Angiotensin-Converting Enzyme Inhibitors in Hypertension
To Use or Not to Use?

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ABSTRACT

Most guidelines for the management of patients with cardiovascular disease recommend angiotensin-converting enzyme (ACE) inhibitors as first-choice therapy, whereas angiotensin receptor blockers (ARBs) are merely considered an alternative for ACE inhibitor-intolerant patients. The aim of this review was to compare outcomes and adverse events between ACE inhibitors and ARBs in patients. In patients with hypertension and hypertension with compelling indications, we found no difference in efficacy between ARBs and ACE inhibitors with regard to the surrogate endpoint of blood pressure and outcomes of all-cause mortality, cardiovascular mortality, myocardial infarction, heart failure, stroke, and end-stage renal disease. However, ACE inhibitors remain associated with cough and a very low risk of angioedema and fatalities. Overall withdrawal rates because of adverse events are lower with ARBs than with ACE inhibitors. Given the equal outcome efficacy but fewer adverse events with ARBs, risk-to-benefit analysis in aggregate indicates that at present there is little, if any, reason to use ACE inhibitors for the treatment of hypertension or its compelling indications. (J Am Coll Cardiol 2018;71:1474–82) © 2018 by the American College of Cardiology Foundation.

The human understanding, once it has adopted opinions, either because they were already accepted and believed, or because it likes them, draws everything else to support and agree with them. And though it may meet a greater number and weight of contrary instances, it will, with great and harmful prejudice, ignore or condemn or exclude them by introducing some distinction, in order that the authority of those earlier assumptions may remain intact and unharmed.

—Francis Bacon, Novum Organum, 1620 (1)

Ever since captopril, the first angiotensin-converting enzyme (ACE) inhibitor, became available in 1981, this drug class has been extensively used in a variety of cardiovascular (CV) diseases. Losartan, the first angiotensin receptor blocker (ARB), was launched in 1995, more than a dozen years after the introduction of the ACE inhibitor captopril. Both ACE inhibitors and ARBs are commonly used in patients with hypertension, heart failure, coronary artery disease, diabetes, and chronic kidney disease (CKD). However, many American and European guidelines for the management of patients with CV
disease recommended ACE inhibitors as a first-choice therapy, whereas ARBs were merely considered alternative therapy for ACE inhibitor-intolerant patients. In the following review, we compare the efficacy and safety of the 2 drug classes (which are now mostly generic) for the treatment of hypertension and hypertension associated with what has been called compelling indications.

MECHANISM OF ACTION

The mechanism of action of ACE inhibitors and ARBs is both similar and different. Although both classes of drugs act on the renin-angiotensin-aldosterone system, ACE inhibitors inhibit the formation of angiotensin II and consequently the downstream effects through the angiotensin II type 1 (AT1) receptor (vasoconstriction, cell growth, sodium and water retention, sympathetic activation) and the angiotensin II type 2 (AT2) receptor. One disadvantage of ACE inhibitors is that the presence of non-ACE pathways results in continued low-level production of angiotensin II despite the inhibition of ACE (Figures 1A and 1B). However, the nonselective inhibition of angiotensin receptors has been shown to be beneficial because the effect of angiotensin II through the AT2 receptor may result in incremental vasodilation and antiproliferative activity. Other investigators maintain that the purported beneficial effects of ACE inhibitors over ARBs are caused by their action to inhibit the breakdown of bradykinin and thereby increase circulating bradykinin levels. Although bradykinin is implicated in the pathogenesis of ACE inhibitor-induced cough and angioedema, it has also been shown to mediate vasodilation incrementally (2). Additionally, bradykinin levels release nitric oxide as well as increase synthesis of vasoactive prostaglandins (3,4). In contrast, ARBs were specifically designed to displace angiotensin II from the AT1 receptor. By facilitating stimulation of the AT2 receptor, ARBs may additionally trigger vasodilation and natriuresis. However, this ARB-associated autocrine cascade with bradykinin, nitric oxide, and vasoactive prostaglandins is clinically considerably less important than that occurring with ACE inhibitors (4).

