medicine's Grey Literature Index

Abbreviations: EU = European Union; FDA = U.S. Food and Drug Administration; NIH = National Institutes of Health; NY = New York; WHO = World Health Organization

In our original report, we conducted additional searches in MEDLINE® for studies of ARBs versus other (non-ACEI) comparators and ACEIs versus other (non-ARB) comparators for potential use in the event that evidence from direct head-to-head trials proved to be insufficient for some or all of the outcomes of interest in the review. The process used to screen this literature and evaluate its relevance is described in Appendix B. Because we did not use the evidence from these indirect comparisons in our original report, we eliminated this step in the current update and did not search for or include such indirect comparison studies.

Our searches identified a total of 1995 citations. We imported all citations into an electronic database (EndNote® version XI.0.1).

Study Selection

We developed criteria for inclusion and exclusion based on the patient populations, interventions, and outcome measures specified in the key questions. The abstract screening criteria we used (Appendix C) were designed to identify only relevant direct head-to-head comparator studies (ACEIs versus ARBs, ACEIs versus direct renin inhibitors, or ARBs versus direct renin inhibitors). We retrieved the full text of all potentially relevant articles for further review. We then applied a second, more stringent set of criteria for inclusion and exclusion (Appendix C).

The remainder of this section describes in greater detail the criteria we used to screen the available literature.

Population and Condition of Interest

As specified in the key questions, this review focused on adult patients (age 18 years or older) with essential hypertension, as defined by study authors. We included studies with patients of mixed ages and mixed diagnoses only if results were reported separately for the relevant subgroups.

Interventions and Comparators of Interest

We included the ACEIs, ARBs, and direct renin inhibitors listed in Table 1. In addition to straightforward comparisons of a single ACEI versus a single ARB or direct renin inhibitor, we also included "grouped" comparisons (e.g., a specific ARB versus "ACEIs" or unspecified "ARBs" versus unspecified "ACEIs") and comparisons of an ACEI + drug X versus an ARB + drug X (e.g., losartan + hydrochlorothiazide [HCTZ] versus enalapril + HCTZ). We excluded comparisons of an ACEI + drug X versus an ARB + drug Y (e.g., enalapril + manidipine vs. irbesartan + HCTZ).

Studies with treatment protocols that permitted the addition of other antihypertensive medications during the trial if certain blood pressure targets were not met were included provided the cointervention protocols were the same in both groups.

Outcomes of Interest

We considered a wide range of outcomes pertaining to the long-term benefits and harms of ACEIs, ARBs, or direct renin inhibitors. These are listed above in the section on "Scope and Key Questions." In order of relative priority, these outcomes were:

Primary outcomes:

- Blood pressure control (we preferred seated trough blood pressure, where reported).
- Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific).
- Morbidity (especially major cardiovascular events [MI, stroke] and measures of quality of life).
- Safety (focusing on serious adverse event rates, overall adverse event rates, withdrawals due to adverse events, withdrawal rates, and switch rates).
- Specific adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia).
- Persistence/adherence.
- Rate of use of a single antihypertensive medication for blood pressure control.

Secondary outcomes:

- Lipid levels (high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol [TC], and triglycerides [TG]).
- Rates of progression to type 2 diabetes.

- Markers of carbohydrate metabolism/diabetes control (glycated hemoglobin [HbA1c], dosage of insulin or other diabetes medication, fasting plasma glucose, or aggregated measures of serial glucose measurements).
- Measures of left ventricular (LV) mass/function (left ventricular mass index [LVMI] and ejection fraction [LVEF]).
- Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria).

Timing

The key questions ask about the comparative *long-term* benefits and harms of ACEIs, ARBs, or direct renin inhibitors for treating essential hypertension, but do not define precisely what is meant by "long-term." We interpreted this to mean 12 weeks or longer.

Setting

We did not restrict the setting of the studies evaluated in our analysis.

Types of Studies

We included comparative clinical studies of any design, including randomized controlled trials (RCTs), nonrandomized controlled clinical trials, retrospective and prospective cohort studies, and case-control studies.

Analytic Framework

Figure 1 depicts the key questions within the context of the population, interventions, comparators of interest, outcomes, timing, and settings (PICOTS) described in the previous section. In general, the figure illustrates how ACEIs, ARBs, and direct renin inhibitors affect (1) measures of blood pressure control, lipid levels, carbohydrate metabolism/diabetes control, measures of LV mass/function, or measures of kidney disease (creatinine/GFR, proteinuria); and/or (2) clinically significant outcomes, such as mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific) or morbidity (especially major cardiovascular events [MI, stroke], rates of progression to type 2 diabetes, and measures of quality of life). In addition, adverse events (including, but not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia) may occur at any point after ACEIs, ARBs, and/or direct renin inhibitors are received.

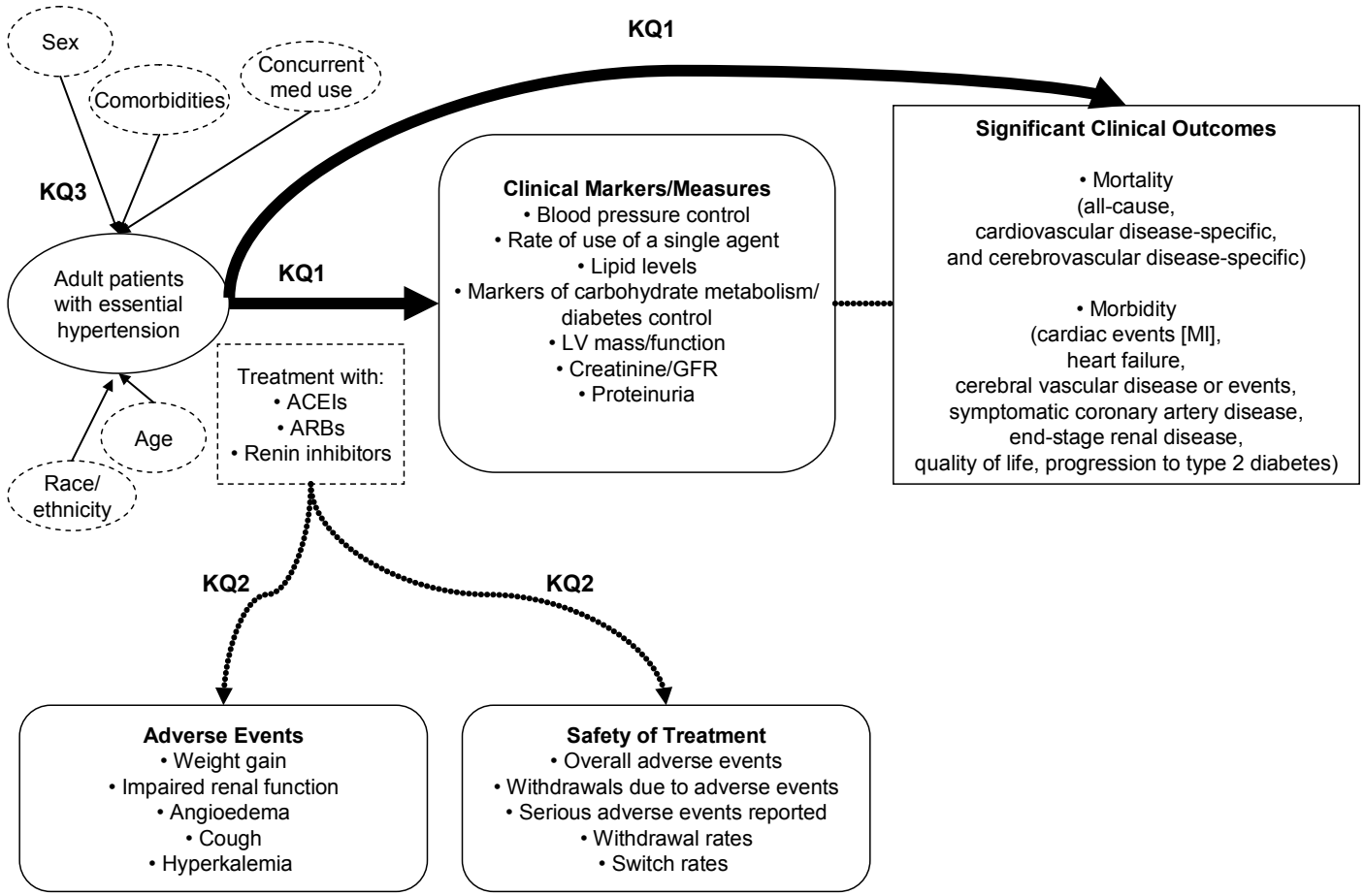


Figure 1. Analytic framework

Data Extraction

We developed a data abstraction form/evidence table template for abstracting data from the included studies (Appendix D) and used the same form for all study designs and to capture data relevant to all three key questions. Abstractors worked in pairs: the first abstracted the data, and the second over-read the article and the accompanying abstraction to check for accuracy and completeness. The completed evidence table, including a row for each study, is provided in Appendix E.

We extracted the following data: geographical location; funding source; study design; interventions (including dose, duration, dose titration protocol [if any], and cointerventions [if any]); population characteristics (including age, sex, race/ethnicity, baseline blood pressure, concurrent medications, and comorbidities); recruitment setting; inclusion and exclusion criteria; numbers screened, eligible, enrolled, and lost to followup; and results for each outcome.

Quality Assessment

We used predefined criteria to assess the quality of individual controlled trials and prospective or retrospective observational (cohort) studies. To assess the quality of clinical trials and cohort studies, we adapted criteria developed by the U.S. Preventive Services Task Force (USPSTF) and the Centre for Reviews and Dissemination (CRD).[12-13] The approach used is similar to that now recommended in AHRQ's draft *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*.[14]

Individual studies were graded as "good," "fair," or "poor" in quality according to the following definitions:

> A "good" study has the least bias and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
>
> A "fair" study is susceptible to some bias, but probably not sufficient to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *possibly* valid, while others are *probably* valid.
>
> A "poor" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

If a study was rated as fair or poor, assessors were instructed to note important limitations on internal validity based on the USPSTF/CRD criteria, as adapted here:

1) Initial assembly of comparable groups:
   - For RCTs: Adequate randomization, including concealment and whether potential confounders were distributed equally among groups.
   - For cohort studies: Consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.

2) Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination).

3) Important differential loss to followup or overall high loss to followup.

4) Measurements: Equal, reliable, and valid (includes masking of outcome assessment).

5) Clear definition of interventions.

6) All important outcomes considered.

7) Analysis: Adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs.

Assessment of each study's quality was made by a single rater and then evaluated by a second rater. Finally, quality assessments were reviewed across studies. Disagreements were resolved by consensus. Final quality assessments for individual studies are included in the evidence table (Appendix E).

Applicability

We did not provide a global rating of applicability (such as "high" or "low") because applicability may differ substantially based on the user of this report. 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.[15] These criteria, slightly adapted by the SRC for the original 2007 report, are reproduced in Appendix F. Assessors were instructed to list the most important (up to three) limitations affecting applicability, if any, based on this list. The approach used is broadly similar to that now recommended in AHRQ's draft *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*.[14]

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the spectrum of patients that will use a drug, have a test, or undergo a procedure than results from highly selected populations in efficacy studies.

Rating the Body of Evidence

For the present update, we assessed the strength of the body of evidence for each key question using the approach recommended in AHRQ's draft *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*.[14] This approach is conceptually similar to the GRADE framework[16] used in the 2007 report. In rating the strength of evidence we considered the number of studies, the size of the studies, strength of study design, and the quality of individual studies. We also assessed risk of bias, directness, precision, consistency across studies of the same design, consistency across different study designs, magnitude of effect, and applicability. Finally, if applicable, we considered (especially for observational studies) the potential influence of plausible confounders. We commented specifically when it was difficult or impossible to assess certain of these dimensions. The overall strength of a given body of evidence was rated qualitatively using the following four-level scale:

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

Data Synthesis

Given that many studies did not have the statistical power to determine equivalence for the outcomes relevant to this review (which were often not the primary outcomes evaluated by study investigators), we considered synthesis (meta-analysis) in an attempt to overcome the type II error.

In evaluating groups of studies reporting the same or similar outcomes for potential data synthesis, we primarily considered clinical diversity. In this assessment, we tended to be inclusive of individual studies unless their populations were clearly dissimilar (e.g., when considering renal outcomes we chose to exclude from pooled analysis studies of patients with renal failure). We considered groups of studies to be suitable candidates for a quantitative synthesis when we were able to identify at least four clinically relatively similar studies that assessed the same outcome (e.g., when considering effects on lipids, we chose not to pool, as the group included different lipid measures.) While not proof of the validity of this approach, it is notable that there were no situations in which pooled estimates of relative efficacy regarding a particular outcome were contrary to the global impression of the reviewers.

When we calculated summary effect sizes, we stratified these by study design, separating RCTs from observational studies. We used Comprehensive Meta-analysis Version 2 (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ [2005]) to test for heterogeneity and to synthesize (while recognizing that the ability of statistical methods to detect heterogeneity is limited, particularly when the number of studies is small). In the presence of statistical heterogeneity, we evaluated likely explanatory clinical and methodological study characteristics to determine whether they could explain the heterogeneity observed. If, after this further scrutiny, studies appeared to be clinically and methodologically similar, we performed the appropriate meta-analysis. To allow for the presence of statistical heterogeneity, we used random-effects models. Meta-analyses combining both study designs were also calculated in order to estimate confidence limits for an overall effect.

When meta-analysis was performed, we used the random-effects model for the primary analysis; in addition, we present summary estimates derived using the fixed-effect model as a sensitivity analysis. Furthermore, for dichotomous outcomes, we used the odds ratio as the effect measure. This was done because it resulted in less heterogeneity than did risk differences.

Given the dearth of studies of the same ACEI versus ARB comparison, and the presumed general similarity of each class, when studies were combined, pooling was performed without regard to the specific drug within the ACEI or ARB class. We stratified the analysis to examine differences between observational studies and randomized controlled trials, as described above.

Results

Literature Search and Screening

Our searches of the literature identified a total of 1995 citations. Table 3 details the number of citations identified from each source.

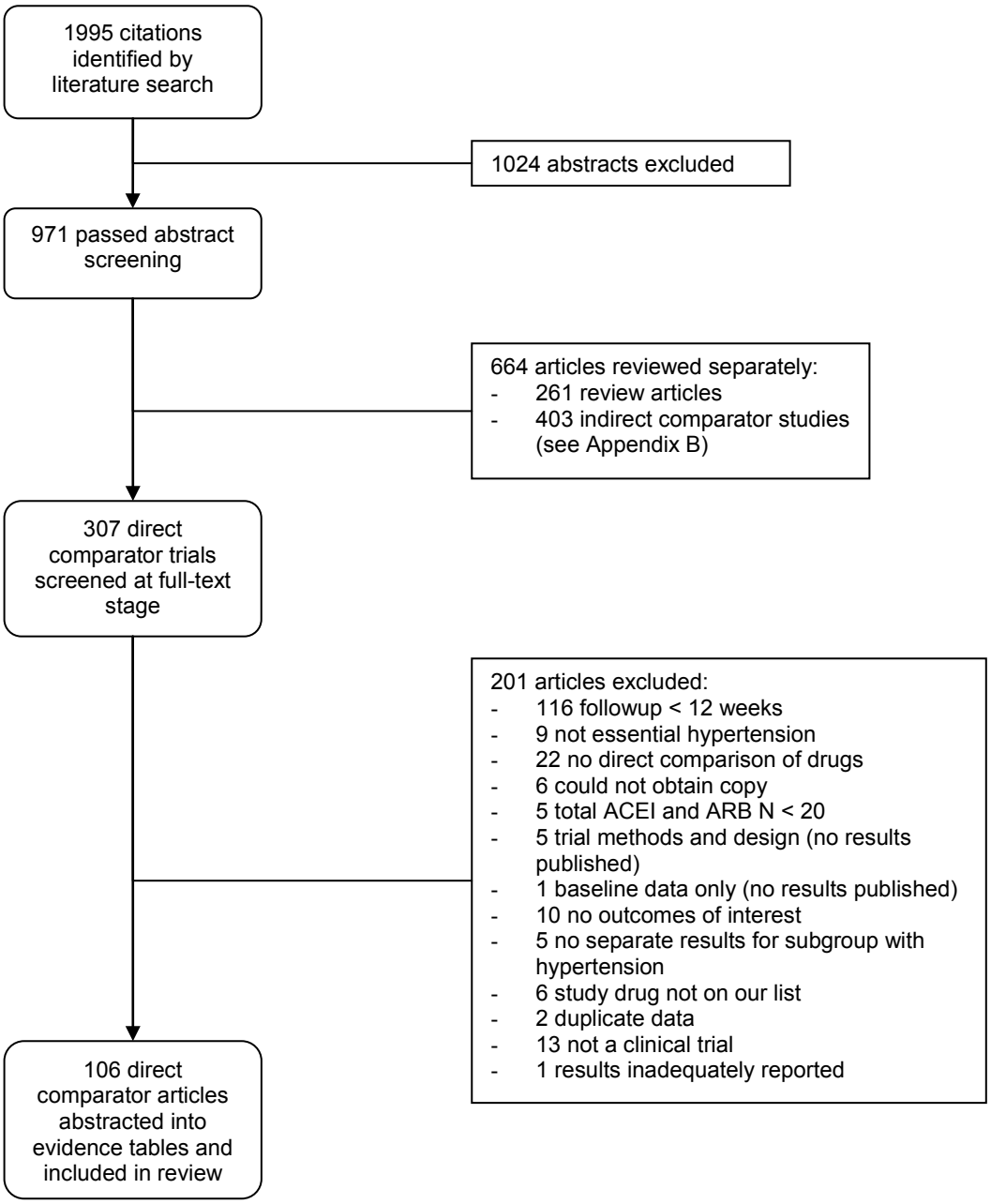
Table 3. Sources of citations

Source	Number of citations
MEDLINE®	1393
EMBASE®	301
Cochrane Central Register of Controlled Trials	45
Register of systematic reviews underway in the Cochrane Hypertension Group	0
References of review articles and primary studies	27
Scientific information packets submitted by pharmaceutical companies	17
Other (recommendations from staff at AHRQ or SRC or from project investigators)	212
Total:	**1995**

Figure 2 describes the flow of literature through the screening process. Of the 1995 citations identified by our searches, 1024 were excluded at the abstract screening stage. Of the 971

citations that passed the abstract screening, 261 were review or methods articles, 403 were indirect comparator studies identified for our original report (see Appendix B), and 307 were direct comparator studies of ACEIs, ARBs, and direct renin inhibitors. The remainder of this section describes results for the direct comparator studies.

