Should Angiotensin Receptor Blockers Be Added to Angiotensin-Converting Enzyme Inhibitors in the Treatment of Heart Failure?

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Angiotensin-converting enzyme (ACE) inhibitors have been the cornerstone of treatment of heart failure. Angiotensin receptor blockers (ARBs) remain an attractive alternative in heart failure patients intolerant of ACE inhibitors. The addition of ARBs to ACE inhibitors in the context of stable heart failure may lead to additional clinical benefits. This is in contrast to heart failure complicating acute myocardial infarction, in which it does not offer any therapeutic advantage.
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Key words: Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers • Heart failure • Renin-angiotensin system

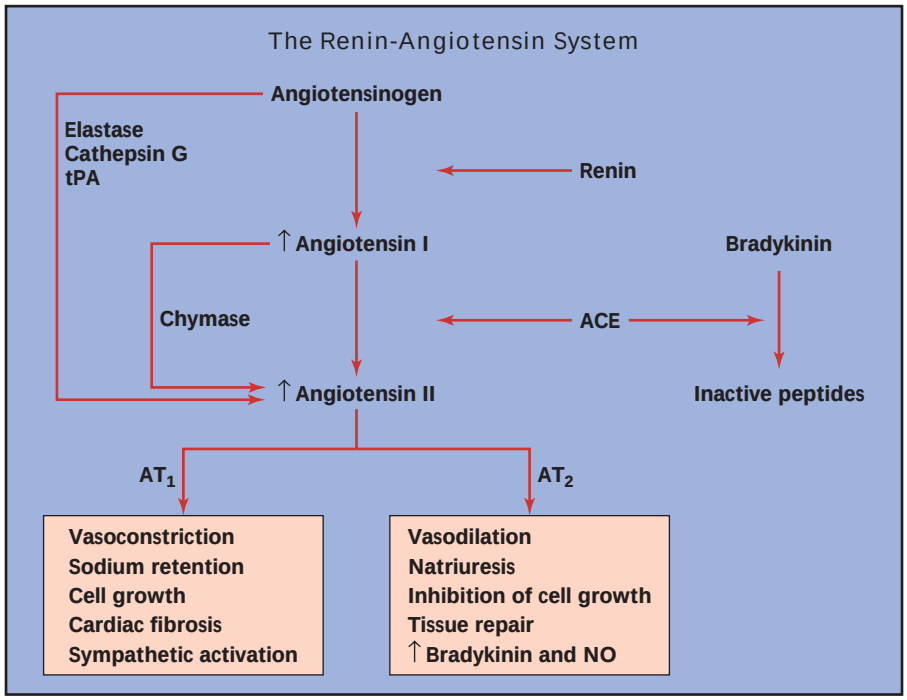
Heart failure remains one of the leading causes of death despite current advanced treatment.[1] The renin-angiotensin system (RAS) is a key player in the progression of heart failure. Angiotensin-converting enzyme (ACE) inhibitors have a proven benefit in treating different stages of heart failure.[2] Data from large-scale trials support the use of angiotensin receptor blockers (ARBs) in the treatment of heart failure.[3-5] ACE inhibitors are thought

to work by blocking the conversion of angiotensin I to angiotensin II (AT-II).[6] Deleterious effects of A-II are exerted through its type 1 receptor (AT_1) and include vasoconstriction, increase in sodium retention, endothelin secretion and vasopressin release, activation of sympathetic activity, promotion of myocyte hypertrophy, stimulation of vascular and cardiac fibrosis, increase in myocardial contractility, and induction of arrhythmias.[7] During ACE inhibition therapy, an "ACE escape" may occur, leading to increasing levels of AT-II over time.[8] A possible explanation is the production of AT-II via enzymes other than ACE (Figure 1). Angiotensinogen can be cleaved directly to AT-II by the actions of elastase, cathepsin G, and tissue plasminogen activator.[9] Angiotensin I also can be converted to AT-II in the extravascular space by chymase and cathepsin G.[10-12] Additionally, serum aldosterone levels, a marker of ventricular failure, remain elevated despite complete inhibition of vascular ACE in patients with heart failure.[13] Treatment with ACE inhibitors, despite strong clinical grounds, appears to be less capable over time of achieving a favorable neurohormonal profile. ARBs selectively block AT_1 receptors[7] and thus provide a more distal inhibition of the RAS.

