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# ACE inhibitors vs ARBs: Is one class better for heart failure?

## ABSTRACT

Although angiotensin-converting enzyme (ACE) inhibitors decrease mortality in heart failure, they incompletely suppress angiotensin II with long-term therapy. Since angiotensin receptor blockers (ARBs) block the biologic effects of angiotensin II more completely than ACE inhibitors, they could be beneficial in the treatment of heart failure.

## KEY POINTS

In the ELITE-II trial, the ARB losartan was found to have no mortality benefit over the ACE inhibitor captopril. Thus, ACE inhibitors should remain first-line treatment for heart failure.

For patients who truly cannot tolerate an ACE inhibitor, ARBs are reasonable substitutes and provide excellent tolerability.

For patients taking an ACE inhibitor but not a beta-blocker, it would be better to add a beta-blocker to the regimen rather than an ARB, since multiple studies have shown a mortality benefit in heart failure patients taking beta-blockers.

The CHARM study will help to delineate the use of ARBs either instead of or in addition to an ACE inhibitor in patients with heart failure.

A 65-YEAR-OLD MAN presents to your office with increasing dyspnea on exertion. He has had hypertension and diabetes for many years, and heart failure was diagnosed 2 years ago. At that time he tried taking an angiotensin-converting enzyme (ACE) inhibitor but developed a cough, so it was stopped.

The patient's medical regimen includes:

- Furosemide 40 mg twice a day
- Digoxin 0.1 mg daily
- Amlodipine 5 mg daily
- Glyburide 5 mg twice a day.

A recent echocardiogram showed left ventricular hypertrophy, left atrial enlargement, trace mitral regurgitation, an ejection fraction of 30% to 35%, and evidence of diastolic dysfunction.

The patient also recently underwent an exercise test (8.5 metabolic equivalents), which revealed ST-segment changes that were not interpretable due to the presence of digoxin, and no evidence of ischemia on radionuclide imaging.

On physical examination, the patient's blood pressure is 120/80 mm Hg, heart rate 90, and jugular venous pressure 10 to 12 cm. His lungs are clear to auscultation and percussion, and he has normal $S_1$ and $S_2$ heart sounds. However, he has an $S_4$, a grade 2/6 systolic murmur at the apex radiating to the axilla, and trace pedal edema.

An electrocardiogram shows normal sinus rhythm with left ventricular hypertrophy.

**What should be the next step?**

- Increase his furosemide dose to 80 mg twice a day?
- Begin treatment with an angiotensin receptor blocker (ARB)?
- Try reinstituting an ACE inhibitor?
- Begin low-dose beta-blocker therapy?

*The author has indicated that he serves as a consultant for and is on the speakers' bureau of the Astra-Zeneca corporation. This paper discusses therapies that are not approved by the US Food and Drug Administration for the use under discussion.

**TABLE 1**

**Currently approved ACE inhibitors and ARBs**

**ACE inhibitors**

- Benazepril (Lotensin)
- Captopril (Capoten)*
- Enalapril (Vasotec)*
- Fosinopril (Monopril)*
- Lisinopril (Prinivil, Zestril)*
- Moexipril (Univasc)
- Quinipril (Accupril)*
- Ramipril (Altace)†
- Trandolapril (Mavik)†

**ARBs**

- Candesartan (Atacand)
- Eprosartan (Teveten)
- Irbesartan (Avapro)
- Losartan (Cozaar)
- Telmisartan (Micardis)
- Valsartan (Diovan)

*Approved by the US Food and Drug Administration for the treatment of heart failure

†Approved by the US Food and Drug Administration for the treatment of heart failure after a myocardial infarction

**Many eligible patients do not get ACE inhibitors or are on low doses**

## CAN ARBs BE USED IN HEART FAILURE?

With the recent introduction of ARBs (TABLE 1), physicians are wondering if these agents can be used in heart failure, either as alternatives to ACE inhibitors or as additions to the regimen.

Before answering the question posed in this case, it is helpful to understand some of the basic mechanisms involved and information from recent clinical trials using ARBs. To determine if they have a role in treating heart failure, we will discuss the rationale for their use, their effects on the renin-angiotensin system, and the clinical data.

## ROOM FOR IMPROVEMENT IN HEART FAILURE TREATMENT

Multiple studies showed that ACE inhibitors decrease the mortality rate in patients with heart failure. However, many patients with heart failure still are not receiving this therapy or are receiving inadequate doses. The reasons include lack of information about the indications for these drugs and concerns about their side effects, including cough, hypotension, hyperkalemia, and renal dysfunction.

Moreover, despite the proven benefits of therapy with ACE inhibitors and beta-blockers for heart failure, the mortality rate remains high, with approximately 50% of patients dead at 5 years.[1]

## THE RENIN-ANGIOTENSIN SYSTEM IN HEART FAILURE

Several neurohormonal systems are activated in the syndromes of hypertension and heart failure. And in a vicious cycle, several of these systems contribute directly to the progression of the disease, particularly the sympathetic nervous system and the renin-angiotensin-aldosterone system.

