



Effective Health Care Program

Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update

Executive Summary

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 55 to 74 years old and approximately three-fourths of those age 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 people 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

Effective Health Care Program

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

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

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. Through 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, 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 differ significantly from 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 by an analysis conducted by the Southern California Evidence-based Practice Center. 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?

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?^{*f}

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.

* Please see footnotes on page 8

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

Key Question	Strength of Evidence	Conclusions
<p>Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes:</p>		
<p>a. Blood pressure control?</p>	<p>High (ACEI vs. ARB); Low or (DRI vs. ACEI ARB)</p>	<p>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 77 studies (70 RCTs, 5 nonrandomized controlled clinical trials, 1 retrospective cohort study, and 1 case-control study) in which 26,170 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.</p> <p>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 the ACEI ramipril (two studies) and no significant difference compared to the ARB losartan (one study).</p>
<p>b. Mortality and major cardiovascular events?</p>	<p>Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)</p>	<p>Due to low numbers of deaths or major cardiovascular events reported, it was difficult to discern any differential effect of ACEIs versus ARBs versus direct renin inhibitors with any certainty for these critical outcomes. In 21 studies that reported mortality, MI, or clinical stroke as outcomes among 38,589 subjects, 38 deaths and 13 strokes were reported. This may reflect low event rates among otherwise healthy patients and relatively few studies with extended followup.</p> <p>Only 3 of these 21 studies (including 1 death) evaluated direct renin inhibitors versus ACEIs or ARBs, and therefore the evidence to discern any differential effects between these drug classes on mortality and major cardiovascular events was insufficient.</p>
<p>c. Quality of life?</p>	<p>Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)</p>	<p>No differences were found between ACEIs and ARBs in measures of general quality of life; this is based on four studies, two of which did not provide quantitative data.</p> <p>No study evaluated the comparative effectiveness of direct renin inhibitors for quality-of-life outcomes.</p>

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for adults with essential hypertension (continued)

Key Question	Strength of Evidence	Conclusions
<p>Key Question 1. For adult patients with essential hypertension, how do ACEIs, ARBs, and direct renin inhibitors differ in the following health outcomes (continued):</p>		
<p>d. Rate of use of a single antihypertensive medication?</p>	<p>High (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)</p>	<p>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.</p> <p>There were no relevant studies evaluating direct renin inhibitors.</p>
<p>e. Risk factor reduction and other intermediate outcomes?</p>	<p>Lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease: Moderate (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)</p>	<p>There were no consistent differential effects of ACEIs, ARBs, 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.</p> <p>There were no studies that evaluated these outcomes in direct renin inhibitors.</p>
	<p>Progression to type 2 diabetes and LV mass/ function: Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)</p>	<p>There was no evidence for an impact of ACEIs, ARBs, or direct renin inhibitors on glucose or A1c, and no included studies evaluated 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, and only one study included evaluation of a direct renin inhibitor.</p>
<p>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?</p>	<p>Cough: High (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)</p>	<p>ACEIs have been consistently shown to be associated with greater risk of cough than ARBs (odds ratio 0.211; 95% CI 0.159 to 0.281). 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 0.2241 to 0.4933).</p>

Table A. Summary of evidence on comparative long-term benefits and harms of ACEIs, ARBs, and direct renin inhibitors for adults with essential hypertension (continued)

Key Question	Strength of Evidence	Conclusions
<p>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? (continued)</p>	<p>Withdrawals due to adverse events: High (ACEI vs. ARB); Low (DRI vs. ACEI or ARB)</p>	<p>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 an absolute difference in withdrawals of 2.3 percent (5.4% vs. 3.1%). 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.</p> <p>There was no evidence of differences across treatments in rates of other commonly reported specific adverse events.</p>
	<p>Angioedema: Low (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)</p>	<p>Although several studies collected data on angioedema, the event rates were very low or zero for all studies; this limited our ability to accurately characterize the frequency of angioedema. In the four studies that did report episodes of angioedema, this adverse event was observed only in patients treated with an ACEI (five patients from three studies) or a direct renin inhibitor (one patient in one study).</p>
	<p>Persistence with drug therapy/ treatment adherence: Moderate (ACEI vs. ARB); Insufficient (DRI vs. ACEI or ARB)</p>	<p>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 three included studies evaluating direct renin inhibitors did not find evidence of differences in treatment adherence compared with ACEIs or ARBs. Persistence was not evaluated in any of the studies including direct renin inhibitors.</p>
<p>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?</p>	<p>Insufficient (ACEI vs. ARB; DRI vs. ACEI or ARB)</p>	<p>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.</p>

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 importance of both ACEIs and ARBs for treatment of essential hypertension, there is little 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 1,000 patients treated with an ACEI, and 1 to 5 of every 10,000 of those treated with an ARB. Furthermore, others have reported a three- to fourfold increased risk of angioedema in African-American patients treated with an ACEI versus Caucasian patients treated with an ACEI. 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 conditions.

Full Report

This executive summary is part of the following document: Sanders GD, Coeytaux R, Dolor RJ, Hasselblad V, Patel UD, Powers B, Yancy WS Jr., Gray RN, Irvine RJ, Kendrick A. Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update. Comparative Effectiveness Review No. 34. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025.) AHRQ Publication No. 11-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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^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:

- Blood pressure control (we will prefer seated trough blood pressure, where reported).
- Mortality (all-cause, cardiovascular disease-specific, and cerebrovascular disease-specific).
- Morbidity (especially major cardiovascular events [myocardial infarction (MI), stroke] and measures of quality of life).
- Safety (focusing on serious adverse event rates, overall adverse event rates, and 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, low-density lipoprotein, total cholesterol, and triglycerides).
- 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 mass/function (left ventricular mass index and ejection fraction).
- Measures of kidney disease (creatinine/glomerular filtration rate [GFR], proteinuria)

^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 not limited to, weight gain, impaired renal function, angioedema, cough, and hyperkalemia.