Figure 2. Literature flow diagram



At the full-text screening stage, 201 of the 307 direct comparator studies were excluded for the reasons summarized in Figure 2, leaving a total of 106 included articles. Appendix G provides a complete list of head-to-head studies excluded at the full-text screening stage, with reasons for exclusion.

The 106 included direct comparator articles reported on 97 distinct studies. Seventy-three (73) of these were RCTs, three were nonrandomized controlled trials, 16 were retrospective cohort studies, three were prospective cohort studies, and one study each was a cross-sectional cohort and a case-control study. Table 4 describes the number of studies that evaluated various possible treatment comparisons.

Table 4. Number of studies (number of publications) that evaluated various treatment comparisons

		ARBs								DRI	
		Unspecified "ARBs"	Candesartan cilexetil	Eprosartan	Irbesartan	Losartan	Olmesartan medoxomil	Telmisartan	Valsartan	Aliskiren	Totals
ACEIs	Unspecified "ACEIs"	19 (21)	1 (1)	0	2 (2)	2 (2)	0	0	0	0	24 (26)
	Benazepril	0	0	0	0	0	0	0	1 (1)	0	1 (1)
	Captopril	0	0	0	0	2 (2)	0	0	0	0	2 (2)
	Enalapril	0	4 (4)	2 (6)	4 (4)	13 (15)	0	4 (4)	2 (2)	0	29 (35)
	Fosinopril	0	0	0	2 (2)	1 (1)	0	0	0	0	3 (3)
	Lisinopril	0	6 (6)	0	1 (1)	0	0	3 (3)	5 (5)	0	15 (15)
	Moexipril	0	0	0	0	0	0	0	0	0	0
	Perindopril	0	1 (1)	0	0	2 (2)	0	3 (3)	0	0	6 (6)
	Quinapril	0	0	0	2 (2)	3 (3)	0	0	0	0	5 (5)
	Ramipril	0	0	0	0	2 (2)	0	4 (4)	2 (2)	2 (2)	10 (10)
	Trandolapril	0	0	0	0	1 (1)	0	0	0	0	1 (1)
DRI	Aliskiren	0	0	0	0	1 (1)	0	0	0	-	1 (1)
	Totals	19 (21)	12 (12)	2 (6)	11 (11)	27 (29)	0	14 (14)	10 (10)	2 (2)	-

As Table 4 illustrates, enalapril was by far the most frequently studied ACEI (29 studies) and losartan the most frequently studied ARB (27 studies), followed by telmisartan (14 studies). The most commonly studied treatment comparison was the generic "ACEIs" versus "ARBs" (19 studies), followed by enalapril versus losartan (13 studies). Other treatment comparisons were fairly sparsely represented.

In terms of quality, 62 studies were rated as fair, 28 as poor, and 16 as good. The distribution of studies by followup time is given in Table 5.

Table 5. Distribution of studies by followup time

Treatment duration/followup time	Report studies
12 weeks	21
14-16 weeks/3-4 months	15
22 weeks	1
24-26 weeks/6 months	21
30 weeks	1
36 weeks	2
10-11 months	2
48 weeks	4
1 year	16
15 months	1
1.8 years	1
720 days	1
2 years	1
33 months	1
3 years	4
39 months	1
4 years	2
5 years	1
~ 70 months	1

There was no obvious correlation between study quality and length of followup. The 16 good-quality studies varied in length from 12 weeks (two studies), 13 to 36 weeks (eight studies), 1 year (four studies), to 2 years (two studies).

Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?

Key Points

- There was no clear difference in blood pressure lowering efficacy between ACEIs and ARBs. Data concerning direct renin inhibitors were limited
- Few deaths or major cardiovascular events occurred in the identified studies comparing ACEIs, ARBs, and direct renin inhibitors; this precluded any assessment of a differential effect of these drug classes on these events.
- No significant difference was observed between ACEIs and ARBs in terms of their impact on quality of life. No evidence was available regarding the impact of direct renin inhibitors on quality of life.
- There was no statistically evident difference in rate of treatment success based on use of a single antihypertensive medication for ARBs compared to ACEIs. No evidence regarding the effect of direct renin inhibitors on this outcome was identified.
- Available evidence suggests that ACEIs and ARBs have a similar lack of impact on lipid levels for individuals with essential hypertension. No evidence regarding the effect of direct renin inhibitors on these outcomes was available.
- Available evidence suggests that ACEIs and ARBs have a similar lack of impact on glucose levels or HbA1c for individuals with essential hypertension. No evidence regarding the effect of direct renin inhibitors on these outcomes was available.
- Evidence does not demonstrate a difference between ACEIs, ARBs, and direct renin inhibitors with regard to their effect on LV mass or function for individuals with essential hypertension.
- There are no consistently demonstrated differential effects related to renal function as measured by creatinine or GFR with use of ACEIs, ARBs, or direct renin inhibitors. There appears to be a small difference in change in renal function favoring ACEIs over ARBs, but the clinical significance of these small effects is uncertain.
- There is a consistent finding of no differential effect related to reduction of urinary protein or albumin excretion among patients with essential hypertension with use of ACEIs, ARBs, or direct renin inhibitors.

Effect on Blood Pressure

Comparisons of ACEIs Versus ARBs

Seventy five (75) studies described in 81 separate publications met our inclusion criteria and reported a blood pressure outcome. Of these, 11 (15 percent) were of good methodological quality,[17-27] 43 (57 percent; 48 papers) were of fair quality,[28-72] and 21 (28 percent) were of poor quality.[73-94] There were four nonrandomized controlled clinical trials,[73,76,81,88] one retrospective cohort study,[43] and one case-control study;[91] the remaining 69 studies were RCTs. Sample sizes

for individual studies ranged from 1529 to 3813 patients, and a total of 24,943 patients received an ACEI or an ARB. Study durations ranged from 12 weeks to 5 years, with a median of 24 weeks.

The mean age of study participants ranged from 33 years to 73 years, with a median of 55 years. The proportion of female patients included ranged from 19 to 100 percent, with a median of 48 percent. Only 33 studies (44 percent; 39 papers) reported the racial demographics of the study participants.[19-20,22-23,25-27,29-34,37,42,46-50,52,55,57-58,63,65,69-71,73,83-84,89,95-100] Of these 33 studies, only 12 (36 percent; 17 papers) enrolled a minimum of 10 percent of ethnic minority participants.[22,30,32-33,37,42,46,48-50,55,57,70,89,95-96,98]

Seven studies (9 percent) were conducted entirely within the United States or Canada,[22,32,46-47,57,70,98] with the remainder carried out in other countries. The funding source was reported in 43 studies (57 percent; 48 papers),[19-26,28,30-34,36-37,42-44,46-56,59-61,63-65,68,72-73,76,84-87,89-91,101] with the majority of these (29 studies) funded by the manufacturer of one of the study medications.

The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the beginning of each study ranged from 127 to 199 mm Hg and 67 to 119 mm Hg, respectively, with a mean starting blood pressure of 157.3/96.7 mm Hg. There was significant heterogeneity in the study protocols and data reporting. Fewer than half of the studies (29/75; 39 percent; 30 papers) did not allow additional hypertension medications during the study;[17,19,29,32,34-35,38-39,41,50-53,58-60,63,66,68-69,71,73,76-77,79,83-84,94,98,100] 29 studies (39 percent; 33 papers) allowed additional medications according to a specified protocol;[20-22,24-27,30,33,37,42,44-49,55,57,61-62,64-65,67,70,72,75,78,80,90-92,101] six studies (eight percent; seven papers) allowed additional medications at the discretion of the treating physician;[23,31,43,54,56,86-87] and 11 studies (15 percent) did not report concomitant hypertension therapy.[18,28,36,40,74,81-82,85,88-89,93] The reported blood pressure endpoints varied as well, with 51 studies (68 percent; 53 papers) reporting the difference in final posttreatment blood pressure;[19-20,22,24-28,34-36,38-41,44,47,50,52,55-62,64-65,68-69,71-76,78-80,82-91,93-94,98] 33 studies (44 percent; 38 papers) reporting the mean change in blood pressure in each study arm;[17-18,20-23,29-34,37-40,42-43,45-46,48-52,54-55,57-58,63,67,69-70,77,83,92,98,100] and four studies (five percent) not providing quantitative data for the blood pressure outcome or reporting only the proportion of patients achieving a target blood pressure.[53,66,81,101]

For the overall comparison of blood pressure lowering between ACEIs and ARBs, 57 studies reported no difference (76 percent; 62 papers),[17-18,20-21,23-28,30-38,40,42,44-49,52-57,59-61,64-68,70-75,78-82,84-93,101] two studies favored ACEIs (three percent; three papers),[22,58,69] 10 studies favored ARBs (13 percent),[19,29,39,41,50-51,63,83,98,100] and five studies (seven percent) did not report the comparison between the two agents.[43,62,76-77,94] We did not detect any specific ACEI or ARB that performed better or worse than other medications in its class.

Blood pressure outcomes were confounded by protocols calling for dose escalation or adding additional blood pressure lowering drugs; such protocols differed substantially between studies, making the blood pressure outcomes difficult to interpret. Overall, there was no clear difference in the blood pressure lowering efficacy between the two classes of agents, no matter what criteria were used for study inclusion. Because of the heterogeneity in study protocols, quantitative meta-analysis was not performed. However, despite some differences in methods for measuring

successful control of blood pressure on a single agent, this outcome seemed to represent a reasonable comparison that was not confounded by substantial differences between studies. Therefore, quantitative meta-analysis was performed for this outcome.

Caveats and concerns include the fact that there was significant heterogeneity in the medication protocols and the use of concomitant hypertension therapy. Many of the studies reported limited data on patient characteristics, and black patients appeared to be significantly underrepresented overall. Very few of the studies were considered to be of good methodological quality. In addition, the majority of the studies reporting a funding source were sponsored by the manufacturer of the ARB.

Comparisons of Direct Renin Inhibitors Versus ACEIs or ARBs

We identified three studies (four publications) comparing the direct renin inhibitor aliskiren with either an ACEI or ARB.[95-97,99] All three studies were good-quality RCTs. Two compared the ACEI ramipril at a maximum dose of 10 mg to aliskiren at a maximum dose of 300 mg and used a similar protocol that allowed additional medications to be added if the blood pressure was above target at 12 weeks. In both studies, aliskiren produced a greater reduction in blood pressure compared to ramipril at 12 weeks, with between-group blood pressure (SBP/DBP) differences of -2.7/1.7 and -1.9/1.7 mmHg.[95-97] The third study compared aliskiren to the ARB losartan and reported no significant differences in blood pressure lowering or in use of single antihypertensive agent.[99]

Effect on Mortality and Major Cardiovascular Events

The literature review identified 26 publications[19-21,23,25,28,30-31,33,37,42,46-47,49,68,80,90,93,95-97,99-100,102-104] describing 21 separate studies that reported patient mortality, MI, or clinical stroke as outcomes. Eighteen studies (23 publications) were RCTs.[19-21,23,25,28,30-31,33,37,42,46-47,49,68,80,90,93,95-97,99-100] The 21 studies reported on 40,664 patients (38,504 of whom received an ACEI, an ARB, or a DRI) and ranged in duration from 12 weeks to 5 years; most reported blood pressure measurements as primary endpoints. The treatment comparisons evaluated were (one study per comparison, unless otherwise noted):

- "ACEIs" versus "ARBs" (2 studies);[102,104]
- Candesartan versus lisinopril;[25]
- Eprosartan versus enalapril (2 studies, 6 publications);[23,30,33,37,42,49]
- Irbesartan versus lisinopril;[28]
- Losartan versus enalapril (2 studies);[47,68]
- Losartan versus fosinopril;[80]
- Losartan versus ramipril;[90]
- Losartan versus quinapirl;[46]
- Telmisartan versus ramipril;[100]
- Telmisartan versus enalapril (2 studies);[31,93]
- Valsartan versus lisinopril (3 studies);[20-21,103]
- Valsartan versus enalapril;[19]

- Aliskiren versus ramipril (3 studies);[95-97] and
- Aliskiren versus losartan.[99]

The studies were of good (n = 8), fair (n = 10), and poor (n = 3) quality. Notably, the majority of studies in this review – including those reporting morality and major cardiovascular events – excluded patients with significant cardiovascular disease and often other comorbid conditions.

The studies evaluated shed little light on the issue of relative rates of mortality, MI, or stroke with ACEIs versus ARBs versus direct renin inhibitors. In 21 studies involving 40,644 patients, 34 patients died. The study by Barnett et al.[31] provided the most and the longest-term data on cardiovascular events. This study evaluated telmisartan versus enalapril in 250 patients with type 2 diabetes and early nephropathy over a 5-year treatment period. In this higher risk population, cardiovascular events occurred at a similar rate in both treatment groups: there were six strokes in each group; nine nonfatal MIs in the telmisartan group and six in the enalapril group; and nine patients with heart failure in the telmisartan group and six in the enalapril group. This study also reported 12 deaths, six in the telmisartan group (three due to stroke, MI, and heart failure), and six in the enalapril group (two due to MI).

Among shorter-term trials, the study by Ruilope et al.,[23] evaluating eprosartan versus enalapril over 12 weeks, reported one death in each group, a 95-year-old patient with cancer and an 80-year-old patient with heart failure. Shibaskaki et al.[68] evaluated losartan versus enalapril versus amlodipine over 6 months and reported one death due to pulmonary hemorrhage, and one patient with MI; the treatment group to which the patient belonged was not specified for either event. The paper by Elliott et al.[37] is the primary report of a trial of eprosartan versus enalapril over 26 weeks. A substudy from this trial published by Gavras et al.[42] reported that one patient assigned to the eprosartan group had an anteroseptal MI and died. Williams et al.[100] evaluated telmisartan versus ramipril over 14 weeks and reported that one patient in the ramipril group had a stroke. An RCT by Andersen et al.[95-96] comparing aliskiren to ramipril noted one death due to mesenteric thrombosis in the ramipril group. An RCT comparing valsartan, lisinopril, or their combination noted one death in the lisinopril group and one in the combination group.[21] Delea et al.[103] performed a retrospective cohort study using administrative data and found cardiovascular event rates to be similar between patients taking valsartan versus lisinopril after adjusting for possible confounding characteristics. Finally, Spinar et al.[90] described two studies in one publication: one a single-arm trial of losartan (n = 4016), and the other an RCT of losartan versus ramipril (n = 3813). The single-arm study reported a mortality rate of 0.1 percent over 1 year, with MI occurring in 0.2 percent of participants and stroke in 0.3 percent of participants. In the RCT, the rates of both mortality and MI were 0.2 percent, and the stroke rate was 0.4 to 0.5 percent in both treatment groups. In none of these trials did investigators attribute any of the events observed directly to therapy.