Activation of the renin-angiotensin-aldosterone system begins when reduced renal blood flow and reduced sodium delivery to the distal tubule lead to renin release, which is exacerbated further by increased sympathetic tone.[2]

Angiotensin II, the end product of the system, is a potent vasoconstrictor that serves to increase peripheral vascular resistance and maintain arterial tone in the face of reduced cardiac output.[3] It also enhances release of catecholamines from noradrenergic nerve endings[4] and directly stimulates the adrenal cortex to increase secretion of aldosterone.[5] On the cellular level, angiotensin II promotes the production of growth factors and migration, proliferation, and hypertrophy of vascular smooth muscle cells and cardiac fibroblasts.[6,7]

While these mechanisms serve initially to maintain cardiac output, over time they become maladaptive and lead to progression of heart failure.

## PROBLEMS WITH ACE INHIBITORS

ACE inhibitors, the most commonly used antagonists of the renin-angiotensin-aldosterone system, have been shown to improve

the prognosis of patients with left ventricular dysfunction and chronic heart failure.[8–12] Despite this benefit, however, left ventricular dysfunction continues to progress in most patients with heart failure.

A problem with ACE inhibitors is that they do not block angiotensin II production completely. Evidence suggests that much production of angiotensin II takes place by non-ACE pathways both systemically and at the tissue level in the heart and vasculature.[13] These alternative pathways include direct formation from angiotensinogen, cathepsin G, and tissue plasminogen activator.[14] Angiotensin I also can be converted to angiotensin II at the tissue level by chymase and cathepsin G.[15,16] Underscoring the importance of these local pathways is the fact that tissue levels of angiotensin II are nearly 1,000 times greater than levels in the circulation.[17]

ACE inhibitors have no effect on angiotensin II formed by these alternate pathways. In contrast, ARBs inhibit the biologic effects of angiotensin II more completely than ACE inhibitors, since they block the pathway more distally at the level of the receptor, whether the angiotensin II is formed by ACE or non-ACE-mediated pathways.

Another problem is that many patients—up to 20%—cannot tolerate ACE inhibitors.[18]

## CLINICAL BENEFITS OF ARBs

### ARBs are better tolerated

The use of ARBs has been proposed for patients who cannot tolerate ACE inhibitors, as ARBs appear to be better tolerated. Adverse effects of ARBs are less frequent than with ACE inhibitors.[19] For example, the incidence of cough with ARBs is similar to that with placebo,[18,20] and significantly less than with ACE inhibitors.[21]

**The SPICE trial** (Study of Patients Intolerant of Converting Enzyme Inhibitors)[22] evaluated the tolerability of candesartan in patients with heart failure, left ventricular systolic dysfunction, and a history of intolerance to ACE inhibitors. Nearly 83% of patients completed the 12-week treatment with candesartan, similar to the percentage of patients who completed the treatment with placebo.

### ARBs improve exercise tolerance

Several studies examined the effects of ARBs on exercise tolerance and symptoms in patients with heart failure. These results suggest that short-term ARB therapy is comparable to ACE inhibition in its effects on exercise tolerance and symptoms of heart failure.

**The STRETCH trial** (Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure)[23] included 844 patients with mild-to-moderate heart failure who, in a double-blind protocol, received either placebo or candesartan 4 mg, 8 mg, or 16 mg daily for 12 weeks. New York Heart Association (NYHA) functional class and dyspnea fatigue index scores improved in all three candesartan groups. Increases in total exercise time were dose-related.

**The Losartan Pilot Exercise Study**[24] showed losartan to be comparable to enalapril in terms of exercise tolerance over a 12-week period in patients with heart failure.

**Havranek et al**[25] found irbesartan to improve exercise tolerance to a magnitude similar to that of an ACE inhibitor.

### ARBs vs ACE inhibitors: Effects on morbidity and mortality

**The ELITE-I study** (Evaluation of Losartan In The Elderly)[26] was one of the first clinical trials to examine the role of ARBs in heart failure. In this randomized trial, 722 patients received either losartan titrated to 50 mg once daily or captopril titrated to 50 mg three times daily for 48 weeks.

The study showed no difference between groups in renal dysfunction, the primary endpoint for the study. However, the mortality rate was lower in the losartan group than in the captopril group (4.8% vs 8.7%). This finding paved the way for further mortality trials of ARBs in heart failure.

**ELITE-I**[27] was a double-blind, randomized, controlled trial in which 3,152 patients received either losartan 50 mg once daily or captopril 50 mg three times a day. The primary end point was all-cause mortality. In contrast to ELITE-I, no improvement in survival was found with losartan compared with captopril; in fact, the mortality rate was higher in the losartan group than in the captopril group (17.7% vs 15.9%).

**Much angiotensin II production is by non-ACE pathways**

These findings suggested that ACE inhibitors should remain first-line therapy for patients with heart failure and left ventricular systolic dysfunction. However, since losartan was better tolerated than captopril, it suggested as well that ARBs could be considered in patients who cannot tolerate ACE inhibitors.