Rationale for Combining ARBs and ACE Inhibitors in Heart Failure

In heart failure patients, the production of AT-II takes place despite the use of maximal recommended doses of ACE inhibitors.[14,15] Adding ARBs to ACE inhibitors may help block harmful effects of progressive AT-II production through the ACE-escape mechanism. A different AT-II receptor, type 2 (AT_2), may help counteract the harmful effects of AT_1,[16] and the selectivity of ARBs can theoretically help shunting of AT-II from AT_1 to AT_2. Unopposed activation of the AT_2 receptor may lead to increased bradykinin, nitric oxide, and cyclic guanosine 3′5′-monophosphate (cGMP), stimulating vasodilation and natriuresis.[17] Combination therapy also prevents degradation of bradykinin through continued inhibition of ACE (also known as kininase II).[18] ACE inhibitors also contribute to the effects of bradykinin beyond preventing its hydrolysis by blocking bradykinin type 2 (B2) receptor desensitization and decreasing B2 receptor internalization.[19] Bradykinin is thought to contribute to the hypotensive and cardioprotective effects of ACE inhibitors.[19,20] The following is a review of heart failure trials using combination therapy of ARBs and ACE inhibitors.

Figure 1. *Different pathways in angiotensin II production. ACE, angiotensin-converting enzyme; AT_1 and AT_2, angiotensin II receptor, types 1 and 2; NO, nitric oxide; tPA, tissue plasminogen activator. Adapted with permission from Burnier M[7] and Baylor College of Medicine.[43]*



Combining ARBs With ACE Inhibitors in Chronic Heart Failure

The addition of ARB therapy for heart failure patients on ACE inhibitor therapy has been studied in different populations for varying times (Table 1). The addition of losartan 50 mg daily to 33 severely symptomatic heart failure patients treated with maximal doses of ACE inhibitors improved exercise capacity and functional class.[21] Other studies on irbesartan and eprosartan were conducted for considerably shorter time periods and also involved a small number of patients on varying doses of ACE inhibitors.[22,23] The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study examined the effects of therapy with candesartan alone, enalapril alone, or candesartan plus enalapril in patients with heart failure.[24] There was no significant difference in the primary endpoint of exercise tolerance (6-minute