Effect on Quality of Life

Four studies described in eight separate papers reported data on quality of life.[30,33,35,37,42,45,49,51] All four were RCTs comparing ACEIs versus ARBs, and all were rated as fair in methodological quality. However, with regard to assessing quality of life, two of the four could be considered poor, as they did not present quantitative data.[45,51]

Sample sizes for the individual studies ranged from 42 to 528 patients, with a total of 1142 patients. Study durations ranged from 12 weeks to 3 years, with a mean of 55 weeks (median 26 weeks). Only one of the four studies reported the racial demographics of the study participants;[37] in that study, 14 percent of participants were members of ethnic minorities. Studies utilized a variety of quality-of-life scales: two administered the Psychological General Well Being with its six subscales;[37,51] two administered the Subjective Symptoms Assessment profile;[35,37] one study employed the MacMaster Overall Treatment Evaluation Questionnaire;[51] and one used the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).[45] Only two studies presented any quantitative data to support their conclusions of no difference in the impact of ACEIs or ARBs on quality of life.[35,37]

None of the studies found any difference between ACEIs and ARBs in their impact on the quality of life of study participants; indeed, no study demonstrated an impact on quality of life for subjects treated with ACEIs *or* ARBs. Finally, none of the studies comparing direct renin inhibitors with ACEIs or ARBs reported data on quality of life.

Effect on Rate of Use of a Single Antihypertensive Agent

We identified 25 studies that reported the outcome of successful monotherapy for ACEIs versus ARBs.[20-23,27,30,39,43-48,54,57,62,64-65,70-71,75,78,80,91,101,105] The definition of "successful" monotherapy differed between studies and included SBP or DBP below a specified cutoff, or monotherapy defined by a lack of additional antihypertensive medication at the end of the study. Five studies were determined to be of good quality, 17 were fair in quality, and four were poor. There were 23 RCTs, two retrospective cohorts, and one case-control study. Sample sizes ranged from 30 to 13,303 patients. Study durations ranged from 12 weeks to 3.3 years, with a median of 26 weeks. The rates of successful monotherapy ranged between 6 percent and 93.3 percent (median 54 percent).

We performed a meta-analysis of data from the 25 studies. Individual study estimates for the differences between ACEIs and ARBs in the proportion of patients achieving successful blood pressure control on a single agent showed no statistical heterogeneity ($Q = 33.5$; $f = 24$; $p = 0.09$). A summary estimate of the odds ratio for the proportion of patients with successful blood pressure control on a single agent with ARBs compared to ACEIs was 1.10 (95 percent CI 0.97 to 1.25; $p = 0.12$; random-effects model).

Table 6 gives a summary of the studies and their estimated odds ratios. The odds ratio represents the odds of successful blood pressure control for ARB patients divided by the odds of successful blood pressure control for ACEI patients.

Table 6. Estimated odds ratios for successful blood pressure control on monotherapy (ARBs vs. ACEIs)

Study	Odds ratio	Ln(OR)	Standard error	Study type
Saito et al., 2004[65]	1.5742	0.4537	0.2199	RCT
Cuspidi et al., 2002[101]	1.0048	0.0048	0.2597	RCT
Ruilope et al., 2001[23]	0.7382	-0.3036	0.4131	RCT
Larochelle et al., 1997[48]	1.4250	0.3542	0.6063	RCT
Lacourciere et al., 2000[47]	0.4375	-0.8267	0.4027	RCT
Ruff et al., 1996[22]	0.3351	-1.0933	0.8076	RCT
Townsend et al., 1995[70]	0.7873	-0.2391	0.2448	RCT
Verdecchia et al., 2000[91]	1.2750	0.2429	0.4940	OBS
Neutel et al., 1999[57]	0.8413	-0.1728	0.1769	RCT
Karlberg et al., 1999[45]	1.0316	0.0311	0.2494	RCT
Malacco et al., 2004[20]	1.0400	0.0392	0.1410	RCT
Fogari et al., 2004[39]	1.3846	0.3254	0.3301	RCT
Rosei et al., 2005[64]	0.8306	-0.1857	0.3622	RCT
Ghiadoni et al., 2003[78]	1.2778	0.2451	0.6329	RCT
Mazzaglia et al., 2005[105]	1.1083	0.1028	0.0711	OBS
Uchiyama-Tanaka et al., 2005[71]	1.1053	0.1001	0.7353	RCT
Argenziano et al., 1999[30]	1.0000	0.0000	0.1881	RCT
Robles et al., 2004[62]	0.7273	-0.3185	0.8006	RCT
Kavgaci et al., 2002[80]	0.7959	-0.2283	0.8342	RCT
Mogensen et al., 2000[54]	1.7609	0.5658	0.4233	RCT
Eguchi et al., 2003[75]	0.8750	-0.1335	0.5804	RCT
Hasford et al., 2002[43]	1.5088	0.4113	0.1328	OBS
Tedesco et al., 2006[27]	0.9240	-0.0791	0.3036	RCT
Hosohata et al., 2007[44]	1.9360	0.6606	0.1920	RCT
Menne et al., 2008[21]	0.9974	-0.0026	0.4838	RCT

Abbreviations: Ln(OR) = natural log of odds ratio; OBS = observational study; RCT = randomized controlled trial

We summarized all studies together and also analyzed RCTs and observational studies separately. Results for both fixed-effect and random-effects analyses are given in Table 7. The analyses include measures of homogeneity (Q-statistic).

Table 7. Meta-analyses of successful blood pressure control on monotherapy by subgroup for ARBs vs. ACEIs

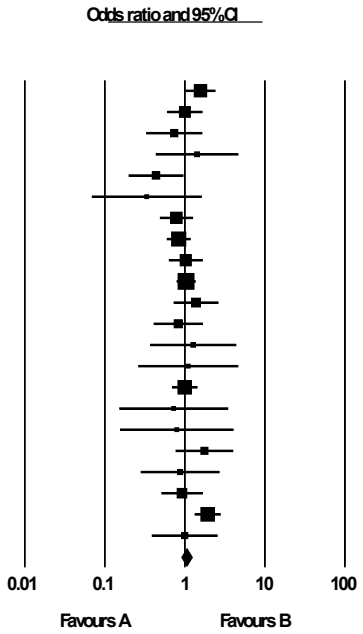
Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	25	1.1220	1.0303	1.2218	2.6458	0.0082	33.4937	24	0.0941
Random	All	25	1.1021	0.9736	1.2477	1.5368	0.1243			
Fixed	Observ	3	1.1885	1.0521	1.3425	2.7761	0.0055	4.2141	2	0.1216
Random	Observ	3	1.2585	0.9837	1.6099	1.8294	0.0673			
Fixed	RCTs	22	1.0618	0.9424	1.1963	0.9853	0.3245	27.6022	21	0.1518
Random	RCTs	22	1.0487	0.9030	1.2179	0.6231	0.5332			

Abbreviations: CI = confidence interval; df = degrees of freedom; Observ = observational studies; OR = odds ratio; RCTs = randomized controlled trials

Because the definition of successful control of blood pressure with a single agent requires that a patient remain on the originally prescribed drug and receive no additional antihypertensive agent, "successful monotherapy" reflects both the efficacy of the medication and tolerability and adherence to the prescribed therapy. When we examined our results separately for observational and experimental studies, the trend favoring ARBs for this outcome appeared to be driven primarily by differences in tolerability and adherence, since the benefit of ARBs appeared different in retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients.

The results for the random-effects analysis of RCTs alone are shown in Figure 3.

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Saito et al., 2004 (61)	1.574	1.023	2.422	2.063	0.039
Cuspidi et al., 2002 (35)	1.005	0.604	1.672	0.018	0.985
Ruilope et al., 2001 (60)	0.738	0.328	1.659	-0.735	0.462
Larochelle et al., 1997 (48)	1.425	0.434	4.676	0.584	0.559
Lacourciere et al., 2000 (47)	0.438	0.199	0.963	-2.053	0.040
Ruff et al., 1996 (70)	0.335	0.069	1.632	-1.354	0.176
Townsend et al., 1995 (67)	0.787	0.487	1.272	-0.977	0.329
Neutel et al., 1999 (56)	0.841	0.595	1.190	-0.977	0.329
Karlberg et al., 1999 (44)	1.032	0.633	1.682	0.125	0.901
Malacco et al., 2004 (50)	1.040	0.789	1.371	0.278	0.781
Fogari et al., 2004 (74)	1.385	0.725	2.644	0.986	0.324
Rosei et al., 2005 (59)	0.831	0.408	1.689	-0.513	0.608
Ghiadoni et al., 2003 (43)	1.278	0.370	4.418	0.387	0.699
Uchiyama-Tanaka et al., 2005 (68)	1.105	0.262	4.671	0.136	0.892
Argenziano et al., 1999 (28)	1.000	0.692	1.446	0.000	1.000
Robles et al., 2004 (83)	0.727	0.151	3.493	-0.398	0.691
Kavgaci et al., 2002 (45)	0.796	0.155	4.083	-0.274	0.784
Mogensen et al., 2000 (54)	1.761	0.768	4.036	1.337	0.181
Eguchi et al., 2003 (38)	0.875	0.281	2.729	-0.230	0.818
Tedesco et al., 2006	0.924	0.510	1.675	-0.260	0.795
Hosohata et al., 2007	1.936	1.329	2.820	3.441	0.001
Menne et al., 2008	0.997	0.386	2.574	-0.005	0.996
	1.049	0.903	1.218	0.623	0.533



Meta Analysis

Figure 3. Random-effects analysis of RCTs for successful blood pressure control on monotherapy (ARBs vs. ACEIs)

The results for this outcome are best summarized by the random-effects analysis of the RCTs shown in Figure 3. This analysis gave an estimated odds ratio of 1.049 (95 percent CI 0.903 to 1.218), suggesting that the odds of successful blood pressure control is only five percent larger with an ARB alone than with an ACEI alone, and this amount is not statistically significant.

These odds ratios need to be compared against the overall successful blood pressure control rate for monotherapy with ACEIs. If we pool all of the RCTs, we get a rate of about 54.7 percent.

The results for the random-effects analysis of the observational studies alone are shown in Figure 4.

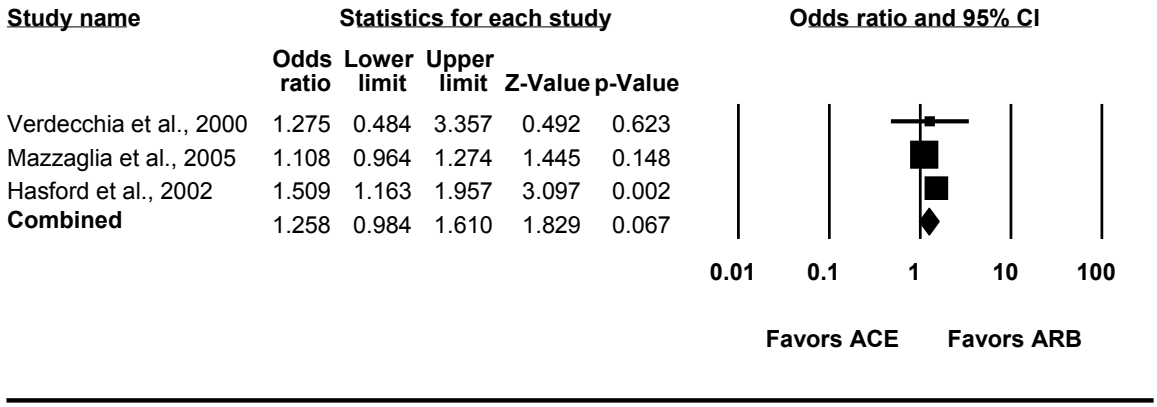


Figure 4. Random-effects analysis of observational studies for successful blood pressure control on monotherapy (ARBs vs. ACEIs)

This analysis gave an estimated odds ratio of 1.258 (95 percent CI 0.984 to 1.610), suggesting that the odds of successful blood pressure control is 26 percent larger with an ARB alone than with an ACEI alone, and this amount is marginally statistically significant (p = 0.0673).

These odds ratios need to be compared against the overall successful blood pressure control rate for monotherapy with ACEIs. If we pool all of the observational studies, we get a rate of about 24.9 percent.

We did not identify any studies comparing a direct renin inhibitor with an ACEI or an ARB for this outcome.

Effect on Serum Lipid Levels

Twenty studies described in 25 papers met our inclusion criteria and evaluated serum lipid changes. Seventeen of the 20 studies were RCTs,[17,19,25,27,37-38,40,47,56,64,67,69,71,78,80,93-94] one was a non-randomized three-arm parallel-group clinical trial,[88] and one was an observational case-control study.[91] One publication[90] reported results from two studies: an RCT and a single-arm clinical trial of an ARB with an ACEI as a preintervention comparison (participants were switched from an ACEI to losartan). The ACEI-versus-ARB treatment comparisons were unique in 14 studies; four studies compared losartan versus enalapril,[27,47,69,91] two compared telmisartan versus perindopril,[56,78] and two compared telmisartan versus enalapril.[31,93] Study periods ranged from 3 to 24 months, all of which were sufficiently long to detect measurable changes in the lipid profile.

Most of the 20 studies were fair in quality and none addressed the use of lipid-lowering agents during the study period. The four studies rated as good in quality[17,19,25,27] took place in Europe and were moderate to large in sample size (range 70 to 520); one study was of short duration (16 weeks);[19] two were of medium duration (12 months);[17,25] and one was long (24 months).[27] Two of the good-quality studies targeted patients with diabetes.[17,25]

The majority of the available head-to-head evidence suggests that ACEIs and ARBs have a similar lack of impact on lipid parameters. Twelve studies found no within-group change during treatment in total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and/or triglyceride (TG) levels during the study period. Four studies found statistically significant within-group treatment effects but did not report between-group comparisons (Table 8): TC and TG decreased with fosinopril, while TG decreased with losartan in one study;[80] TC decreased with losartan in another study;[27] TC decreased with losartan and enalapril, LDL decreased with losartan, and TG decreased with enalapril in a third study;[47] and TC, TG, and LDL decreased, while HDL increased, with both ramipril and valsartan in the fourth study.[94]

Twelve studies directly compared outcomes between ACEI and ARB groups.[17,19,38,40,56,64,67,69,88,90-91,93] Of these 12, only two found different effects between the medications compared (Table 8). One study reported a decrease in LDL that was statistically greater in the ACEI group (perindopril -14 percent versus candesartan -4 percent).[17] Another study found a statistically greater decrease in triglyceride (telmisartan -28 percent versus enalapril -6 percent, $p < 0.01$) and greater increase in HDL (telmisartan +18 percent versus enalapril -3 percent, $p < 0.05$) for telmisartan compared with enalapril.[93] Thus, for the two studies in which a difference between groups was found, the difference was discrepant (i.e., results favored ACEI in one study and favored ARB in the other). Of these two studies, only one was rated as good in quality.[17]

Table 8. Studies reporting significant changes in lipid profiles with ACEIs and/or ARBs

Study	N	Population	Quality	Comparators	ΔTC	ΔLDL	ΔHDL	ΔTG
Lacourciere et al., 2000[47]	103	- Mean age 58 - 96% white - Canada - Diabetes	Fair	Losartan vs. enalapril	-2.1%* vs. -4.2%*	-6.5%* vs. NR	NR	NR vs. -11.3%*
Derosa et al., 2003[17]	96	- Mean age 54 - 100% white - Europe - Diabetes	Good	Candesartan vs. perindopril	NR	-4% vs. -14%†	+2% vs. -2%	+2% vs. -22%
Kavgaci et al., 2002[80]	33	- Mean age 53 - 100% white - Turkey - Diabetes	Poor	Losartan vs. fosinopril	+0.01% vs. -0.1%*	NR	NR	-0.23%* vs. -0.21%*
Tedesco et al., 2006[27]	520	- Mean age 54 - 100% white - Italy - No diabetes	Good	Losartan vs. enalapril	-10 mg/dL* vs. +1 mg/dL	NR	NR	NR
Yilmaz et al., 2007[94]	96	- Mean age 48 - Turkey - Metabolic	Poor	Ramipril vs. valsartan	14.3 to 12.0 mmol/L* vs. 14.9 to 12.6	7.3 to 5.5 mmol/L* vs. 7.7 to 6.1	2.0 to 2.4 mmol/L* vs. 1.9 to 2.3	8.8 to 7.6 mmol/L* vs. 11.0 to 8.9

Study	N	Population	Quality	Comparators	ΔTC	ΔLDL	ΔHDL	ΔTG
		syndrome			mmol/L*	mmol/L*	mmol/L*	mmol/L*
Xu et al., 2007[93]	96	- Mean age 51 - China - Abnormal serum lipids	Poor	Telmisartan vs. enalapril	6.1 to 5.8 mmol/L vs. 6.1 to 5.9 mmol/L	3.1 to 2.3 mmol/L vs. 3.1 to 3.0 mmol/L	1.5 to 1.7 mmol/L† vs. 1.4 to 1.4 mmol/L	2.8 to 2.0 mmol/L† vs. 2.8 to 2.6 mmol/L

*Statistically significant within-treatment change (baseline to followup).
† Statistically significant comparison between treatments.