SURROGATE ENDPOINT: BLOOD PRESSURE REDUCTION. No clinically meaningful difference in antihypertensive efficacy has been shown between the classes of renin-angiotensin system blockers (5). In fact, meta-analyses of clinical trials suggest numerically greater reductions in office systolic and diastolic blood pressure (BP) with ARBs when compared with ACE inhibitors (Figure 2) (6-8). When using ambulatory BP measurements, the BP-lowering efficacy of ARBs is similar or numerically higher than that of ACE inhibitors (Figure 3) (9). Although within the same class the BP-lowering efficacy of various ARBs and ACE inhibitors differs, recent randomized trials have shown superior efficacy (office systolic BP reduction of 20.6 mm Hg vs. 12.2 mm Hg; p < 0.001) with azilsartan compared with ramipril (10). Similar superior reduction in central systolic BP with olmesartan when compared with perindopril (~13.72 mm Hg vs. ~10.21 mm Hg) was seen even when these drugs were used in combination with amiodipine in the SEVITENSION (Sevikar Compared to the Combination of Perindopril Plus Amlodipine on Central Arterial Blood Pressure in Patients With Moderate-to-Severe Hypertension) study (11). Even when compared as monotherapy in older patients, olmesartan provided more effective and sustained 24-h BP control than did ramipril (12). In a meta-analysis of 354 randomized trials by Law et al. (13), dose-response analysis among antihypertensive drug classes showed that ARBs had numerically higher reductions in office systolic BP compared with ACE inhibitors (Figure 4) shows that a reduction of 10 mm Hg occurred with a standard ARB dose, whereas the same reduction required almost twice the standard ACE inhibitor dose.

TARGET ORGANS: LEFT VENTRICULAR HYPERTROPHY AND PROTEINURIA

In a meta-analysis of 80 trials with 146 active treatment arms and 17 placebo arms, adjusted for treatment duration and change in diastolic BP, there was a numerically better decrease in left ventricular mass index with ARBs by 13% than with ACE inhibitors by 10%, although the difference was not statistically significant (14). Urinary protein excretion was similarly reduced by ACE inhibitors and ARBs in another meta-analysis of 17 randomized controlled trials including 17,951 patients (15).

COMPARISON OF OUTCOMES

PATIENTS WITHOUT HEART FAILURE. In hypertension, there is no prospective randomized controlled trial that shows a morbidity or mortality reduction with ACE inhibitors or ARBs against placebo. The HOPE (Heart Outcomes Prevention Evaluation) (16) study provided outstanding evidence of ramipril efficacy in patients at high risk of CV events, but it cannot truly be considered a study in hypertension (hypertension was present in ~47% of patients at baseline). Similarly, CAMELOT (Comparison of
Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (17), in which enalapril was not better than placebo, was not designed as a hypertension trial (mean systolic BP at baseline of 129 mm Hg). In ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (18), there were no differences in the primary endpoint among lisinopril, chlorthalidone, and amlodipine, but the trial had no placebo arm.

In the propensity score-adjusted REACH (Reduction of Atherothrombosis for Continued Health) (19) cohort of 40,625 patients (91% with hypertension) (ACE inhibitors 67.9% and ARBs 32.1%), the incidence of the primary outcome, a composite of CV mortality, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for CV reasons, was lower in patients taking ARBs compared with patients taking ACE inhibitors (29.2% vs. 33.4%; adjusted hazard ratio [HR]: 0.90; 95% confidence interval [CI]: 0.86 to 0.95; p < 0.001) during the 4-year follow-up. Similar results were observed for CV mortality (6.9% vs. 8.2%; HR: 0.83; 95% CI: 0.75 to 0.93; p = 0.001) and all-cause mortality (11.6% vs. 12.6%; HR: 0.89; 95% CI: 0.82 to 0.97; p = 0.005). In a Cochrane meta-analysis of 9 randomized trials and 11,007 participants with primary hypertension (20), no differences between ACE inhibitors and ARBs were seen for all-cause mortality (relative risk [RR]: 0.98; 95% CI: 0.88 to 1.10), total CV events (RR: 1.07; 95% CI: 0.78 to 1.08), or CV mortality (RR: 0.98; 95% CI: 0.85 to 1.13). Moreover, in our comprehensive meta-analysis of 106 randomized trials with 254,301 patients without heart failure, evidence from placebo-controlled trials (restricted to trials after 2000), active controlled trials, and head-to-head randomized trials suggested that ARBs were as efficacious and safe as ACE inhibitors (21) (Figure 4, Central Illustration). Similarly, in a network meta-analysis of randomized trials of patients at high CV risk but without heart failure, ARBs were similar to ACE inhibitors in preventing the composite endpoint of CV death, MI, and stroke (RR: 0.92; 95% CI: 0.78 to 1.08) (22). Compared with ARBs, there was no evidence of statistical superiority for ACE inhibitors in preventing incident risk of all-cause death, CV death, MI, stroke, new-onset diabetes mellitus, and new-onset heart failure (22). Thus, the data in aggregate attest to equal efficacy of ARBs and ACE inhibitors in reducing outcomes in patients with hypertension or in patients at high risk of CV events.