## COMBINATION THERAPY WITH ACE INHIBITORS AND ARBs

### Combination therapy improves exercise tolerance

Several studies evaluated the effect of combination therapy on exercise tolerance and symptoms in heart failure.

**Hamroff et al**[28] randomized patients with severe congestive heart failure who were receiving an ACE inhibitor in maximal doses to receive either placebo or losartan 50 mg daily, with evaluations of peak aerobic capacity and NYHA class at 0, 3, and 6 months. The losartan group had a significant improvement in peak aerobic capacity and alleviation of their symptoms.

**The RESOLVD pilot study** (Randomized Evaluation of Strategies for Left Ventricular Dysfunction)[29] included 768 patients who were randomized to receive either candesartan, candesartan plus enalapril, or enalapril alone for 43 weeks.

**In mild fluid overload, resist the temptation to increase the diuretic immediately**

At the end of the study there was no difference among the groups in NYHA functional class, quality of life, or 6-minute walking distance. There was, however, a trend towards a higher ejection fraction in the candesartan-plus-enalapril group compared with the groups receiving either therapy alone. There also was a significant benefit with combination therapy in blood pressure control and less of an increase in end-diastolic volume and end-systolic volume. The investigators concluded that most patients tolerated combination therapy, and that there may be some benefits to using it.

### Effect on morbidity and mortality

**Val-HeFT** (the Valsartan Heart Failure Trial)[30] aimed to determine if there is a clinical benefit to adding an ARB (valsartan 40 mg twice a day titrated to 160 mg twice a day) to an ACE inhibitor in 5,010 patients with heart failure. Patients were also receiving diuretics, digoxin, and beta-blockers. The primary end points were time to death and combined all-cause morbidity and mortality. The mean duration of follow-up was 23 months.

The trial found no difference in all-cause mortality: 19.7% in the valsartan group vs 19.4% in the placebo group. However, there was a significant 13.3% risk reduction in the combined end point of all-cause mortality and morbidity in the valsartan group. This difference was almost entirely due to a reduction in the number of hospitalizations for heart failure, with a 27.5% risk reduction for heart failure hospitalizations in the valsartan group compared with placebo. Beneficial effects also were seen in a number of secondary end points, including NYHA class, ejection fraction, and quality-of-life measurements.

**The CHARM study** (Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality)[31] should further delineate the role of ARBs in heart failure. This multicenter, randomized, placebo-controlled trial has enrolled 7,601 patients with NYHA class II to IV heart failure, and includes patients with ejection fractions both greater than and less than 40%. The group with an ejection fraction lower than 40% is divided into ACE inhibitor (combination)-treated and ACE inhibitor-intolerant groups, and each of these groups has been randomized to receive either candesartan or placebo. All patients will be followed for 42 months, and the primary overall end point is all-cause mortality. The trial is scheduled to finish in 2003.

## CASE DISCUSSION

In the case presented, the patient's medical regimen includes no therapy shown to prevent progression of his disease, which already has progressed from hypertension to moderate left ventricular dysfunction.

Although this patient shows signs and symptoms of mild fluid overload, the temptation to increase the diuretic dose immediately should be avoided: although this might relieve symptoms temporarily, it will lead to further activation of the renin-angiotensin-aldosterone system.

This would not be the optimal time to begin a beta-blocker, since the patient is not yet on therapy aimed at inhibiting the renin-angiotensin-aldosterone system, and the benefit of beta-blockade in patients with heart failure appears to be greatest in the presence of a renin-angiotensin-aldosterone inhibitor.

This leaves the choice of either beginning an ARB or trying to restart an ACE inhibitor. While ARBs are reasonable for patients who truly cannot tolerate ACE inhibitors, this patient may not have been given an ample opportunity for demonstrating intolerance to the ACE inhibitor. Many patients develop a cough from pulmonary congestion due to the underlying disease process, so a cough in a patient with heart failure may not in fact be due to the ACE inhibitor.

Given the proven benefit of ACE inhibitors in patients with left ventricular dysfunction (with or without symptoms of heart failure), and the lack of evidence showing a benefit of ARBs over ACE inhibitors, the best course of action for the patient presented would be to try reinstituting an ACE inhibitor.

If the cough develops again and is too severe for the patient to tolerate, then the ACE inhibitor should be stopped and an ARB should be started, after which a beta-blocker should be started.

While the Prospective Randomized Amlodipine Survival Evaluation Study Group (PRAISE) trial[32] showed that amlodipine can be used safely in patients with heart failure, it should be continued only if the patient remains hypertensive following titration of the renin-angiotensin-aldosterone inhibitor and beta-blocker to maximal doses.

Since the major benefit of combination therapy with ACE inhibitors and ARBs appears to be in reducing hospitalizations, and this patient has yet to show a problem with heart failure hospitalizations, there is no strong indication to combine the two agents in this patient.

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