Abbreviations: HDL = low-density lipoprotein; LDL = low-density lipoprotein; N = number of subjects; NR=not reported; TC = total cholesterol; TG = triglyceride

Effect on Markers of Carbohydrate Metabolism/Diabetes Control

Twenty-two studies described in 27 papers met our inclusion criteria and measured glucose or HbA1c. All but four[73,88,91,102] were RCTs. Overall, only three studies were rated as good in quality;[17,19,25] the remainder were rated as either fair (11 studies[37-38,40,47,54,56,66-67,69,71,102]) or poor (eight studies[73,78,80,88,90-91,93-94]). The ACEI-versus-ARB comparisons tested were unique in 13 studies; of the remaining nine studies, enalapril and losartan were compared in five,[47,69,73,88,91] candesartan and lisinopril in two,[25,54] and perindopril and telmisartan in two.[56,78]

It is relevant that none of the 22 studies measuring glucose or HbA1c changes addressed hypoglycemic therapy during the study period, and only seven were specifically performed in diabetic populations.[17,25,38,47,54,67,80] Of the other 15 studies, four permitted controlled diabetic patients but did not describe their proportion in the cohort;[37,66,69,91] five permitted diabetic subjects;[56,71,88,90,102] and six specifically excluded individuals with diabetes.[19,40,73,78,93-94]

The majority of the available head-to-head evidence suggests that ACEIs and ARBs have a similar lack of impact on glucose levels or HbA1c. Eleven studies directly compared outcomes between the ACEI and ARB groups.[17,19,38,40,56,66,69,73,91,93,102] One study reported a small decrease in glucose that was statistically greater in the ACEI group (perindopril -15 ± 4 mg/dL, candesartan -8 ± 2 mg/dL),[17] and one reported a significant increase in HbA1c (+ 0.25 percent enalapril versus + 0.6 percent losartan) but did not directly compare the two groups.[47] One study reported significantly lower 2-hour blood glucose levels at 6 months in the telmisartan group (5.48 mmol/L ± 1.46) compared to the enalapril group (6.70 mmol/L ± 1.41, $p < 0.05$).[93] Of these three studies, only one[17] was rated as good in quality. The other eight studies that analyzed differences in outcomes between the two groups did not find a difference. Fifteen studies compared baseline to followup glucose levels or HbA1c and found no change for either the ACEI or ARB groups.

Effect on Measures of LV Mass or Function

Thirteen studies presented results on left ventricular (LV) mass or function assessed either by LV mass index (LVMI; 7 studies),[24,26-27,35,73,91,99] LV ejection fraction (LVEF; 2 studies),[74,85] both (3 studies),[68,84,101] or LV posterior wall thickness.[79] Table 9 summarizes relevant characteristics of

all 13 studies. Six of these studies had fewer than 50 patients,[26,35,68,73,79,85] two had between 50 and 100 patients,[24,91] and five had 100 or more patients.[27,74,84,99,101] All but two studies[73,91] were RCTs. Only two studies had relatively long-term followup (≥ 3 years);[35,91] however, the majority of studies had between 6 and 12 months of followup,[24,26,68,73-74,79,84,99,101] while one study had only 3 months of followup.[85] Because duration of therapy may significantly impact the ability to observe changes in LV mass or function, negative results must be interpreted with caution in studies with short-term followup.

Table 9. Characteristics of studies reporting LV mass/function outcomes

Study	Agents studied	Population	Design and size*	Duration	Quality	Outcome	Result
Cuspidi et al., 2002[101]	Candesartan vs. enalapril	LVH (29-32%)	RCT N = 196 (145)	48 wk	Fair	LVMI & LVEF	↓LVMI both, no difference between agents, no change in LVEF
Spoelstra-de Man et al., 2006[26]	Candesartan vs. lisinopril	DM and HTN (? %LVH)	RCT N = 46	12 mo	Good	LVMI	↓LVMI both, but ARB not compared to ACEI
Schieffer et al., 2004[85]	Irbesartan vs. enalapril	CAD (? %LVH)	RCT N = 60 (48)	3 mo	Poor	LVEF	No difference No detailed data by treatment group
Guntekin et al., 2008[79]	Irbesartan vs. quinapril	New HTN (? %LVH)	RCT N = 65 (38)	12 mo	Poor	LV posterior wall thickness	↓LV posterior wall thickness both, no difference reported between agents
Avanza et al., 2000[73]	Losartan vs. enalapril	LVH (100%)	Non-rand controlled clinical trial N = 30	10 mo	Poor	LVMI	↓LVMI both, no difference between agents, combo ACEI/ARB best
De Rosa et al., 2002[35]	Losartan vs. enalapril	LVH (44-53%)	RCT N = 50 (42)	3 yr	Fair	LVMI	Non-statistical ↓LVMI both, no difference between agents
Shibasaki et al., 2002[68]	Losartan vs. enalapril	ESRD with LVH (100%)	RCT N = 20	6 mo	Fair	LVMI & LVEF	↓LVMI both, ARB better than ACEI, no change in LVEF
Tedesco et al., 2006[27]	Losartan vs. enalapril	HTN (30-33% LVH)	RCT N = 259 (185)	2 yr	Good	LVMI	↓LVMI both, ARB more than ACEI, but ARB higher baseline
Verdecchia et al., 2000[91]	Losartan vs. enalapril	LVH (23-24%)	Case-control N = 88	3.3 yr	Poor	LVMI	↓LVMI both, no difference between agents
Rajzer et al., 2003[84]	Losartan vs. quinapril	HTN (? %LVH)	RCT N = 118	6 mo	Poor	LVMI & LVEF	No change in LVMI or LVEF in either group No detailed data by treatment group

Study	Agents studied	Population	Design and size*	Duration	Quality	Outcome	Result
Scaglione et al., 2007[24]	Losartan vs. ramipril	HTN (53% LVH)	RCT N = 57	24 wks	Good	LVMI	↓LVMI both, no difference between agents
Celik et al., 2005[74]	Telmisartan vs. ramipril	HTN (? %LVH)	RCT N = 100	6 mo	Poor	LVEF	No change in LVEF in either group
Solomon et al., 2009[99]	Aliskiren vs. losartan	HTN (100% LVH)	RCT N = 465 (400)	34 wks	Good	LVMI	↓LVMI both, no difference between groups (aliskiren, ARB, combination)

* Size of study includes total enrolled in ACEI, ARB, direct renin inhibitor, or combination arms, with relevant followup population (if different) in parentheses.

Abbreviations: CAD = coronary artery disease; ESRD = end-stage renal disease; HTN = hypertension; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; mo = months; RCT = randomized controlled trial; wk = weeks; yr = years

Evidence provided by the 13 studies identified did not demonstrate a difference between ACEIs and ARBs with regard to LV mass or function for individuals with essential hypertension. Ten studies reported detailed data by treatment groups,[24,26-27,35,68,73-74,91,99,101] while one reported summary data,[84] and two described changes without presenting any data.[79,85] In general, the quality ratings of these studies describing changes in LV mass or function was poor,[73-74,79,84-85,91] although some of the more recent ones were rated as being good-quality studies.[24,26-27,99] Various ARBs and ACEIs were studied, including seven studies with losartan[24,27,35,68,73,84,91] and seven studies with enalapril.[27,35,68,73,85,91,101] Only one study evaluated the newer direct renin inhibitor, aliskiren.[99] Among the nine studies that presented detailed data on outcomes, six assessed LVMI,[24,27,35,73,91,99] one assessed LVEF,[74] and two assessed both LVMI and LVEF.[68,101]

The best and largest (n = 259) comparative study (an RCT) assessed LVMI at baseline and after 24 months of followup.[27] The authors reported similar decreases in mean LVMI in both groups in per-protocol analyses (12.3 percent on losartan versus 7.5 percent on enalapril). The trial with the longest followup (3 years; RCT) also reported similar reductions in mean LVMI in both groups; however, these changes did not reach statistical significance.[35] Two non-randomized studies reported similar decreases in LVMI,[73,91] with one[73] demonstrating additional benefit in LVMI reduction with combination ACEI and ARB therapy. Only one study demonstrated a difference between groups for reduction in LVMI,[68] with lower reduction among those treated with losartan versus enalapril (24.7 ± 3.2 percent versus 11.2 ± 4.1 percent; $p = 0.026$). However, definitive conclusions from this study are limited because it was conducted in patients with end-stage renal disease, included only 10 patients per treatment group, and had only moderate duration of followup (6 months). Finally, among the studies that reported results for LVEF, none demonstrated any differential effects between the ACEI and ARB groups.

Despite differences in sample size, study design, length of followup, study quality, therapeutic agents, and outcome measure, most of the studies demonstrated either similar improvements in LV mass or function between the ACEI and ARB groups[24,26-27,68,73,79,91,101] or no change.[35,84] Similar improvements in LV mass were also observed in the direct renin inhibitor study.[99] Reductions in LVMI appear to have occurred particularly among patients with established LV

hypertrophy.[35,68,73,101] No changes in LVEF were observed in any of the studies. In sum, this body of poor- to fair-quality evidence does not demonstrate any differential effects in the ability of ACEIs, ARBs, and direct renin inhibitors to improve or stabilize LVMI in patients with essential hypertension.

Effect on Serum Creatinine/GFR and Proteinuria

Overview

Review of the literature on the relative effects of ACEIs, ARBs, and direct renin inhibitors on changes in intermediate renal outcomes identified 30 studies described in 37 publications. One of these studies was conducted in patients with end-stage renal disease who had been on maintenance hemodialysis for at least 1 month.[68] This study is not considered further here, as no changes would be expected in the outcome assessed (serum creatinine) in the population studied. Of the remaining 29 studies, 12 assessed either serum creatinine or GFR;[19,35,37-38,53,63,71,73,86,90-91,97] six assessed proteinuria;[17,21,25,54,95,106] and 11 assessed both.[31,36,47,56,64,67,69,72,80,82,102] Most studies included fewer than 100 patients; however, 10 had approximately 200 patients or more.[31,37,53-54,63,67,69,90,96-97] All but four[73,91,102,106] were RCTs. One study[31] followed patients for 5 years, and approximately half of the studies had at least 1 year of followup; however, four studies followed patients for less than 4 months.[38,53,69,86]

Results for Creatinine-related Outcomes

The 24 studies that described changes in creatinine or GFR did not consistently demonstrate differential effects related to renal function with use of ACEIs versus ARBs. Sixteen of these studies reported detailed data by treatment groups,[19,31,35-36,38,53,56,67,71-73,80,86,91,97,102] while three reported summary data,[47,69,90] and five described the changes without presenting any quantitative data.[37,63-64,82,96] Among the 16 studies that reported data on renal function, two were rated as being good-quality studies;[19,97] four were of poor quality;[73,80,86,91] three were nonrandomized studies;[73,91,102] and five had more than 100 patients.[19,31,53,67,97] All but six[31,53,56,67,72,102] compared losartan with a specific ACEI; the ACEI most frequently studied was enalapril.[19,31,35,73,86,91] Studies comparing direct renin inhibitors with either ACEIs or ARBs also did not demonstrate differential effects related to renal function, but they were generally larger and of higher quality.[96-97]

The best comparative study assessed GFR by renal scintigraphy at baseline and after 3 years of followup.[35] The authors reported increases in mean GFR in both groups, but there was no statistically significant difference between groups. One of the larger studies in this group (n = 190) reported a greater short-term increase (12-week study) in mean serum creatinine in the enalapril group (change 0.03 mg/dL [95 percent CI 0 to 0.06]) compared with the irbesartan group (change 0.01 mg/dL [95 percent CI -0.02 to 0.04]).[53]

Among seven fair- to good-quality studies that reported on changes in renal function, all reported small differences during treatment without differences by class of angiotensin antagonist.[19,36,56,67,72,97,102] Of two poor-quality studies that reported on changes in creatinine clearance, one reported no change.[86] Although the other study reported significant and similar

decreases in creatinine clearance in both groups,[80] these changes did not correspond to the changes in serum creatinine reported, which calls into question the reliability of the data. Of the two studies that reported summary data, one found a nine percent mean decline in GFR assessed by radio-labeled excretion in each group ($p < 0.001$ at 52 weeks),[47] while the other found no change in mean percent change in serum creatinine.[69] Of the five studies that did not present detailed data, two reported that there were no overall differences between groups;[64,82] another that the degree and direction of insignificant change in renal function were comparable in both treatment groups;[37] and the last two described that a few patients developed an increase in serum creatinine: 2 out of 192 patients treated with losartan developed an increase in serum creatinine during the 12-week study,[63] while 3 out of 422 patients treated with ramipril developed an increase in serum creatinine during the 26-week study.[95]

Meta-analyses of Studies Reporting Creatinine-related Outcomes

Several studies reported pre- and posttreatment creatinine-related values. These included serum creatinine, creatinine clearance, and glomerular filtration rate (GFR). Using the pre- to posttreatment difference as an endpoint requires the standard deviation of the difference or the intra-class correlation. In most cases, neither was available. For this reason we chose to look at the posttreatment values without reference to the pretreatment values. We used the standardized difference in means (ARB mean minus ACEI mean) as our effect measure.

Table 10 gives a summary of the studies reporting serum creatinine and their estimated standardized mean differences.

Table 10. Estimated standardized mean differences for studies reporting serum creatinine (ARB minus ACEI)

Study	Mean difference	Standard error	Variance	Study type
Avanza et al., 2000[73]	0.000	0.365	0.133	OBS
Verdecchia et al., 2000[91]	0.133	0.246	0.061	OBS
Uchiyama-Tanaka et al., 2005[71]	0.000	0.309	0.096	RCT
Fogari et al., 2002[38]	0.000	0.217	0.047	RCT
Hermida et al., 2008[19]	0.143	0.165	0.027	RCT
Nakamura et al., 2009[56]	0.190	0.275	0.076	RCT
Zhu et al., 2008[72]	0.138	0.259	0.067	RCT

Abbreviations: OBS = observational study; RCT = randomized controlled trial

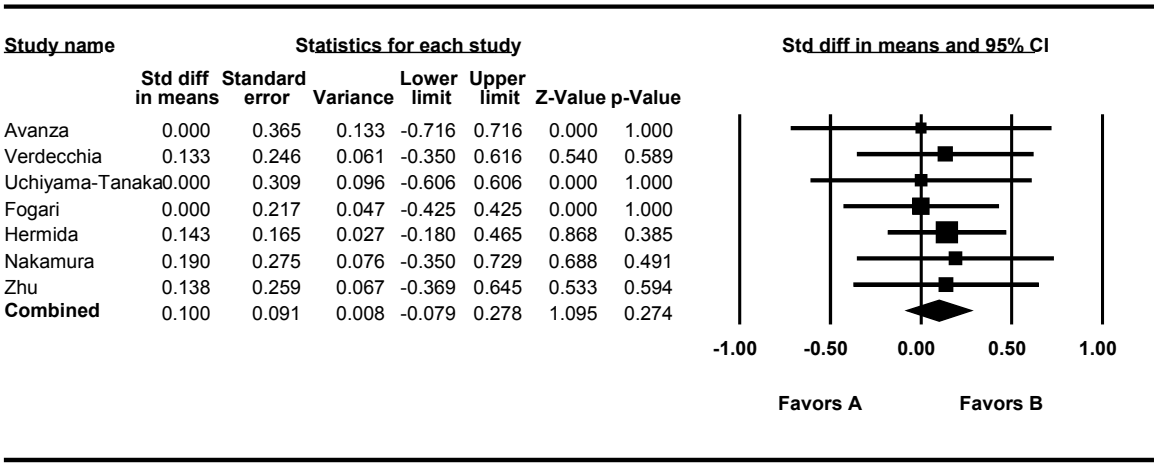
We summarized all studies together, as well as analyzing certain subgroups. We compared RCTs to observational studies. The results are summarized in Table 11. The analyses include measures of homogeneity (Q-statistic).

Table 11. Meta-analyses of serum creatinine by subgroup for ARB minus ACEI

Model	Analysis subgroup	No. of studies	Mean difference	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	7	0.100	-0.079	0.278	1.0945	0.2737	0.605	6	0.9963
Random	All	7	0.100	-0.079	0.278	1.0945	0.2737			
Fixed	Observ	3	0.2839	0.2210	0.3649	-9.8409	0.0000	0.1373	2	0.9337
Random	Observ	3	0.2839	0.2210	0.3649	-9.8409	0.0000			
Fixed	RCT	5	0.102	-0.098	0.301	0.9997	0.3174	0.512	4	0.9723
Random	RCT	5	0.102	-0.098	0.301	0.9997	0.3174			

Abbreviations: CI = confidence interval; df = degrees of freedom; Observ = observational study; RCT = randomized controlled trial

The results for the random-effects analysis of all studies are shown in Figure 5.



Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Avanza	0.000	0.365	0.133	-0.716	0.716	0.000	1.000
Verdecchia	0.133	0.246	0.061	-0.350	0.616	0.540	0.589
Uchiyama-Tanaka	0.000	0.309	0.096	-0.606	0.606	0.000	1.000
Fogari	0.000	0.217	0.047	-0.425	0.425	0.000	1.000
Hermida	0.143	0.165	0.027	-0.180	0.465	0.868	0.385
Nakamura	0.190	0.275	0.076	-0.350	0.729	0.688	0.491
Zhu	0.138	0.259	0.067	-0.369	0.645	0.533	0.594
Combined	0.100	0.091	0.008	-0.079	0.278	1.095	0.274

Figure 5. Random-effects analysis of all studies reporting serum creatinine (ARB mean minus ACEI mean)

The analysis of all studies gave an estimated standardized mean difference of 0.100 (95 percent CI -0.079 to 0.278), suggesting that mean post creatinine levels are slightly higher for the ARB studies, but the difference is clearly not statistically significant.