**COMPELLING INDICATIONS.** Patients with coronary artery disease. In patients with coronary artery disease and preserved left ventricular systolic function, the superiority of ACE inhibitors over ARBs remains to be proven. In fact, in the CAMELOT (17) trial of patients with coronary artery disease, enalapril was inferior to amlodipine and not better than placebo. We also found that only indirect comparisons formed the basis of the so-called myocardial infarction paradox (i.e., that ARBs may increase the risk of MI). This concept ignored the wealth of solid data from direct head-to-head trials (23), which invariably lead us to the conclusion that ARBs reduce CV events, including the risk of MI, as effectively as but more safely than ACE inhibitors (24).
Patients with heart failure. In contrast to hypertension, in heart failure ACE inhibitors and ARBs have been compared with placebo in multiple clinical trials. CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) (25) showed an impressive 31% reduction in mortality at 1 year in patients with severe heart failure who were treated with enalapril when compared with placebo. In the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) trial program, candesartan was either added to ACE inhibitors (CHARM-Added) (26) or substituted when ACE inhibitors were not tolerated (CHARM-Alternative) (27). In both trials candesartan reduced each of the components of the primary outcome significantly, as well as the total number of hospital admissions for heart failure.

A recent network meta-analysis showed that treatment with ACE inhibitors, ARBs, beta-blockers, mineralocorticoid antagonists, and angiotensin receptor-neprilysin inhibitor and their combinations were better than treatment with placebo in reducing all-cause mortality rates (28). In comparison with placebo, ACE inhibitor use was associated with a 16% reduction in mortality, whereas the combination of ACE inhibitors, beta-blockers, and mineralocorticoid antagonists was associated with a 56% reduction in mortality compared with placebo (28). ACE inhibitor-based therapy was superior to placebo for all-cause mortality, whereas ARB-based therapy was not. However, the data on ACE inhibitors versus placebo used 4 times more patient-years as their basis than did the data on ARBs (23,293.2 vs. 5,880.3 patient-years). Moreover, in the same meta-analysis, there was no difference between ACE inhibitors and ARBs for all-cause mortality (RR: 0.94; 95% CI: 0.68 to 1.29). Packer and McMurray (29) attributed the heightened efficacy of ACE inhibitors to endogenous compensatory vasoactive peptides that are operative in ACE inhibitors but not in ARBs. This action could result in what these investigators called “broadening the benefits of inhibitors of the renin-angiotensin system in patients with heart failure by potentiation of endogenous vasoactive peptides” (29). Of note, this effect seems to be much more pronounced with valsartan and sacubitril than with ACE inhibitors and may be particularly helpful in treatment of residual hypertension in heart failure (30).

Patients with chronic kidney disease. In >17,000 patients at high vascular risk from ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial), the effect of telmisartan on major renal outcomes (composite of dialysis, doubling of serum creatinine, and death) was similar to that of ramipril (31).

Estimated glomerular filtration rate declined less with ramipril compared with telmisartan (−2.82 ± 17.2 ml/min/1.73 m² vs. −4.12 ± 17.4 ml/min/1.73 m²; p < 0.0001), although the rates of renal impairment

Reductions in systolic (blue bars) and diastolic (orange bars) blood pressure (BP) for angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and direct renin inhibitors (DRIs) compared with other antihypertensive agents. Angiotensin receptor blockers showed the highest reduction in systolic and diastolic blood pressure compared with angiotensin-converting enzyme inhibitors and direct renin inhibitors. Data from the Cochrane meta-analyses of Musini et al. (6) and Heran et al. (7,8).
mortality rates than in ARBs users. This finding was true in all patients (HR: 1.17; 95% CI: 1.07 to 1.27; p = 0.03) and in a subgroup of diabetic patients (HR: 1.32; 95% CI: 1.18 to 1.48; p = 0.03) (33).

**Patients with diabetes.** In a prospective, multicenter, double-blind, 5-year study of 250 subjects with type 2 diabetes and early nephropathy, Barnett et al. (34) found telmisartan not inferior to enalapril in providing long-term renoprotection. In addition, the effects of the 2 agents on the secondary endpoints were not significantly different after 5 years. Similarly, in a network meta-analysis of 71 trials with 103,120 diabetic participants, no significant differences were documented between ACE inhibitors and ARBs with respect to all-cause mortality, CV mortality, MI, stroke, angina pectoris, hospitalization for heart failure, end-stage renal disease, or doubling of serum creatinine levels (35). In the REACH cohort ARBs were superior to ACE inhibitors in reducing the primary outcome regardless of diabetes history (19).