Table 1
Trials Combining ARBs with ACE Inhibitors in Heart Failure

Study	Heart Failure Class and LVEF	Patients, n	ARB Target Doses	Control	Mean Follow-up	Results
Hamroff et al[21]	NYHA III-IV, mean LVEF 26%	33	Losartan 50 mg daily (plus ACE inhibitor)	Placebo	6 mo	1. Enhanced peak aerobic capacity ($P < .02$). 2. Improvement of functional class ($P < .001$).
Tonkon et al[22]	NYHA II-III, LVEF ≤ 40%	109	Irbesartan 150 mg once daily (plus ACE inhibitor)	Placebo	12 wk	1. A trend toward improvement in exercise time (41 to 64 sec) and LVEF (estimated difference of 1.7 units [95% CI, 1.3-4.8]). 2. Not powered to demonstrate statistically significant benefits.
ADEPT[23]	NYHA II-IV, LVEF ≤ 40%	36	Eprosartan 400-800 mg daily (plus ACE inhibitor)	Placebo	8 wk	1. Significant reduction in diastolic blood pressure (−7.3 mm Hg [95% CI, −14.2 to −0.4]). 2. A trend toward a reduction in systolic blood pressure (−8.9 mm Hg [95% CI, −18.6 to 0.8]). 3. No effect on LVEF ($P = .97$).
RESOLVD[24]	NYHA II-III, LVEF < 45%	768	1. Candesartan (4, 8, 16 mg) daily 2. Candesartan 4 mg daily and enalapril 10 mg twice daily 3. Candesartan 8 mg daily and enalapril 10 mg twice daily	Enalapril 10 mg twice daily	43 wk	1. No differences among groups with regard to 6-minute walk distance, functional class, or quality of life. 2. Combination therapy decreased aldosterone ($P < .05$) at 17 but not 43 wk, and BNP ($P < .01$). 3. Not powered to assess morbidity and mortality.
Val-HeFT[25-28]	NYHA II-IV (62% II, 36% III, 1.7% IV), mean LVEF 27%	5010	Valsartan 160 mg twice daily (plus ACE inhibitor in 93%)	Placebo	23 mo	1. No significant difference in all-cause mortality (relative risk, 1.02 [98% CI, 0.88-1.18]; $P = .80$). 2. Reduction in the risk of heart failure hospitalization by 27.5% ($P < .001$). 3. Significant improvements in NYHA class, ejection fraction, and quality of life ($P < .01$). 4. Significant reduction in plasma aldosterone and BNP ($P < .00001$).
CHARM-Added[29]	NYHA II-IV (24.5% II, 73% III, 2.6% IV), mean LVEF 28%	2548	Candesartan 32 mg once daily (plus ACE inhibitor)	Placebo	41 mo	1. Significant reduction in cardiovascular mortality or heart failure hospitalization (unadjusted hazard ratio, 0.85 [95% CI, 0.75-0.96]; $P = .011$). 2. No significant difference in all-cause mortality (hazard ratio, 0.89 [95% CI 0.77-1.02]; $P = .086$).
VALIANT[5]	Killip class (27% I, 50% II, 17% III), mean LVEF 35%	14,808	Captopril 50 mg 3 times daily plus valsartan 80 mg twice daily	Valsartan 160 mg twice daily or captopril 50 mg 3 times daily	24.7 mo	1. Noninferiority of valsartan compared with captopril with regard to mortality ($P = .004$) and composite endpoint of fatal and nonfatal cardiovascular events ($P < .001$). 2. Combination therapy did not improve survival and led to more adverse events.

ACE, angiotensin-converting enzyme,: ADEPT, Addition of the AT_1 Receptor Antagonist Eprosartan to ACE Inhibitor Therapy in Chronic Heart Failure Trial; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CHARM-Added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity in Patients Taking Angiotensin-Converting Enzyme Inhibitors; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; Val-HeFT, Valsartan Heart Failure Trial; VALIANT, Valsartan in Acute Myocardial Infarction Trial.

walk test) or New York Heart Association (NYHA) functional class among treatment groups. Combination therapy in the RESOLVD study appeared to have favorable effects on the neurohormonal profile (Table 1). There was a trend toward a greater number of events in either the candesartan alone or combination groups compared with the enalapril-treated patients, leading to a 6-week early termination. The small number and the separation of patients into 6 treatment groups hindered the ability to draw final conclusions.

The Valsartan Heart Failure Trial (Val-HeFT) was designed to test the efficacy and safety of valsartan in combination with standard heart failure therapy (diuretics, 85%; ACE inhibitors 93%; β-blockers, 35%; and digoxin, 67%).[3] The 2 primary endpoints were all-cause mortality and the combined endpoint of mortality and morbidity (ie, cardiac arrest with resuscitation, heart failure hospitalization, or intravenous inotropic agents or vasodilators for over 4 hours). There was no difference in all-cause mortality between the valsartan and placebo groups (Table 1). A significant reduction was noted in the rate of hospitalization, mostly in patients with the most severe left ventricular remodeling.[3,25] In the subgroup of patients who were taking an ACE inhibitor and a β-blocker at baseline, mortality was significantly higher ($P = .009$), with a nonsignificant trend toward an increased risk of combined morbidity and mortality ($P = .10$) in the valsartan group compared with the placebo group. However, in the subgroups receiving neither drug or either ACE inhibitors or β-blockers alone, there was a significant improvement in the combined endpoint. As in RESOLVD, the neurohormonal profile improved in the treatment group, with sustained reduction in aldosterone and brain natriuretic peptide and improvement in norepinephrine levels.[26-28]