Table 12 gives a summary of the studies reporting creatinine clearance and their estimated standardized mean differences.

Table 12. Estimated standardized mean differences for studies reporting creatinine clearance (ARB minus ACEI)

Study	Mean difference	Standard error	Variance	Study type
Shand et al., 2000[86]	-0.770	0.385	0.148	RCT
Kavgaci et al., 2002[80]	-0.241	0.389	0.151	RCT
Deyneli et al., 2006[36]	-0.100	0.409	0.167	RCT
Sengul et al., 2006[67]	-0.085	0.204	0.042	RCT

We summarized all studies. The results are summarized in Table 13. The analyses include measures of homogeneity (Q-statistic)

Table 13. Meta-analyses of creatinine clearance for ARB minus ACEI

Model	Analysis subgroup	No. of studies	Mean difference	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	4	-0.217	-0.515	0.080	-1.4315	0.1523	2.567	3	0.4633
Random	All	4	-0.217	-0.515	0.080	-1.4315	0.1523			

Abbreviations: CI = confidence interval; df = degrees of freedom

The results for the random-effects analysis of all studies are shown in Figure 6.

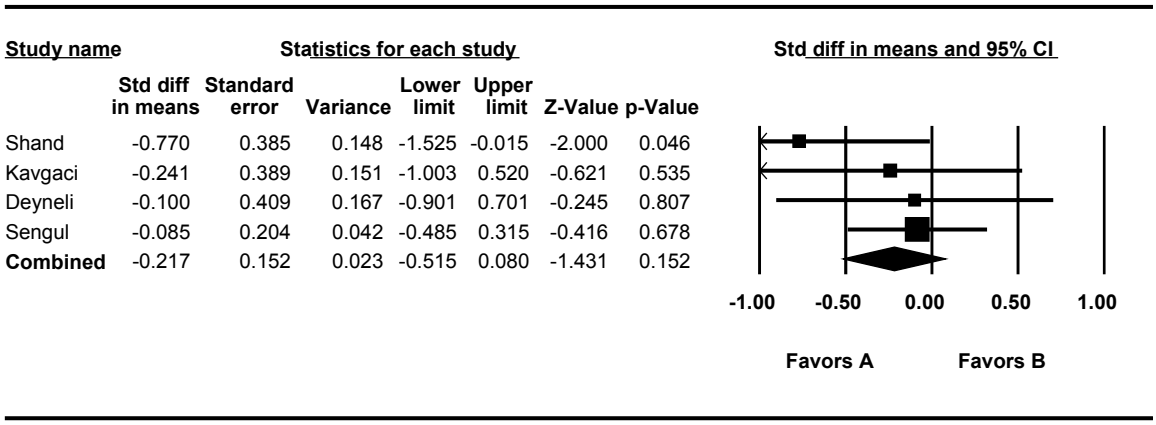


Figure 6. Random-effects analysis of all studies reporting creatinine clearance (ARB mean minus ACEI mean)

The analysis of all studies gave an estimated standardized mean difference of -0.217 (95 percent CI -0.515 to 0.080), suggesting that mean post creatinine clearance levels are slightly lower for the ARB studies, but the difference is not statistically significant (p = 0.1523).

Table 14 gives a summary of the studies reporting glomerular filtration rate (GFR) and their estimated standardized mean differences.

Table 14. Estimated standardized mean differences for studies reporting GFR (ARB minus ACEI)

Study	Mean difference	Standard error	Variance	Study type
Derosa et al., 2003[17]	-0.336	0.285	0.081	RCT
Barnett et al., 2004[31]	-0.248	0.137	0.019	RCT
Cotter, et al., 2008[102]	-0.608	0.245	0.060	OBS
Duprez, et al., 2009[97]	0.000	0.067	0.004	RCT

Abbreviations: OBS = observational study; RCT = randomized controlled trial

We summarized all studies. The results are summarized in Table 15. The analyses include measures of homogeneity (Q-statistic).

Table 15. Meta-analyses of GFR for ARB minus ACEI

Model	Analysis subgroup	No. of studies	Mean difference	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	4	-0.089	-0.201	0.022	-1.5691	0.1166	8.377	3	0.0388
Random	All	4	-0.227	-0.486	0.032	-1.7154	0.0863			

Abbreviations: CI = confidence interval; df = degrees of freedom

The results for the random-effects analysis of all studies are shown in Figure 7.

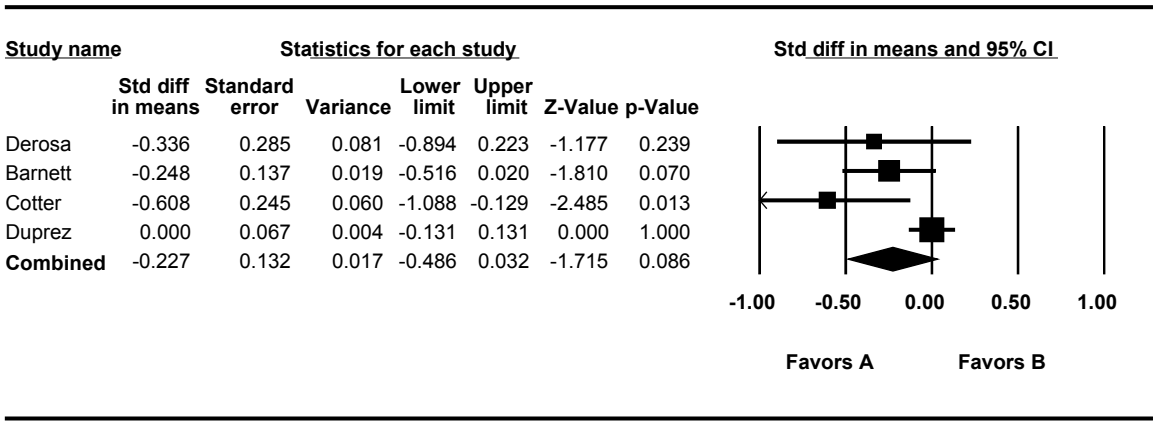


Figure 7. Random-effects analysis of all studies reporting GFR (ARB mean minus ACEI mean)

The analysis of all studies gave an estimated standardized mean difference of -0.227 (95 percent CI -0.486 to 0.032), suggesting that mean posttreatment GFRs are slightly lower for the ARB studies, and the difference is marginally statistically significant (p = 0.0863).

Table 16 summarizes results for both flow rates from all studies. The analyses include measures of homogeneity (Q-statistic).

Table 16. Meta-analyses of all flow rate studies for ARB minus ACEI

Model	Analysis subgroup	No. of studies	Mean difference	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	8	-0.105	-0.210	-0.001	-1.9720	0.0486	11.566	7	0.1158
Random	All	8	-0.212	-0.396	-0.028	-2.2617	0.0237			

Abbreviations: CI = confidence interval; df = degrees of freedom; GFR = glomerular filtration rate

The analysis of all flow studies gave an estimated standardized mean difference of -0.227 (95 percent CI -0.396 to -0.028), suggesting that mean flow rates are slightly lower for the ARB studies, and the difference is statistically significant (p = 0.0237).

Results for Proteinuria

The 17 studies that described changes in urine albumin or protein excretion consistently demonstrated no differential effects related to reduction of urinary protein or albumin excretion among patients with essential hypertension with use of ACEIs versus ARBs. Overall fair in quality, 15 of 17 studies reported detailed data by treatment groups, while two reported summary data in graphical format.[25,102] Among the 15 studies that reported data, two were rated as being good-quality studies,[17,21] three were of poor quality;[80,82,106] one was a nonrandomized cohort study;[106] and only four had more than 100 patients.[21,31,54,69] Various ARBs were used, including two studies with telmisartan,[31,67] four studies with candesartan,[17,54,64,106] four with losartan,[36,47,69,80] one with both candesartan and losartan,[82] and two with valsartan.[21,72] All studies assessed urinary albumin excretion except for one study that assessed urinary protein excretion.[82] Studies also varied in length of followup, with only one long-term study (5 years);[31] the remainder ranged from 12 weeks to 1 year. However, despite these differences in study quality, sample size, therapeutic agents, outcome measure and length of followup, all of the studies demonstrated declines in urinary protein/albumin excretion that were similar between the ACEI and ARB groups. In the only study that described changes among patients with essential hypertension treated with aliskiren, a greater reduction in urinary albumin to creatinine ratio was observed overall, but there were no differences among those with baseline microalbuminuria or proteinuria.[96]

Discussion

The lack of an apparent differential impact of ACEIs versus ARBs on intermediate renal parameters must be considered in light of concerns about the available literature. Some concerns may reinforce the conclusion. For example, the study by Matsuda et al.[82] provided sufficient data only on the subgroup of patients with moderate proteinuria and thus would likely favor ACEIs, yet there were no significant differential effects between the ACEI and ARB groups within the entire study sample after 48 weeks (p > 0.5). Numerous other studies also failed to demonstrate a differential effect. On the other hand, because duration of therapy may significantly impact the ability to observe meaningful changes in renal function or proteinuria, negative results must be interpreted with caution in studies with short-term followup.

Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?

Key Points

- Cough was more frequently observed as an adverse event in groups treated with ACEIs than in groups treated with ARBs or direct renin inhibitors. .
- Withdrawals due to adverse events were modestly more frequent for groups receiving an ACEI rather than an ARB or direct renin inhibitor; this is consistent with differential rates of cough.
- No significant between-class differences were observed in the rates of any other commonly reported adverse events.
- Angioedema was not reported in the majority of studies, making it impossible to accurately characterize its frequency and timing in this population. In the studies that did report episodes of angioedema, this adverse event was observed only in patients treated with an ACEI or a direct renin inhibitor.
- Treatment adherence – in terms of pill counts in RCTs – is similarly high with both ACEIs and ARBs. However, persistence with drug therapy is generally lower with ACEIs, which may be explained largely by withdrawals due to cough (as above). None of the included direct renin inhibitor studies reported adherence or persistence.

Safety and Adverse Events

Rates of Serious and Overall Adverse Events

Thirteen reports describing 12 studies met our inclusion criteria and reported overall rates of serious adverse events.[19-21,45,53,63-64,90,95-96,98-100] Five of these studies were rated as good in methodological quality, six were rated as fair, and one was poor. However, the nature of serious adverse event reporting was inconsistent, and rates of serious adverse events were low (on the order of 0 to 6 percent, depending on definition); thus, data on these events were not deemed useful for assessing a differential effect of ACEIs versus ARBs.

A potentially salient and serious adverse event, angioedema, was reported in only four studies (Table 17).[45,52,57,95] One of the reported cases occurred in a patient treated with a direct renin inhibitor; the other cases were in patients treated with an ACEI. We did not pool these studies because in studies that did not report angioedema, it was not clearly valid to infer that there were no events simply because the studies did not report explicitly that an episode of angioedema did not occur. Thus we are unable to estimate the frequency of angioedema in this population.

Table 17. Studies reporting angioedema

Study	Study design (blinding)	Interventions (numbers of patients)	Duration	Quality	Results
Andersen et al., 2008[95]	RCT (double-blinded)	Ramipril (n = 422) Aliskiren (n = 420)	26 weeks	Good	No cases of angioneurotic edema with ramipril 1 case angioneurotic edema in one patient receiving aliskiren
Karlberg et al., 1999[45]	RCT (double-blinded)	Telmisartan (n = 139) Enalapril (n = 139)	26 weeks	Fair	No cases of angioedema with telmisartan 1 case ("severe disabling Quincke's angioneurotic edema") with enalapril
McInnes et al., 2000[52]	RCT (double-blinded)	Candesartan (n = 237) Lisinopril (n = 116)	26 weeks	Fair	No cases of angioedema with candesartan 2 cases with lisinopril
Neutel et al., 1999[57]	RCT (double-blinded)	Telmisartan (n = 385) Lisinopril (n = 193)	48 weeks	Fair	No cases of angioedema with telmisartan 2 cases with lisinopril

Of the 46 reports and 45 studies that met inclusion criteria and reported overall adverse event rates,[17-24,27,29,31-32,34,36-37,39,41,45-46,48,50-53,56-57,63-64,67,69-70,72,75,77,81,83,86,90,93,95-101] only 14 were assessed as being good in quality. There was significant variation across studies in the manner in which adverse events data were collected and reported. Several studies reported only "severe" or "major" adverse events, and no consistent method was used across studies to classify the severity of events. For these reasons, data on overall rates of adverse events were not considered further.

Specific Adverse Events

Forty-seven papers describing of 46 studies reported rates of one or more specific adverse events,[17-24,27,29,32,34-37,39,41,45-48,50-53,55-57,63,67,69-70,72,81,83,90,93,95-101,106-108] including cough (43 studies), dizziness (29 studies), headache (28 studies), fatigue or asthenia (14 studies), upper respiratory infection (11 studies), and nausea (10 studies). Back pain, diarrhea, hypotension, and dyspepsia were each reported as an adverse event in four studies. Viral infection, sinusitis, peripheral edema, and nasophyrangitis were reported as adverse events by three studies each. Palpitations, myalgia, malaise, urinary tract infection, vertigo, and musculoskeletal pain, were reported by two studies each. Accident/injury, pharyngitis, rhinitis, dyspnea, abdominal pain, abnormal taste, constipation, dry mouth, feeling sick, pyrosis, insomnia, fever, impotence, flatulence, epigastric discomfort, increased sweating, erythematous rash, flushing, cold hands/feet, atrial flutter, hypertensive crisis, death, cor pulmonale, adverse events related to the nervous system, adverse events related to the cardiovascular system, and adverse events related to the gastrointestinal system were reported as a specific adverse events by one study each.

Given the large number of commonly reported specific adverse events, we focused on three specific events with the largest difference in absolute rates across studies: dizziness, headache,

and cough. Rates of dizziness in studies reporting this event (n = 29) ranged from 1 to 20 percent in ARB-treated groups (mean 4.1 percent), from 0 to 18 percent in ACEI-treated groups (mean 5.0 percent), and from 3 to 8 percent in the three studies involving direct renin inhibitors (mean 6.0 percent). For headache (n = 28 studies), rates ranged from 1 to 22 percent in ARB-treated groups (mean 6.1 percent), from 0 to 34 percent in ACEI-treated groups (mean 7.8 percent) and 9 to 11 percent in direct renin inhibitor-treated groups (mean 10.0 percent). These results suggest that there is no differential impact of ACEIs and ARBs or direct renin inhibitors with regard to dizziness or headache.

The one adverse event for which significant differential effects were apparent is cough. Forty-three studies reported cough as an adverse event; of these, 38 studies compared cough in subjects treated with ACEIs or ARBs, and two compared cough rates in subjects treated with an ACEI or a direct renin inhibitor.[95,97] The single eligible study that compared adverse events between an ARB and a renin inhibitor[99] did not report cough as an adverse event in either treatment arm. In terms of quality, seven of the 38 studies were rated as good, 24 as fair, and seven as poor. Thirty-five of the studies were RCTs, two were prospective cohort studies, and one was a cross-sectional cohort study. Sample sizes for the studies ranged from 24 to 51,410 patients, with a total of 67,693 patients. Study durations ranged from 12 weeks to 3 years. The mean patient age of study participants was 58 years. The proportion of female patients included ranged from 24 to 100 percent (mean 48 percent). Twenty-four studies (63 percent) reported the racial demographics of the study participants. Of these 24 studies, 11 (46 percent) enrolled a minimum of 10 percent of ethnic minority participants.

Rates of cough in these studies ranged from 0 to 13 percent for ARB-treated groups (mean 3.0 percent), and from 0 to 23 percent in ACEI-treated groups (mean 8.8 percent). Cough rates associated with direct renin inhibitors were 4.1 and 4.2 percent in the two studies that compared an ACEI with a direct renin inhibitor.[95,97] All 38 studies that compared cough rates between ACEI and ARB treatments demonstrated higher rates of cough in ACEI-treated participants, but statistical significance was not always reported, and the magnitude of the differences in rates were sometimes small.

For the meta-analysis of studies reporting cough as an adverse event, we included all studies that reported on cough rates. Table 18 gives a summary of the studies and their estimated odds ratios. The odds ratio represents the odds of having a cough for the ARB patients divided by the odds of having a cough for the ACEI patients.