**Patients with cerebrovascular disease.** In TRANSCEND (Telmisartan Randomised AssessmeNt Study in ACE iNtolerant Subjects with cardiovascular Disease) (36), telmisartan in patients unable to tolerate ACE inhibitors had no significant effect on the primary outcome. However, this drug modestly reduced the risk of the composite outcome of CV death, MI, or stroke. In the multicenter PROFeSS (Prevention Regimen For Effectively Avoiding Second Strokes) trial (37) involving 20,332 patients, therapy with telmisartan initiated soon after an ischemic stroke and continued for 2.5 years did not significantly lower the rate of recurrent stroke, major CV events, or diabetes. Most meta-analyses, as well as REACH cohort data, showed no difference in stroke rates between ARBs and ACE inhibitors in head-to-head comparisons. In our recent meta-analysis in older patients (>65 years old) with predominantly systolic hypertension, ACE inhibitors reduced CV outcomes compared with placebo, but the drugs notably failed to prevent stroke (38).

**SAFETY AND ADVERSE EVENTS.** ACE inhibitors are well tolerated in general, with a dry, irritating cough being their most common adverse effect. However, when compared with ARBs, ACE inhibitors have several-fold higher incidence of side effects at most doses (13), with a dry, irritating cough being the most common. In our meta-analysis of 125 studies including 198,130 patients, the pooled weighted incidence of cough for enalapril was found to be 11.48% (95% CI: 9.54% to 13.41%) (39). The pooled weighted withdrawal rate resulting from cough for enalapril was 2.57% (95% CI: 2.40% to 2.74%). However, the prevalence of cough in Asian patients is
more than 2.5 times higher than in Caucasian patients, and withdrawal rates exceed 30% (40,41). For this reason, many Asian physicians are no longer prescribing ACE inhibitors. In a recent nationwide cross-sectional survey of antihypertensive drug classes in China (42), ARBs were used more than twice as often as ACE inhibitors. A much less common adverse event of ACE inhibitor therapy is angioedema, which is most prevalent in black patients of African origin and occasionally can be fatal. In 26 trials with 74,857 patients, we found the weighted incidence of angioedema with ACE inhibitors to be 0.30% (95% CI: 0.28% to 0.32%) (43). Angioedema affects about 1 in 2,500 patients during the first week of exposure (44-46). However, it can first appear from a few hours to 8 years after an ACE inhibitor is initiated (36). The subsequent incidence of angioedema with ACE inhibitors is around 1 in 500 patients/year (46). Banerji et al. (47) recently showed that among 134,945 patients who were prescribed an ACE inhibitor, 0.7% (n = 888) developed angioedema during the subsequent 5 years. In this study, there was a 0.07% incidence of angioedema within 1 month of prescription of an ACE inhibitor and a 0.23% incidence during the first year. Thereafter, the annual incidence of angioedema was relatively constant over the subsequent 4 years (0.10% to 0.12%) (47). In the prospective OCTAVE (Omapatrilat Cardiovascular Treatment vs. Enalapril) study (48) of 12,557 patients, the overall prevalence of angioedema associated with
enalapril was 0.68%. Among all instances of angioedema, about 20% of cases are life-threatening, affecting the larynx and upper respiratory tract (49). Among these, about 20% of cases are fatal unless the patient is intubated (50,51). An autopsy study from Columbus, Ohio reported 7 fatalities, all in African Americans, between 1998 and 2000 caused by ACE inhibitor-induced angioedema (52). Because antihypertensive efficacy is also diminished, there is no good clinical reason to initiate therapy with ACE inhibitors in black patients.

When compared with placebo in a Cochrane meta-analysis (7), the pooled estimate of withdrawal rates resulting from adverse events (WDAEs) for all doses resulted in a statistically nonsignificant RR of 0.85 (95% CI: 0.67 to 1.07) (7). In contrast, for ARBs when all doses were pooled, there was a statistically significant reduction in WDAEs compared with placebo (RR: 0.68; 95% CI: 0.54 to 0.87) (8). This finding would indicate that independent of the dose, WDAEs of ARBs are 32% lower than WDAEs of placebo. In other words, in contrast to ACE inhibitors, ARBs are better tolerated than placebo. In our meta-analysis of head-to-head randomized trials of ACE inhibitors vs. ARBs in patients without heart failure, there was a lower risk of drug WDAEs with ARBs (RR: 0.72; 95% CI: 0.65 to 0.81) (21). Thomopoulos et al. (53) found that, compared with placebo, ACE inhibitors, and not ARBs, significantly increased discontinuation rates for adverse events (RR: 2.78; 95% CI: 1.37 to 5.47). Similarly, in randomized head-to-head comparison trials, ARBs were the only class associated with a significantly lower risk of adverse events (RR: 0.71; 95% CI: 0.58 to 0.87) compared with other drug classes (53).

