Number 10

Effective Health Care

Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension

Executive Summary

Background

More than 65 million American adults—approximately one-third—have hypertension. The prevalence of hypertension increases with advancing age such that more than half of people 60-69 years of age and approximately three-fourths of those 70 years of age and older are affected. In addition to being the number one 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 morbidity and mortality attributable to hypertension, control 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)

Effective Health Care Program

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

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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. The primary site of renin release is the kidney, and release is 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; stimulates the adrenal cortex to release aldosterone, leading to increased sodium and water reabsorption and potassium excretion; promotes secretion of antidiuretic hormone, leading to fluid retention; stimulates thirst; promotes adrenergic function; and increases 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, therapies fall into one of two classes of angiotensin antagonists: the angiotensin-converting enzyme inhibitors (ACEIs) and the angiotensin II receptor antagonists (ARBs, or angiotensin receptor blockers). ACEIs block conversion of angiotensin I to angiotensin II. ARBs selectively inhibit angiotensin II from activating the angiotensin-specific receptor (AT_1).

While ACEIs and ARBs both target the renin system and are regarded by clinicians as effectively equivalent, it is not clear that this is appropriate. ACEIs, for example, do not entirely block production of angiotensin II because of the presence of unaffected converting enzymes. Also, ACEIs are associated with well-known adverse events not shared by ARBs, including cough (estimated incidence 5-20 percent) and the possibly related phenomenon of angioedema (estimated incidence 0.1-0.2 percent). It would be clinically useful to have a clear understanding of the state of the science with regard to the relative effectiveness of ACEIs and ARBs.

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

Key Question 1. For adult patients[1] with essential hypertension, how do ACEIs and ARBs[2] differ in blood pressure control, cardiovascular risk reduction, cardiovascular events, quality of life, and other outcomes?[3]

Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety,[4] adverse events,[5] tolerability, persistence, and adherence?

Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?

Conclusions

Summary 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 vs. ARBs for adults with essential hypertension.

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[1] "Adult patients" are defined as adults age 18 years or older.

[2] 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®).

[3] Outcomes considered include:

Intermediate outcomes—Blood pressure control; rate of use of a single antihypertensive agent for blood pressure control; lipid levels; progression to type 2 diabetes; markers of carbohydrate metabolism/diabetes control; measures of left ventricular (LV) mass/function; and measures of kidney disease.

Health outcomes—Mortality (all-cause mortality, cardiovascular disease-specific mortality, and cerebrovascular disease-specific mortality) and morbidity (cardiac events [myocardial infarction], heart failure, cerebral vascular disease or events [including stroke], symptomatic coronary artery disease, end stage renal disease, peripheral vascular disease, and quality of life).

[4] Safety outcomes considered were overall adverse events, withdrawals due to adverse events, serious adverse events reported, withdrawal rates, and switch rates.

[5] Specific adverse events included, but were no limited to, weight gain, impaired renal function, angioedema, and cough.

Summary Table A. Evidence on comparative long-term benefits and harms of ACEIs vs. ARBs for essential hypertension

Key question	Strength of evidence	Conclusions
1. Key Question 1. For adult patients with essential hypertension, how do ACEIs and ARBs 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 50 studies (47 RCTs, 1 nonrandomized controlled clinical trial, 1 retrospective cohort study, and 1 case-control study) in which 13,532 patients receiving an ACEI or an ARB were followed for periods from 12 weeks to 5 years (median 16.5 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols.
b. Mortality and major cardiovascular events	Moderate	Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it was not possible to discern any differential effect of ACEIs vs. ARBs for these critical outcomes. In 9 studies that reported mortality, MI, or clinical stroke as outcomes among 3,356 subjects, 16 deaths and 13 strokes were 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 4 studies, 2 of which did not provide quantitative data.
d. Rate of use of a single antihypertensive	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.
e. Risk factor reduction and other intermediate outcomes	Moderate (lipid levels, markers of carbohydrate metabolism/ diabetes control, progression of renal disease) to Low (progression to type 2 diabetes and LV mass/function)	There were no consistent differential effects of ACEIs vs. ARBs on several potentially important clinical outcomes, including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, measures of LV mass or function, and progression of renal disease (either based on creatinine, GFR, or proteinuria). Relatively few studies assessed these outcomes over the long term.

Summary Table A. Evidence on comparative long-term benefits and harms of ACEIs vs. ARBs for essential hypertension (continued)

Key question	Strength of evidence	Conclusions
2. Key Question 2. For adult patients with essential hypertension, how do ACEIs and ARBs differ in safety, adverse events, tolerability, persistence, and adherence?	High (cough, withdrawals due to adverse events) to Moderate (persistence/ adherence) to Low (angioedema)	ACEIs have been consistently shown to be associated with greater risk of cough than ARBs: pooled odds ratio (Peto) = 0.32. For RCTs, this translates to a difference in rates of cough of 6.7 percent (NNT = 15); however, for cohort studies with lower rates of cough, this translates to a difference of 1.1 percent (NNT = 87). This is generally consistent with evidence reviewed regarding withdrawals due to adverse events, in which the NNT is on the order of 27—that is, 1 more withdrawal per 27 patients treated with an ACEI vs. an ARB. There was no evidence of differences in rates of other commonly reported specific adverse events. Angioedema was reported only in patients treated with ACEIs; however, because angioedema was rarely explicitly reported in the included studies, it was not possible to estimate its frequency in this population. ACEIs and ARBs have similar rates of 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.
3. Key Question 3. Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups, sex), use of other medications concurrently, or comorbidities for which ACEIs or ARBs are more effective, associated with fewer adverse events, or better tolerated?	Very low	Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACEIs and ARBs for any particular patient subgroup.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker/antagonist; GFR = glomerular filtration rate; LV = left ventricular; MI = myocardial infarction; NNT = number needed to treat; RCT = randomized controlled trial.

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 data on adverse events are inconsistently reported. Only nine studies compared ACEIs and ARBs for periods longer than 1 year.

Future Research

With the exception of rates of cough, the hypothesis that ACEIs and ARBs 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 research in this area should consider:

- 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.

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.

Full Report

This executive summary is part of the following document: Matchar DB, McCrory DC, Orlando LA, Patel MR, Patel UD, Patwardhan MB, Powers B, Samsa GP, Gray RN. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension. Comparative Effectiveness Review No. 10. (Prepared by Duke Evidence-based Practice Center under Contract No. 290-02-0025.) Rockville, MD: Agency for Healthcare Research and Quality. November 2007. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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