Table 18. Estimated odds ratios for cough (ARBs vs. ACEIs)

Study	Odds ratio	Ln(OR)	Standard error	Study type
Sato et al., 2003[106]	0.162	-1.819	1.576	OBS
Cuspidi et al., 2002[101]	0.275	-1.290	0.665	RCT
Malmqvist et al., 2000[51]	0.023	-3.761	1.437	RCT
McInnes et al., 2000[52]	0.160	-1.830	0.379	RCT
Derosa et al., 2003[17]	0.200	-1.609	1.563	RCT
Elliott, 1999[37]	0.514	-0.666	0.236	RCT

Study	Odds ratio	Ln(OR)	Standard error	Study type
Ruilope et al., 2001[23]	0.092	-2.390	1.055	RCT
Koylan et al., 2005[81]	0.087	-2.446	0.613	RCT
Coca et al., 2002[34]	0.095	-2.349	1.058	RCT
Larochelle et al., 1997[48]	0.168	-1.781	0.697	RCT
Mimran et al., 1998[53]	0.446	-0.807	0.482	RCT
Gregoire et al., 2001[107]	0.300	-1.202	0.533	OBS
Mackay et al., 1999[108]	0.284	-1.259	0.132	OBS
Roca-Cusachs et al., 1997[63]	0.905	-0.100	0.407	RCT
De Rosa et al., 2002[35]	0.280	-1.273	1.192	RCT
Lacourciere et al., 2000[47]	0.057	-2.873	1.475	RCT
Ruff et al., 1996[22]	0.638	-0.450	0.807	RCT
Tikkanen et al., 1995[69]	0.072	-2.631	0.742	RCT
Townsend et al., 1995[70]	0.246	-1.402	0.800	RCT
Neutel et al., 1999[57]	0.411	-0.888	0.404	RCT
Amerena et al., 2002[29]	0.078	-2.551	0.743	RCT
Karlberg et al., 1999[45]	0.368	-0.999	0.416	RCT
Lacourciere et al., 2006[98]	0.028	-3.574	1.018	RCT
Williams et al., 2006[100]	0.084	-2.478	0.741	RCT
Ragot et al., 2002[83]	0.160	-1.834	0.770	RCT
Black et al., 1997[32]	0.127	-2.060	0.570	RCT
Malacco et al., 2004[20]	0.129	-2.049	0.439	RCT
Fogari et al., 2004[39]	0.240	-1.428	1.130	RCT
Naidoo et al., 1999[55]	0.363	-1.012	0.362	RCT
Deyneli et al., 2006[36]	0.307	-1.182	1.683	RCT
Fogari, et al., 2006[41]	0.195	-1.635	1.557	RCT
Fogari et al., 2008[18]	0.109	-2.214	1.496	RCT
Kloner et al., 2008[46]	0.150	-1.898	1.518	RCT
Nakamura et al., 2009[56]	0.192	-1.648	1.574	RCT
Spinar et al., 2009[90]	0.122	-2.105	0.530	RCT
Tedesco et al., 2006[27]	0.108	-2.226	1.496	RCT
Xu et al., 2007[93]	0.209	-1.567	1.563	RCT
Zhu et al., 2008[72]	0.187	-1.677	1.571	RCT

Abbreviations: Ln(OR) = natural log of odds ratio; OBS = observational study; RCT = randomized controlled trial

We summarized all studies, as well as comparing RCTs to observational studies. The results are summarized in Table 19. The analyses include measures of homogeneity (Q-statistic).

Table 19. Meta-analyses of cough by subgroup for ARBs versus ACEIs

Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	38	0.2700	0.2305	0.3162	-16.2450	0.0000	54.7691	37	0.0301
Random	All	38	0.2298	0.1797	0.2940	-11.7081	0.0000	-	-	-
Fixed	Observ	3	0.2839	0.2210	0.3649	-9.8409	0.0000	0.1373	2	0.9337
Random	Observ	3	0.2839	0.2210	0.3649	-9.8409	0.0000	-	-	-
Fixed	RCTs	35	0.2611	0.2131	0.3201	-12.9351	0.0000	54.3738	34	0.0147
Random	RCTs	35	0.2116	0.1574	0.2844	-10.2865	0.0000	-	-	-

Abbreviations: CI = confidence interval; df = degrees of freedom; Observ = observational studies; OR = odds ratio; RCTs = randomized controlled trials

The results for the random-effects analysis of RCTs are in Figure 8.

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cuspidi et al., 2002	0.275	0.075	1.013	-1.941	0.052
Malmqvist et al., 2000	0.023	0.001	0.389	-2.616	0.009
McInnes et al., 2000	0.160	0.076	0.337	-4.829	0.000
Derosa et al., 2003	0.200	0.009	4.278	-1.030	0.303
Elliott, 1999	0.514	0.324	0.815	-2.826	0.005
Ruilope et al., 2001	0.092	0.012	0.724	-2.266	0.023
Koylan et al., 2005	0.087	0.026	0.288	-3.991	0.000
Coca et al., 2002	0.095	0.012	0.759	-2.221	0.026
Larochelle et al., 1997	0.168	0.043	0.660	-2.556	0.011
Mimran et al., 1998	0.446	0.174	1.147	-1.676	0.094
Roca-Cusachs, 1997	0.905	0.408	2.009	-0.246	0.806
Derosa et al., 2002	0.280	0.027	2.896	-1.068	0.286
Lacourciere et al., 2000	0.057	0.003	1.017	-1.948	0.051
Ruff et al., 1996	0.638	0.131	3.098	-0.558	0.577
Tikkanen et al., 1995	0.072	0.017	0.308	-3.546	0.000
Townsend et al., 1995	0.246	0.051	1.182	-1.752	0.080
Neutel et al., 1999	0.411	0.186	0.908	-2.200	0.028
Amerena et al., 2002	0.078	0.018	0.334	-3.435	0.001
Karlberg et al., 1999	0.368	0.163	0.832	-2.404	0.016
Lacourciere et al., 2006	0.028	0.004	0.206	-3.512	0.000
Williams et al., 2006)	0.084	0.020	0.358	-3.346	0.001
Ragot et al., 2002	0.160	0.035	0.723	-2.382	0.017
Black et al., 1997	0.127	0.042	0.390	-3.613	0.000
Malacco et al., 2004	0.129	0.054	0.305	-4.666	0.000
Fogari et al., 2004	0.240	0.026	2.198	-1.263	0.207
Naidoo et al., 1999	0.363	0.179	0.738	-2.799	0.005
Deyneli 1431	0.307	0.011	8.309	-0.702	0.483
Fogari 283	0.195	0.009	4.127	-1.050	0.294
Fogari 1221	0.109	0.006	2.052	-1.480	0.139
Kloner 079	0.150	0.008	2.937	-1.250	0.211
Nakamura 019	0.192	0.009	4.207	-1.047	0.295
Spinar 036	0.122	0.043	0.345	-3.968	0.000
Tedesco 249	0.108	0.006	2.024	-1.488	0.137
Xu 1288	0.209	0.010	4.462	-1.003	0.316
Zhu 1220	0.187	0.009	4.062	-1.068	0.286
Combined	0.212	0.157	0.284	-10.287	0.000

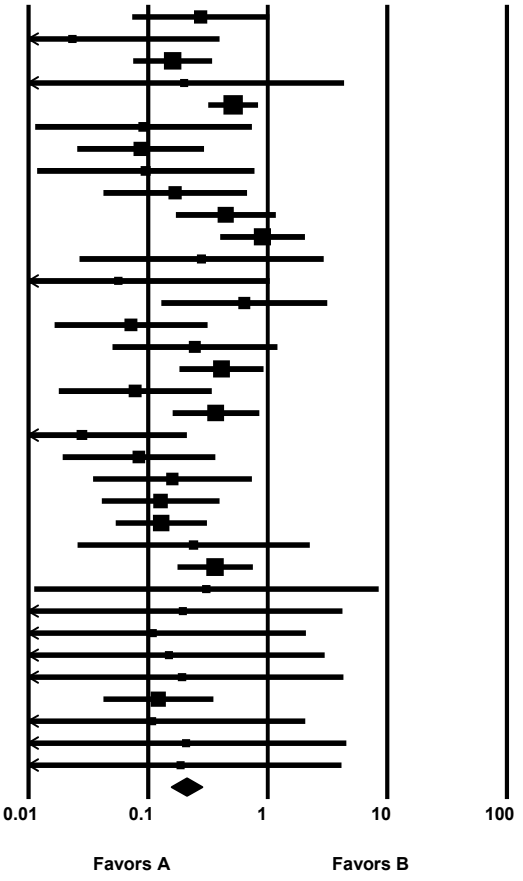


Figure 8. Random-effects analysis of RCTs for cough (ARBs vs. ACEIs)

The results are best summarized by the random-effects analysis of the RCTs. This analysis gave an estimated odds ratio of 0.212 (95 percent CI 0.157 to 0.284) suggesting that the odds of having a cough is only one-fifth as large with an ARB as it is with an ACEI.

These odds ratios need to be compared against the overall cough rate for ACEIs. The Mackay et al. observational study[108] (which is by far the largest study) would suggest that this rate is about 1.5 percent. If we pool all of the RCTs, we get a rate of about 9.9 percent.

There were two studies (both RCTs) comparing a direct renin inhibitor with an ACEI. Their results are summarized in Table 20.

Table 20. Meta-analyses of cough for direct renin inhibitors vs. ACEIs

Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	RCTs	2	0.3325	0.2241	0.4933	-5.4704	0.0000	0.7622	1	0.3826
Random	RCTs	2	0.3325	0.2241	0.4933	-5.4704	0.0000	-	-	-

Abbreviations: CI = confidence interval; df = degrees of freedom; OR = odds ratio; RCTs = randomized controlled trials

This analysis gave an estimated odds ratio of 0.333 (95 percent CI 0.2241 to 0.4933), suggesting that the odds of having a cough is only one-third as large with a direct renin inhibitor as it is with an ACEI.

Withdrawals Due to Adverse Events

Forty (40) studies met our inclusion criteria and reported withdrawals due to adverse events.[18-21,24-27,29,31-32,34-37,41,45-47,50,52-57,63,69-70,72-73,81,86,91,93,95,97-99,101] Of these, 10 (25 percent) were of good methodological quality, 24 (60 percent) were fair in quality, and six (15 percent) were poor. Thirty-eight studies were RCTs, one was a nonrandomized controlled clinical trial, and one was a case-control study. Sample sizes for the individual studies ranged from 46 to 1213 patients, with a total of 12,184 patients. Study durations ranged from 12 weeks to 5 years. The proportion of female patients included ranged from 24 to 100 percent (mean 48 percent). Twenty-one studies (53 percent) reported the racial demographics of the study participants. Ten of these (25 percent of the 40 total studies) enrolled a minimum of 10 percent of ethnic minority participants, while six enrolled only white patients.

Rates of withdrawals due to adverse events ranged from 1 to 20 percent, with a mean of 3.0 percent for patients on ARBs, and a mean of 5.5 percent for patients on ACEIs. In 28 of the 36 trials (78 percent of which reported withdrawals due to adverse events for both ACEIs and ARBs), there were more withdrawals in the ACEI-treated groups. However, there was significant variation in the study protocols and data reporting.

We conducted a meta-analysis of the studies that reported withdrawals due to adverse events. Table 21 gives a summary of the studies and their estimated odds ratios. The odds ratio represents the odds of withdrawing for the ARB patients divided by the odds of withdrawing for the ACEI.

Table 21. Estimated odds ratios for withdrawals due to adverse events (ARBs vs. ACEIs)

Study	Odds ratio	Ln(OR)	Standard error	Study type
Cuspidi et al., 2002[101]	0.4700	-0.7550	0.5116	RCT
McInnes et al., 2000[52]	0.4574	-0.7822	0.3964	RCT
Mogensen et al., 2000[54]	0.9688	-0.0317	1.0158	RCT
Schram et al., 2005[25]	3.0000	1.0986	1.1952	RCT
Elliott, 1999[37]	1.0000	0.0000	1.4169	RCT
Koylan et al., 2005[81]	0.0174	-4.0531	1.4315	RCT

Study	Odds ratio	Ln(OR)	Standard error	Study type
Coca et al., 2002[34]	0.6850	-0.3783	0.9227	RCT
Mimran et al., 1998[53]	3.1895	1.1599	1.1635	RCT
Mallion et al., 1995[50]	0.9899	-0.0102	0.5749	RCT
Roca-Cusachs et al., 1997[63]	0.4128	-0.8849	0.6004	RCT
Avanza et al., 2000[73]	0.2635	-1.3337	1.5177	OBS
De Rosa et al., 2002[35]	0.1159	-2.1550	1.5395	RCT
Lacourciere et al., 2000[47]	2.0000	0.6931	1.2410	RCT
Shand et al., 2000[86]	0.2903	-1.2368	1.6749	RCT
Tikkanen et al., 1995[69]	0.4176	-0.8731	0.4984	RCT
Townsend et al., 1995[70]	0.7561	-0.2796	0.4590	RCT
Verdecchia et al., 2000[91]	0.4500	-0.7985	0.8074	OBS
Neutel et al., 1999[57]	0.0602	-2.8097	1.0644	RCT
Amerena et al., 2002[29]	0.4808	-0.7324	0.6187	RCT
Karlberg et al., 1999[45]	0.6606	-0.4145	0.4115	RCT
Black et al., 1997[32]	0.8950	-0.1109	0.4526	RCT
Malacco et al., 2004[20]	0.3854	-0.9535	0.3975	RCT
Naidoo et al., 1999[55]	0.9827	-0.0175	0.8236	RCT
Barnett et al., 2004[31]	0.6667	-0.4055	0.3215	RCT
Deyneli et al., 2006[36]	0.3067	-1.1820	1.6833	RCT
Fogari, et al., 2006[41]	0.4872	-0.7191	0.8809	RCT
Fogari et al., 2008[18]	0.1967	-1.6261	1.1030	RCT
Hermida et al., 2008[19]	2.0000	0.6931	1.2353	RCT
Kloner et al., 2008[46]	0.3561	-1.0326	1.6388	RCT
Lacourciere et al., 2006[98]	0.5098	-0.6738	0.3633	RCT
Nakamura et al., 2009[56]	0.1925	-1.6479	1.5738	RCT
Menne et al., 2008[21]	0.8063	-0.2154	0.7947	RCT
Spoelstra-de Man et al., 2006[26]	3.0000	1.0986	1.1952	RCT
Tedesco et al., 2006[27]	0.3937	-0.9322	0.8461	RCT
Xu et al., 2007[93]	0.2086	-1.5673	1.5627	RCT
Zhu et al., 2008[72]	0.1869	-1.6773	1.5709	RCT

Abbreviations: Ln(OR) = natural log of odds ratio; OBS = observational study; RCT = randomized controlled trial

We summarized all studies, as well as comparing RCTs to observational studies. The results are summarized in Table 22. The analyses include measures of homogeneity (Q-statistic).

Table 22. Meta-analyses of withdrawals due to adverse events by subgroup for ARBs vs. ACEIs

Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	All	36	0.5599	0.4500	0.6966	-5.2027	0.0000	28.8562	35	0.7584
Random	All	36	0.5599	0.4500	0.6966	-5.2027	0.0000	-	-	-
Fixed	Obs	2	0.3999	0.0989	1.6169	-1.2859	0.1985	0.0969	1	0.7555
Random	Obs	2	0.3999	0.0989	1.6169	-1.2859	0.1985	-	-	-
Fixed	RCTs	34	0.5646	0.4526	0.7044	-5.0639	0.0000	28.5308	33	0.6893
Random	RCTs	34	0.5646	0.4526	0.7044	-5.0639	0.0000	-	-	-

Abbreviations: CI = confidence interval; df = degrees of freedom; OR = odds ratio; Obs = observational studies; RCTs = randomized controlled trials

The results for the random-effects analysis of RCTs are shown in Figure 9.