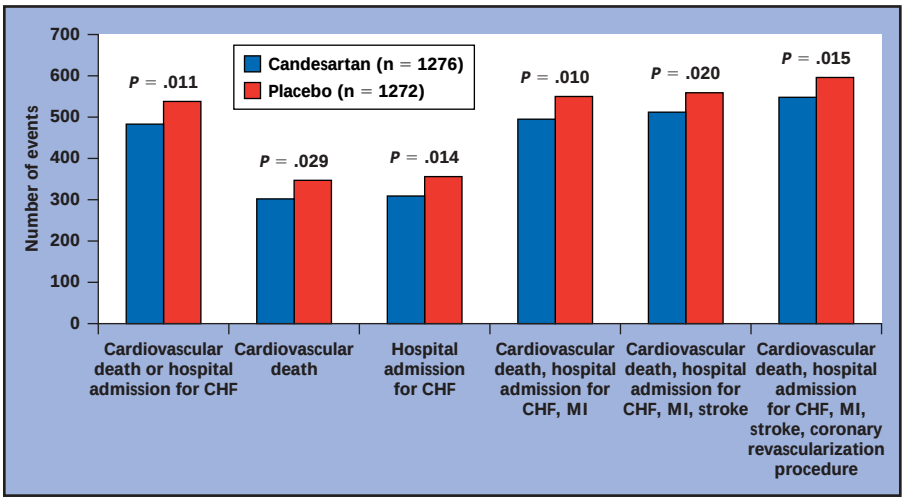


Figure 2. *Primary and secondary outcomes from CHARM-Added (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity in Patients Taking Angiotensin-Converting Enzyme Inhibitors) Trial. CHF, congestive heart failure; MI, myocardial infarction.*

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM-Added) trial included a population similar to that of Val-HeFT (diuretics, 90%; ACE inhibitors, 100%; β-blockers, 55%; and digoxin, 57%).[29] The primary outcome was a composite of cardiovascular mortality and hospitalization for the treatment of heart failure. The candesartan group experienced a significant reduction in both cardiovascular death and hospital admissions, but all-cause mortality was not significantly reduced (Table 1). Favorable effects were also noted in the significant reduction in each of the secondary outcomes, including cardiovascular death, hospital admission for heart failure, myocardial infarction, stroke, and coronary revascularization procedure (Figure 2). These benefits were consistent across all patient subgroups including those taking β-blockers, unlike what was seen in subgroup analysis in Val-HeFT.[3,29] This comparison may be unfair, however, as CHARM-Added used prespecified subgroups of patients versus underpowered post hoc analyses of subgroups in Val-HeFT. The difference in trial duration (Val-HeFT, 1.9 years; CHARM-Added, 3.4 years) could also account for different outcomes in both studies. Discontinuation of the study drug because of adverse events (hypotension, increased serum creatinine, and hyperkalemia) occurred

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Table 2
ACE Inhibitor Mean Doses Used in CHARM-Added, Val-HeFT, and Reference Outcome Trials

	Mean Daily Dose of ACE Inhibitor, mg		
ACE Inhibitor	**CHARM-Added**	**Val-HeFT**	**Outcome Trial**
Enalapril	16.8	17	16.6 (SOLVD-T)[30]
Lisinopril	17.7	19	32.2 (ATLAS)[31]
Captopril	82.2	80	121 (SAVE)[32]
Ramipril	6.8	6	8.7 (AIRE)[33]

ACE, angiotensin-converting enzyme; AIRE, Acute Infarction Ramipril Efficacy (trial); ATLAS, Assessment of Treatment with Lisinopril and Survival (trial); CHARM-Added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity in Patients Taking Angiotensin-Converting Enzyme Inhibitors; SAVE, Survival and Ventricular Enlargement (trial); SOLVD-T, Studies of Left Ventricular Dysfunction-Treatment Arm; Val-HeFT, Valsartan Heart Failure Trial.

significantly more in the treatment group compared with placebo in both Val-HeFT and CHARM-Added.[3,29]

In ATLAS, all-cause mortality was not significantly different in the 2 treatment groups, but the combined endpoint of all-cause death and all-cause hospitalization was significantly less common in patients receiving high-dose lisinopril, as was the overall number of hospitalizations (24% reduction, P = .002).