**COST AND PRACTICAL CONSIDERATIONS**

In the past, the main argument against using ARBs was that they were not available in a generic formulation. As of today most if not all ACE inhibitors and ARBs are available as generic formulations; thus acquisition cost should not tip the scale in favor of 1 class or the other. However, even among generic formulations there are distinct cost differences among formularies and from country to country. Moreover, many fixed drug combinations of both ACE inhibitors and ARBs with thiazides and amlodipine are at hand in most countries, thereby allowing simplification of the therapeutic regimen.

**DISCUSSION**

The foregoing data establish that in terms of efficacy there is little, if any, difference between ACE inhibitors and ARBs. This holds true for the surrogate endpoint of BP, as well as for outcomes such as stroke, coronary artery disease, and CV and all-cause mortality. Head-to-head comparison trials are the only iron-clad way to compare the efficacy and safety of 2 drug classes objectively and to test whether the ARB MI paradox really holds true. In patients without heart failure, we found no significant difference in any of the CV efficacy outcomes between ACE inhibitors and ARBs, a finding that is consistent with data from recent placebo-controlled trials and from active controlled trials. The perceived differences between ACE inhibitors and ARBs mostly reflect the so-called generation gap between the 2 sets of trials (Table 1). Concomitant statin therapy was distinctly less common in ACE inhibitor trials than in ARB trials. For instance, in the 2 studies with the same principal investigator, statin use doubled over a period of 8 years: in ONTARGET it was 61%, and in HOPE it was 29% (16,54). Conceivably, in patients with heart failure the vasoactive peptides of ACE inhibitors may provide modest incremental benefits, although the evidence for such benefits is unsubstantiated (29).

In terms of safety, there is no question that ARBs are better tolerated than are ACE inhibitors. In head-to-head comparisons withdrawal rates with ARBs were 22% lower than with ACE inhibitors (20). This number can be expected to differ even more in favor of ARBs in Asian patients. Although ACE inhibitor-related cough is not dose dependent (13) and is considered merely a nuisance adverse event, it invariably triggers a telephone call to the prescribing physician or may necessitate an additional visit and/or additional tests. With the prescription of an ARB instead of an ACE inhibitor, both events can be avoided. The fact that in a Cochrane analysis (8) withdrawal rates of ARBs were 32% lower than with placebo merely reflects the fact that hypertensive CV
Disease is not an entirely silent clinical entity. It can be associated with nonspecific symptoms such as headache, fatigue, dizziness, impaired exercise capacity, and sexual dysfunction. Hansson et al. (55) documented in 7 randomized, double-blind, placebo-controlled trials, in which 2,673 patients with mild to moderate hypertension were randomized to the ARB irbesartan or placebo, that ARB use was associated with a significant reduction in the incidence of headache (p = 0.003). These data suggest that nonspecific symptoms occurring with hypertension such as headache can be reduced by antihypertensive treatment with a favorable adverse effect profile.

As documented earlier, angioedema is a very rare adverse event of ACE inhibitors. However, because 20 to 30 million patients are taking these drugs worldwide, use of ACE inhibitors could result in several hundred fatalities per year (46). Admittedly some of the foregoing numbers are extrapolations, but they still beg the question whether ACE inhibitors remain acceptable at all, not only for the treatment of hypertension but also as ingredients in polypills (56).

**CONCLUSIONS**

In patients with hypertension and hypertension with compelling indications, there is no difference in efficacy between ARBs and ACE inhibitors with regard to the surrogate endpoint of BP and the outcomes of all-cause mortality, CV mortality, MI, heart failure, stroke, and end-stage renal disease. ACE inhibitors are associated with cough and very low risks of angioedema and fatalities that are more prevalent in dark-skinned people. Overall, rates of WDAEs are significantly lower with ARBs than with ACE inhibitors. Because efficacy is similar but adverse events are fewer with ARBs, risk-to-benefit analysis in aggregate indicates that at present there is little, if any, clinical reason to use ACE inhibitors for the treatment of hypertension and so-called compelling indications.

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