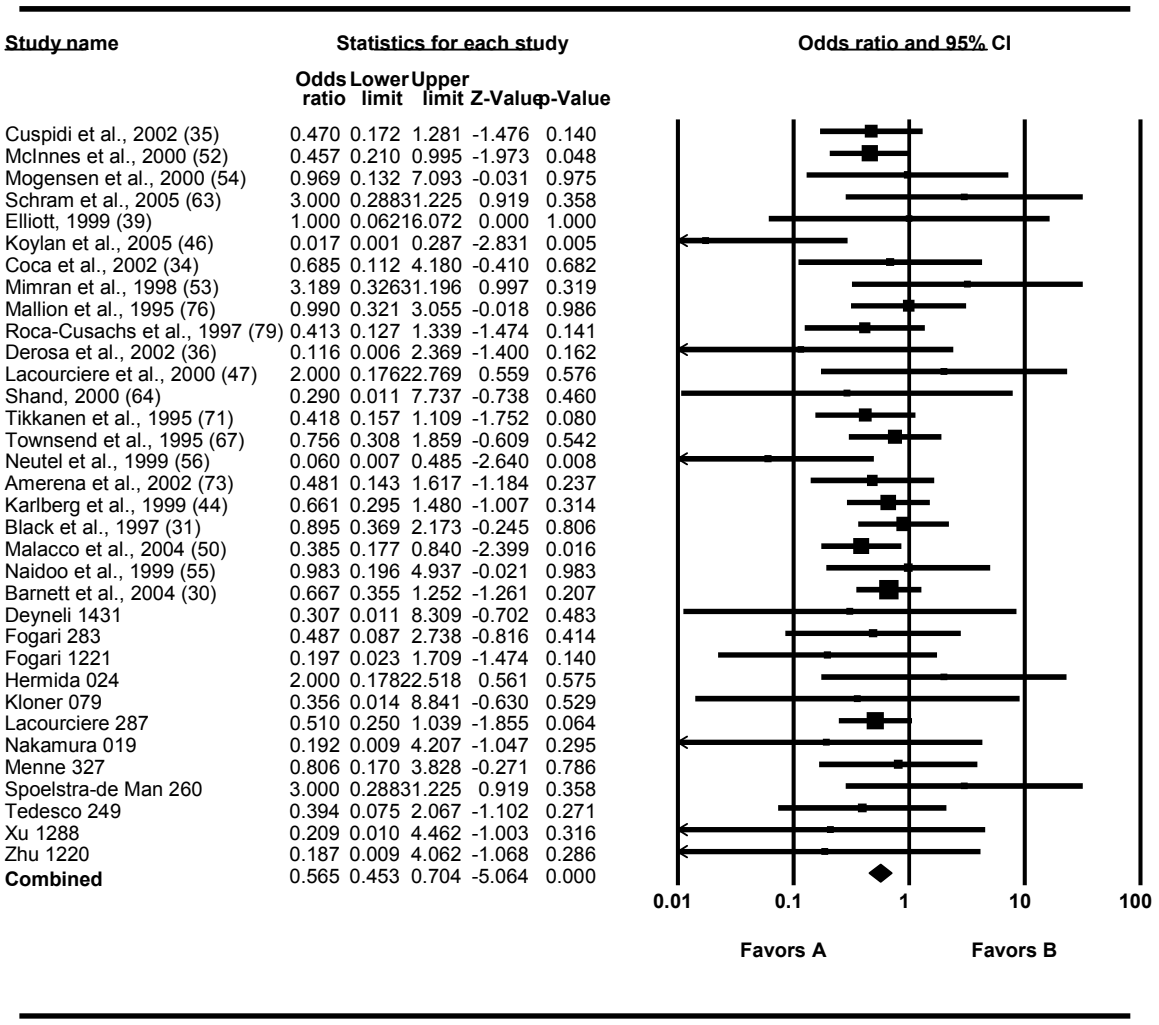


Figure 9. Random-effects analysis of RCTs for withdrawals due to adverse events (ARBs vs. ACEIs)

The results are best summarized by the random-effects analysis of the RCTs. This analysis gave an estimated odds ratio of 0.565 (95 percent CI 0.453 to 0.704), suggesting that the odds of withdrawing due to an adverse event are only 56 percent as large with an ARB as with an ACEI.

These odds ratios need to be compared against the overall withdrawal rate for ACEIs. If we pool all of the RCTs, we get a rate of about 5.4 percent.

There were two studies (both RCTs) comparing a direct rennin inhibitor with an ACEI. Their results are summarized in Table 23.

Table 23. Meta-analyses of withdrawals due to adverse events for direct renin inhibitors vs. ACEIs

Model	Analysis subgroup	No. of studies	OR estimate	95% CI lower limit	95% CI upper limit	Z value	P value	Q value	df (Q)	P value
Fixed	RCTs	2	0.8282	0.5747	1.1935	-1.0113	0.3119	2.9951	1	0.0835
Random	RCTs	2	0.8861	0.4581	1.7136	-0.3595	0.7193	-	-	-

Abbreviations: CI = confidence interval; df = degrees of freedom; OR = odds ratio; RCTs = randomized controlled trials

This analysis gave an estimated odds ratio of 0.886 (95 percent CI of 0.458, 1.714), suggesting that the estimated odds of withdrawing due to adverse events is only 89 percent as large with a direct renin inhibitor as it is with an ACEI, but this value is not significantly different from 1.00 (100 percent).

Caveats and concerns in relation to these data include the fact that only nine of the 40 studies were considered to be of good methodological quality. Also, there was significant heterogeneity in the reporting of withdrawal data. Many studies reported limited data on withdrawal rates. Moreover, only one trial analyzed data to assess variation in withdrawal rates by specific demographic subgroups.[108]

Adherence and Persistence

Forty-two papers describing 40 distinct studies reported at least some quantitative information on persistence or adherence.[18-19,21,26-27,29,34,36,41,43-44,46,51-52,56,64-65,67,72,81,92-93,95,97-100,105,109-121] Studies of adherence consisted of RCTs that assessed reported pill counts or subject dropout. Since subject dropout did not uniformly reflect adherence with medication (as opposed to adherence with the study protocol, for example), we focused on the nine studies that measured pill counts. Fifteen studies of persistence – whether patients remain on the initial ACEI, ARB, or direct renin inhibitor – included two RCTs as well as 13 longitudinal cohorts in which patients were followed in a real-world setting. Two studies evaluated adherence to an ACEI versus a direct renin inhibitor, and one evaluated adherence to an ARB versus a direct renin inhibitor. All the other studies compared ACEIs to ARBs. While adherence and persistence were lower in cohort studies than in the randomized trials, the general conclusions from the two groups of studies were similar.

With the possible exception of the study by Koylan et al.,[81] adherence with ACEIs and ARBs was similar (Table 24). Moreover, adherence was high: above 90 percent in all studies, and at least 97 percent in five of the nine studies assessed. Most studies appeared to define adherence as the percentage of patients taking approximately 100 percent of the prescribed pills, although not every article was precise in reporting how this figure was derived. The absolute magnitude of adherence depended on the width of the acceptable range (e.g., McInnes et al.[52] used a narrow range of 90 to 110 percent of prescribed pills and so might be expected to report lower adherence than Malmqvist et al.,[51] which considered a wider range of 75 to 125 percent of prescribed pills to be acceptable). Also, randomized trials, which engender such biases as motivated volunteers and a Hawthorne effect, will tend to overestimate adherence in comparison with usual practice. Nevertheless, the overall conclusion that adherence was good and similar between ACEIs and ARBs seems well supported.

Table 24. Studies of treatment adherence with ACEIs and ARBs

Study	Adherence with ACEIs	Adherence with ARBs	Definition of adherence
Amerena et al., 2002[29]	99%	99%	Pill counts at 6 weeks
	98%	98%	Pill counts at 12 weeks
Coca et al., 2002[34]	98.4%	98.3%	Taking 80-110% of pills
Fogari et al., 2006[41]	92%	94%	Pill count at each study visit
Koylan et al., 2005[81]	~ 94%	~ 96%	Taking pills daily at 1 month visit
	~ 86%	~ 96%	Taking pills daily at 3 month visit
	~ 87%	~ 96%	Taking pills daily at 6 month visit
Malmqvist et al., 2000[51]	> 98%	> 98%	Taking 75-125% of pills at 6 weeks
	> 98%	> 98%	Taking 75-125% of pills at 12 weeks
McInnes et al., 2000[52]	90%	90%	Taking 90-110% of pills
Rosei et al., 2005[64]	98.2%	97.8%	Not specifically defined
Tedesco et al., 2006[27]	> 90%	> 90%	Pill count at study visits
Williams et al., 2006[100]	> 98.8%	> 98.8%	Taking 80-120% of pills

Regarding persistence, the majority of evidence came from nonexperimental studies, which are subject to a variety of caveats, described below. These caveats notwithstanding, the results were quite consistent in that persistence with ARBs was modestly better than persistence with ACEIs (Table 25). Noting both the consistency of this finding across studies and the rather modest degree of differences in persistence, the conclusion that ARBs exhibit somewhat better persistence than ACEIs can be drawn with a moderate degree of confidence. No study reported persistence associated with direct renin inhibitor treatment.

Table 25. Studies of persistence with ACEIs and ARBs

Study	Duration	ACEIs			ARBs		
		Continued	Switched	Discontinued	Continued	Switched	Discontinued
Randomized trials							
Saito et al., 2004[65]	6 mo	71%	28%	2%	89%	9%	2%
Koylan et al., 2005[81]	6 mo	~ 82%	-	-	~ 89%	-	-
Hosohata et al., 2007[44]	12 mo	55%	-	-	88%	-	-
Veronesi et al.,2007[92]	24 mo	61.5%	-	-	68.5%	-	-
Longitudinal cohort studies							
Hasford et al., 2002[43]	1 yr	42%	-	-	44.7 to 60.8%	-	-
Mazzaglia et al., 2005[105]	1 yr	~ 50%	~ 8%	~ 42%	~ 50%	~ 10%	~ 40%
Bloom et al., 1998[109]/Conlin et al., 2001[112]	1 yr	58%	9%	33%	64%	7%	29%
	4 yr	46.5%	18.9%	34.6%	50.8%	16.5%	32.7%
Erkens et al., 2005[115]	1 yr	59.7%	-	-	62.0%	-	-
Marentette et al., 2002[116]	1 yr	-	-	~ 35%	-	-	~ 15%
Bourgault et al., 2005[110]	1 yr	-	-	41%	-	-	34%
	2 yr	-	-	53%	-	-	44%
	3 yr	-	-	60%	-	-	47%
Burke et al., 2006[111]	1 yr	-	-	37.8%	-	-	29.4%
	2 yr	-	-	48.0%	-	-	41.3%
	3 yr	-	-	54.8%	-	-	50.3%
	4 yr	-	-	60.4%	-	-	57.8%
Wogen et al., 2003[117]	1 yr	50%	-	-	63%	-	-
Degli Esposti et al., 2002[113-114]	1 yr	30.7%	9.4%	59.9%	33.4%	24.6%	42.0%
Hasford et al., 2007[118]	1 yr	28.2%	-	-	26.4%	-	-
	2 yr	18.6%	-	-	15.3%	-	-
	3 yr	14.0%	-	-	10.6%	-	-
Patel et al., 2007[120]	1 yr	48.0%	-	-	51.9%	-	-
Lachaine et al., 2008[119]	2 yr	58.9%	-	-	60.9%	-	-
Simons et al., 2008[121]	33 mo	45%	-	-	47%	-	-

Study	Duration	ACEIs			ARBs		
		Continued	Switched	Discontinued	Continued	Switched	Discontinued
		(95% CI 44 to 46%)			(95% CI 46 to 48%)		

The results of the longitudinal studies should be considered in light of several caveats. The longitudinal cohort studies typically use administrative databases and, even though investigators control for differing patient characteristics as much as possible, this design cannot assure that patients receiving different medications are similar, even after statistical adjustment. Consequently, the consistency of results across multiple studies is crucial. Results of multi-predictor analyses, when present, yielded substantially similar conclusions to the simple comparison of unadjusted persistence provided above; accordingly, we focus on the unadjusted results.

The ideal outcome would disaggregate patients into four mutually exclusive and exhaustive categories: (1) continued initial medication without change; (2) continued initial medication but added another medication from a different class; (3) changed to another medication from a different class; and (4) discontinued medication entirely. Almost all of the reports aggregated the first two categories, which we have combined throughout. Within each category, definitions are not entirely consistent, but are close enough for purposes of comparison.

As a final caveat, several of the longitudinal cohort studies (e.g., Marentette et al.,[116] Bourgault et al.,[110] Burke et al.,[111] Wogen et al.,[117] and Degli Esposti et al.[113-114]) corresponded in time to the introduction of ARBs, and thus have relatively small sample sizes for this class of medication. Accordingly, for these studies persistence is estimated with less precision than might be desired.

Key Question 3. Are there subgroups of patients – based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent us of other medications) – for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?

Key Points

- Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs, ARBs, and direct renin inhibitors for any particular patient subgroup.

Blood Pressure

Comparisons of ACEIs Versus ARBs

We did not identify any subgroup of patients in whom one ACEI or ARB was clearly superior. Two of 75 studies reporting blood pressure outcomes included only women,[40,51] and two additional studies reported results for a female subgroup.[45,50] Three of these four found no significant difference in blood pressure effects between the ACEI and the ARB treatment arms; however, the largest of the four[51] reported superior blood pressure lowering in the ARB arm compared to the ACEI (n = 286, mean between group difference 5.5/2.2 mm Hg; $p \leq 0.01$). There were three studies conducted exclusively in elderly patients (age $\geq$ 65), and three additional studies that reported separate results for this age group.[23,30,39,45,50,70] Four of these studies showed no difference between ACEI and ARB treatment in elderly patients,[23,30,45,50] and the remaining two studies reported better blood pressure lowering in the ARB arm.[39,70] Ten studies were conducted only in diabetic patients with hypertension, none of which showed a difference between the two classes of medication.[17,25,31,38,46-47,54,64,76,80] In four studies, blood pressure was reported as an outcome in a subgroup of black patients.[22,49,55,70] Three of these studies found no difference in the efficacy of ACEIs versus ARBs in black patients, while one reported significantly better DBP lowering in ARB-treated patients compared to ACEI-treated patients.[70]

Comparisons of Direct Renin Inhibitors Versus ACEIs or ARBs

Of the three studies comparing the direct renin inhibitor aliskiren to an ACEI or ARB, one was conducted solely in patients over age 65.[97] Aliskiren provided greater blood pressure lowering than the ACEI ramipril; however, this result was also reported in a similar study comparing aliskiren and ramipril which was not restricted to patients over age 65 (two publications[95-96]), suggesting that this effect is unlikely to be unique to an elderly subgroup.

Mortality and Major Cardiovascular Events

Because of scant data on mortality, MI, and stroke, it was not possible to assess whether ACEIs and ARBs have any differential effect on event rates in any subgroups of patients based on demographic characteristics, use of other medications concurrently, or comorbidities.

Quality of Life

None of the included trials reported any differential impact of ACEIs versus ARBs (or versus direct renin inhibitors) on quality-of-life measures by clinically relevant subgroup.

Safety and Adverse Events

In general, there is no evidence supporting differential rates of adverse events for ACEIs versus ARBs or direct renin inhibitors with regard to any specific subgroup. However, one study included only women in the study population.[51] The overall rates of cough reported by the study

were similar to those reported by other studies that included men and women. One study reported results for a female subgroup.[108] The proportion of women in the latter study was 55.7 percent, and rates of cough in this study were higher for women treated with ACEIs (statistically significant for two of the three ACEIs studied in the trial) than they were for women treated with ARBs.

Adherence and Persistence

There is not sufficient evidence that particular patient subgroups are more or less likely to be persistent in taking an ACEI versus an ARB, and we did not identify any studies on persistence that included patients taking a direct renin inhibitor. However, some observations emerge regarding persistence with ACEIs or ARBs (Table 26). The most consistent result is that persistence increased with age: patients in the 65- to 84-year-old age range tended to exhibit the highest persistence of all. The contribution of sex was inconsistent. There is some evidence that a history of cardiovascular disease is associated with greater persistence, a possible explanation being that such a history could make hypertension management more salient to the patient.

Table 26. Predictors of persistence with ACEIs and ARBs

Study	Predictors of persistence
Mazzaglia et al., 2005[105]	Increasing age, family history of cardiovascular diseases and diabetes, no severe hypertension, low chronic disease score
Bloom et al., 1998[109] (1yr)/Conlin et al., 2001[112] (4 yr)	1 yr: Increasing age, < 1 dose per day, male sex 4 yr: Increasing age, female sex
Erkens et al., 2005[115]	Increasing age, male sex, antidiabetic drugs, lipid lowering drugs, previous cardiovascular hospitalizations
Marentette et al., 2002[116]	Increasing age, female sex
Degli Esposti et al.,2002[114] (1 yr)/Degli Esposti et al., 2002[113] (3 yr)	1 yr: Increasing age, medications for heart disease or diabetes, previous cardiovascular hospitalizations, ≥ 2 comorbidities 3 yr: Increasing age, male sex, younger general practitioner, male sex of general practitioner
Simons et al. , 2008[121]	Age < 40 years associated with lowest persistence (16% persistence, and 3 months median persistence time) Age 60-69 years associated with highest persistence (50% persistence, and 33 months median persistence time) No significant difference by sex

Lipids

Several potentially relevant subgroups were identified, but none had a clear difference between the compared medications in lipid parameter outcomes. Six studies evaluated patients with

diabetes.[17,25,38,47,54,80] These included three that found small changes in various lipid parameters,[17,47,80] but the other three found none.[25,38,54] Another study examined patients with hypertension and components of the metabolic syndrome (at least two of: high triglycerides, low HDL, high blood glucose, or high waist circumference); it found improvements in TC, TG, HDL, and LDL for ramipril and valsartan, but no differences between the medications.[94] One study targeting postmenopausal women,[40] one taking place in Japan,[71] and two taking place in Turkey[67,80] did not have detectable changes in the lipid profile. Another study taking place in Turkey[94] found improvement in all lipid parameters with both ramipril and valsartan, while another study taking place in China[93] found greater improvements in TG and HDL with telmisartan than with enalapril.

Diabetes Markers

In the seven studies requiring diabetes as an inclusion criteria, five found no difference in individuals receiving ACEIs or ARBs in glucose or HbA1c levels;[25,38,54,67,80] one found no change in glucose but a small statistically significant increase in HbA1c for the ARB (+ 0.25 percent enalapril, + 0.6 percent losartan; data not reported for between-group comparisons);[47] and one found no change in HbA1c but a decline in glucose levels for both which was statistically greater for the ACEI (perindopril -15 ± 4 mg/dL, candesartan -8 ± 2 mg/dL).[17] Thus, for the two studies for which a difference was found, the difference was discrepant (i.e., an increase in HbA1c in one and a decline in glucose in the other), and only one directly analyzed differences between the two groups.

In addition to studies of individuals with diabetes, measures of glucose or HbA1c were performed for several other subgroups including Asians,[56,71,88,93] Turks,[67,80,94] Brazilians,[73] Portuguese,[102] Spaniards,[19] Argentineans,[66] Czechs,[90] and postmenopausal women.[40] None of these studies identified a difference in the impact of ACEIs and ARBs with regard to fasting glucose or HbA1c.

LV Mass/Function

Although 10 of the 13 studies that presented results on LV mass or function demonstrated some decreases in LVMI (or equivalent measure), the sum of the evidence does not demonstrate a difference between ACEIs, ARBs, and direct renin inhibitors with regard to their effect on LV mass or function for individuals with essential hypertension. No subgroup analyses were performed by study investigators to help identify subgroups of patients who were more likely to have improvements in LV mass or function in any of the studies.

GFR/Proteinuria

There are no consistently demonstrated differential effects with use of ACEIs, ARBs, or direct renin inhibitors related to either renal function (as measured by creatinine or GFR) or reduction of urinary protein or albumin excretion. As a result, we were not able to identify subgroups of patients for whom either ACEIs or ARBs are more effective in preserving renal function or decreasing urinary protein or albumin excretion, or are better tolerated without causing sustained elevations in serum creatinine.

Summary and Discussion

A succinct summary of the results of this review of the comparative long-term benefits and harms of ACEIs, ARBs, or direct renin inhibitors for adults with essential hypertension is provided in three tables. First, we give an aggregated view of the strength of evidence and brief conclusions (Table 27). Second, we describe the nature and quality of the evidence in a format recommended by the GRADE Committee (Table 28). Finally, we summarize the quantitative analyses of outcomes, offering an estimate of the comparative outcomes for ACEIs (Table 29).

Table 27. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for essential hypertension

Key question	Strength of evidence	Conclusions
1. Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes:		
a. Blood pressure control?	High	ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence from 75 studies (69 RCTs, four nonrandomized controlled clinical trials, one retrospective cohort study, and one case-control study) in which 24,943 patients receiving an ACEI or an ARB were followed for periods from 12 weeks to 5 years (median 24 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols. Evidence concerning the effect of direct renin inhibitors on blood pressure is very limited and currently based on only three studies. These studies found the direct renin inhibitor to have a greater reduction in blood pressure compared to an ACEI (two studies) and no significant difference compared to an ARB (one study).
b. Mortality and major cardiovascular events?	Low	Due to insufficient numbers of deaths or major cardiovascular events reported, it was not possible to discern any differential effect of ACEIs versus ARBs versus direct renin inhibitors for these critical outcomes. In 21 studies that reported mortality, MI, or clinical stroke as outcomes among 38,504 subjects, there were 346 deaths and 13 strokes reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup.
c. Quality of life?	Low	No differences were found in measures of general quality of life; this is based on four studies, two of which did not provide quantitative data. No study evaluated the comparative effectiveness of direct renin inhibitors for quality-of-life outcomes.
d. Rate of use of a single antihypertensive medication?	High	There was no statistically evident difference in the rate of treatment success based on use of a single antihypertensive

Key question	Strength of evidence	Conclusions
		for ARBs compared to ACEIs. The trend toward less frequent addition of a second agent to an ARB was heavily influenced by retrospective cohort studies, where medication discontinuation rates were higher in ACEI-treated patients, and by RCTs with very loosely defined protocols for medication titration and switching. There were no relevant studies evaluating direct renin inhibitors.
e. Risk factor reduction and other intermediate outcomes?	Moderate (lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease) Low (progression to type 2 diabetes and LV mass/function)	There were no consistent differential effects of ACEIs, ARBs, or direct renin inhibitors on several potentially important clinical outcomes, including lipid levels and markers of carbohydrate metabolism/diabetes control. There appears to be a small difference in change in renal function between ACEIs and ARBs (favoring ACEIs), but this difference is both small and most likely not clinically meaningful or significant. Relatively few studies assessed these outcomes over the long term. There were no included studies evaluating rates of progression to type 2 diabetes mellitus. Although we included 13 studies of LV mass/function, these were dominated by poor-quality studies with small sample sizes.
2. Key Question 2. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in safety, adverse events, tolerability, persistence with drug therapy, and treatment adherence?	High (cough, withdrawals due to adverse events) Low (angioedema) Moderate (persistence with drug therapy/ treatment adherence)	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs (odds ratio 0.212; 95% CI 0.157 to 0.284). For RCTs, this translates to a difference in rates of cough of 7.8 percent; however, for cohort studies with lower rates of cough, this translates to a difference of 1.2 percent. There were only two studies comparing direct renin inhibitors to ACEIs and these gave an estimated odds ratio of 0.333 (95% CI of 0.2241 to 0.4933). The withdrawal rate for ARBs was found to have an estimated odds ratio of 0.565 (95% CI 0.453 to 0.704) compared with ACEIs. For RCTs, this translated to a difference in withdrawals of 2.3 percent. The direct renin inhibitor trials did not find a statistically significant difference (odds ratio 0.886; 95% CI 0.458 to 1.714) when compared with the withdrawal rate associated with ACEIs. There was no evidence of differences across treatments in rates of other commonly reported specific adverse events. Angioedema was not reported in the majority of studies, making it impossible to accurately characterize its frequency and timing in this population. In the studies that did report episodes of angioedema, this adverse event was observed only in patients treated with an ACEI (five patients) or a direct renin inhibitor (one patient). ACEIs and ARBs have similar rates of treatment adherence based on pill counts; this result may not be applicable outside the clinical trial setting. Rates of continuation with therapy appear to be somewhat better with ARBs than with ACEIs; however, due to variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small

Key question	Strength of evidence	Conclusions
		sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify. The studies evaluating direct renin inhibitors did not find evidence of differences in treatment adherence compared with ACEIs or ARBs.
3. Key Question 3. Are there subgroups of patients – based on demographic and other characteristics (i.e., age, race, ethnicity, sex, comorbidities, concurrent use of other medications) – a for whom ACEIs, ARBs, or direct renin inhibitors are more effective, are associated with fewer adverse events, or are better tolerated?	Insufficient	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs, ARBs, and direct renin inhibitors for any particular patient subgroup.

Abbreviations: ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CI = confidence interval; GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; RCTs = randomized controlled trials

Table 28. GRADE summary table

Studies	Design	Quality	Consistency	Directness	SD	SA	DR	PC
Outcome: Blood pressure control								
69	RCTs	Confounded by additional treatments, dose escalation	Consistent results	Direct	-	-	-	-
6	4 non-randomized controlled trials, 1 cohort study, 1 case-control	Confounded by additional treatments, dose escalation	Consistent results	Direct	-	-	-	-
Outcome: Mortality and major cardiovascular events								
18	RCTs	No serious limitations	Consistent results	Direct	+	-	-	-
3	1 prospective observational study, 2 retrospective studies	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Morbidity/quality of life								
4	RCTs	No serious limitations	Consistent results	Direct	-	-	-	-
Outcome: Safety (serious and overall adverse events, withdrawals due to adverse events)								
12 – serious AEs	RCTs	Variation in study protocols	Consistent results	Direct	-	-	-	-

Studies	Design	Quality	Consistency	Directness	SD	SA	DR	PC
43 – overall AEs 38 – withdrawals due to AEs		and data reporting						
2 – overall AEs 2 – withdrawals due to AEs	1 non-randomized controlled trial; 1 case-control	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Specific adverse events								
43	RCTs	Variation in data reporting	Consistent results	Direct	-	-	-	-
3	3 cohort studies	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Persistence with drug therapy/treatment adherence								
27	RCTs	Variation in data reporting	Consistent results	Direct	-	-	-	-
13	13 cohort studies	Limitations based on study design	Consistent results	Direct	-	-	-	-
Outcome: Rate of use of a single agent for blood pressure control								
22	RCTs	No serious flaws	Consistent results	Direct	-	-	-	-
3	2 cohort studies, 1 case-control	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Lipid levels								
18	RCTs	No serious flaws	Inconsistent results between studies and between lipid parameters	Direct	-	-	-	-
2	1 non-randomized clinical trial, 1 case-control	Limitations based on study design	Inconsistent results between studies and between lipid parameters	Direct	+	-	-	-
Outcome: Rates of progression to type 2 diabetes								
0	NA	NA	NA	NA	+	-	-	-

Studies	Design	Quality	Consistency	Directness	SD	SA	DR	PC
Outcome: Markers of carbohydrate metabolism/diabetes control								
18	RCTs	No serious flaws	Inconsistent results between head-to-head studies and placebo-controlled studies	Direct	-	-	-	-
4	2 non-randomized controlled trials, 1 case-control, 1 prospective observational study	Limitations based on study design	Consistent results	Direct	+	-	-	-
Outcome: Measures of LV mass/function								
11	RCTs	Poor quality studies; small sample sizes	Consistent results	Direct	-	-	-	-
2	1 non-randomized controlled trial; 1 case-control	Poor quality studies; small sample sizes	Consistent results	Direct	+	-	-	-
Outcome: Measures of kidney disease								
21 – GFR 16 – proteinuria	RCTs	Poor quality studies; different parameters measured	Consistent results Inconsistent results	Direct Direct	- -	- -	- -	- -
3 – GFR 1 – proteinuria	1 non-randomized controlled trial, 1 cohort study, 1 case-control, 1 prospective observational study	Limitations based on study design	Consistent results	Direct	+	-	-	-

Abbreviations: AEs = adverse events; DR = dose response; GFR = glomerular filtration rate; LV = left ventricular; PC = all plausible confounders would reduce the effect; RCT(s) = randomized controlled trial(s); SA = strong association (+ = very strong, ++ = extremely strong); SD= sparse data

Table 29. GRADE balance sheet

Outcome	Number of patients treated with ACEIs, ARBs, or direct renin inhibitors and assessed for outcome of interest			Effect based on meta-analysis	Quality	Relative importance
	ACEI	ARB	Direct renin inhibitor	Effect (95% CI)		
BP reduction	~ 13,600	~ 13,600	1104	-	High	Critical
Rate of use of a single antihypertensive for BP control	~12,840	~12,840	No data	Estimated odds ratio of ARBs vs. ACEIs 1.049 (95% CI 0.903 to 1.218)	High	
Mortality and major CV events	~18,700	~18,700	1104	-	Moderate	Critical
Morbidity/Quality of life	~ 550	~ 550		No difference detected	Low	-
Cough	45,441	22,437	877	Estimated odds ratio of ARBs vs. ACEIs 0.212 (95% CI 0.157 to 0.284) Estimated odds ratio of direct renin inhibitors vs. ACEIs 0.333 (95% CI 0.2241 to 0.4933)	High Low	
Adverse events – withdrawals	4744	4935	877	Estimated odds ratio of ARBs vs. ACEIs 0.565 (95% CI 0.453 to 0.704) Estimated odds ratio of direct renin inhibitors vs. ACEIs 0.886 (95% CI 0.458 to 1.714)	High	Critical
Persistence/ adherence	158,571	157,706	877	-	Moderate	
Lipid levels	5112	5278	No data	-	Moderate	-
Progression to type 2 diabetes	No data	No data	No data	-	Low	-
Markers of carbohydrate metabolism/diabetes control	5042	5191	No data	-	Moderate	-
Measures of LV mass/function	~777	~545	~233	-	Low	-
Measures of kidney disease – creatinine/GFR	1004	483	457	Serum creatinine: Standardized mean difference of ARBs vs. ACEIs 0.100 (95% CI -0.079 to 0.278)	Moderate	-

Outcome	Number of patients treated with ACEIs, ARBs, or direct renin inhibitors and assessed for outcome of interest			Effect based on meta-analysis	Quality	Relative importance
	ACEI	ARB	Direct renin inhibitor	Effect (95% CI)		
				Creatinine clearance: Standardized mean difference of ARBs vs. ACEIs -0.217 (95% CI -0.515 to 0.080) GFR: Standardized mean difference of ARBs vs. ACEIs -0.227 (95% CI -0.486 to 0.032) All flow studies: Standardized mean difference of ARBs vs. ACEIs -0.227 (95% CI -0.396 to -0.028)		
Measures of kidney disease – proteinuria	334	242	73	-	Low	-

Abbreviations: BP = blood pressure; CI = confidence interval; CV = cardiovascular; GFR = glomerular filtration rate; LV = left ventricular

Future Research

With the exception of rates of cough, the hypothesis that ACEIs, ARBs, and direct renin inhibitors have clinically meaningful differences in long-term outcomes in individuals with essential hypertension is not strongly supported by the available evidence. Given the importance of these issues, it is notable how few large, long-term, head-to-head studies have been published.

Further comparative studies in this area should emphasize:

- Subgroups of special importance such as individuals with essential hypertension and diabetes mellitus, congestive heart failure, chronic kidney disease, and dyslipidemia.
- 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.
- Outcomes over several years.
- Outcomes measured according to current clinical standards.
- Broader representation of groups such as the elderly and ethnic and racial minorities.

- Evaluation of specific pairs of ACEIs and ARBs to allow differentiation within class. (Only one direct renin inhibitor, aliskiren, is currently available.)
- Long-term comparisons of direct renin inhibitors with ACEIs and ARBs.

In addition, we think that research aimed at generating additional evidence regarding four specific areas should be prioritized. These areas include:

(1) The incidence, timing, and clinical consequences of angioedema in patients treated with ACEIs, ARBs, or direct renin inhibitors.

Comment: Angioedema is a well known adverse reaction to ACEIs and ARBs; however, due to its infrequent occurrence, we lacked sufficient evidence to directly compare the incidence, timing, and clinical consequences of this reaction among patients treated with ACEIs, ARBs, or direct renin inhibitors. Others have estimated that angioedema is experienced by 1 in every 1000 patients treated with an ACEI,[122-123] and 1 to 5 of every 10,000 of those treated with an ARB.[124-125] Furthermore, others have reported a 3- to 4-fold increased risk of angioedema in African-American patients. Future research should utilize large databases with sufficient sample sizes to obtain more precise estimates of this rare but serious event. Assessment of study designs or analyses that could explore the impact of angioedema should be prioritized.

(2) Relative persistence with drug therapy across the different classes of drugs.

Comment: Although we report with moderate confidence that persistence with drug therapy is greater with ARB treatment than with ACEI treatment, the medication discontinuation rates varied significantly across studies. Because medication discontinuation often requires followup visits and initiation of alternative medications, it has important health economic implications. Future studies that more precisely estimate discontinuation rates in usual clinic settings, the additional health care utilization following discontinuation, and the conditional tolerability of an ACEI or ARB following prior intolerance to one of these agents would be valuable in understanding the consequences of differential medication discontinuation.

(3) The impact of cough on patients' quality of life.

Comment: Given the demonstrated higher incidence of cough with ACEIs, it would also be valuable to gain more precise understanding of the impact of cough on quality of life, care patterns (e.g., use of therapeutic agents for cough symptoms or conditions associated with cough), and health outcomes, particularly for individuals who continue to use ACEIs.

(4) The potential to gain insight on the comparative benefits and harms of ACEIs, ARBs, and direct renin inhibitors based on findings from studies evaluating patients with other, related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease.

Comment: While our review is restricted to patients with essential hypertension, the agents studied here have been compared in large studies for related conditions such as congestive heart failure, ischemic heart disease, and chronic kidney disease. Trials

comparing ACEIs, ARBs, and direct renin inhibitors in these target conditions often report the outcomes of interest in this review. For evaluation of rarer events (e.g., mortality or angioedema) it may be worth combining data across target conditions. Future research should consider this strategy and evaluate the extent to which results differ across target condition.

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Abbreviations

ACE	Angiotensin-converting enzyme
ACEI(s)	Angiotensin-converting enzyme inhibitor(s)
AHRQ	Agency for Healthcare Research and Quality
ARB(s)	Angiotensin II receptor blocker(s)/antagonist(s)
AT_1	Angiotensin specific receptor
CER	Comparative Effectiveness Review
CRD	Centre for Reviews and Dissemination
DBP	Diastolic blood pressure
EF	Ejection fraction
EPC	Evidence-based Practice Centers
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HbA1c	Glycated hemoglobin
HCTZ	Hydrochlorothiazide
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MeSH	Medical Subject Headings
MI	Myocardial infarction
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SRC	Scientific Resource Center
TC	Total cholesterol
TG	Triglyceride
UAE	Urinary albumin excretion
USPSTF	U.S. Preventive Services Task Force