A common theme in these large-scale studies is the variation of ARB and ACE inhibitor dosing (Table 1). RESOLVD used smaller doses of candesartan in combination with a standard dose of enalapril. Both Val-HeFT and CHARM-Added used high doses of ARBs but used ACE inhibitors at moderate doses. The addition of ARBs was without first titrating ACE inhibitors to their recommended doses by outcome trials (Table 2).[30-33] Such titration is understandably difficult in outcome studies using add-on therapy but carries considerable importance for 2 major reasons. First, synergism, resulting from blocking the RAS at 2 successive sites along the renin-dependent AT-II–producing pathway (Figure 1) is lost with the use of high doses of ACE inhibitors.[34,35] Second, higher doses of ACE inhibitor have been proven to be superior to lower-dose therapy, as seen in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial.[31] In ATLAS, all-cause mortality was not significantly different in the 2 treatment groups, but the combined endpoint of all-cause death and all-cause hospitalization was significantly less common in patients receiving high-dose lisinopril, as was the overall number of hospitalizations (24% reduction, $P = .002$).[31,36] This reveals an interesting similarity when compared with outcomes obtained in both Val-HeFT and CHARM-Added. Spironolactone was used in 17% of patients in CHARM-Added and 5% in Val-HeFT, providing triple inhibition of the RAS.[3,29] Whether these patients were sicker than the others, as one can assume from the Randomized Aldactone Evaluation Study,[37] or if they had a different clinical outcome was not clear in either study. The improvement of the neurohormonal profile seen with combination therapy was accompanied by no improvement or by a modest improvement in survival with combination therapy. This dissociation between clinical outcome and possible excessive blockade of neurohormonal systems in heart failure patients was seen in the Moxonidine Congestive Heart Failure (MOXCON) trial[38] and the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME II),[39] in which a decrease in circulating levels of plasma norepinephrine was accompanied by an increase in adverse events.

Overall, the decrease in morbidity and the rate of hospitalization seen with dual RAS inhibition is not in itself a bad therapeutic outcome as it is the basis for digoxin use, which has a neutral effect on survival in heart failure patients.[40] Given, however, the results of the ATLAS trial, it is difficult at this time to recommend adding ARBs to the therapy of stable heart failure patients before the simple titration of ACE inhibitors. In

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Combining ARBs With ACE Inhibitors After Myocardial Infarction With Left Ventricular Dysfunction

The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) compared losartan with captopril in acute myocardial infarction patients with signs or symptoms of heart failure. A nonsignificant difference in total mortality was found in favor of captopril (relative risk, 1.13 [95% CI, 0.99-1.28]; $P = .07$).[41] This suggested keeping ACE inhibitors as first-choice treatment in patients after complicated acute myocardial infarction. Valsartan in Acute Myocardial Infarction (VALIANT) was the only trial to address combination therapy in heart failure patients after acute myocardial infarction (Table 1).[5] VALIANT compared treatment with valsartan versus captopril versus the combination of the 2 agents, with a mean follow-up of 2.1 years. Noninferiority of valsartan was statistically significant compared with captopril. Combination therapy did not offer any therapeutic advantage with regard to the primary endpoint (death from any cause) and to the composite endpoint of fatal and nonfatal cardiovascular events, and was accompanied by significantly more adverse events (hypotension, renal causes).[5] A post hoc analysis of cumulative hospital admissions for myocardial infarction or heart failure showed a significant difference in favor of combination therapy.

In the decision to add ARBs to ACE inhibitors, one should remember that the majority of patients in Val-HeFT (98%) and CHARM-Added (97.5%) were in NYHA classes II and III.

The lack of clinical benefits in combination therapy in VALIANT compared with benefits seen in Val-HeFT and CHARM-Added could have resulted from 2 factors. First, VALIANT used an ACE inhibitor titrated to a level of proven efficacy (mean captopril dose, 117 mg), and thus the addition of further AT_1 blockade may have failed to add any extra benefit. This is in agreement with the loss of synergetic effect of combination therapy with the use of high-dose ACE inhibition mentioned earlier, and with the use of combination therapy in a rat model of postischemic heart failure.[42] The second factor lies in the escape mechanism seen with chronic ACE therapy. In VALIANT, about 60% of the patients were ACE naïve, and the simultaneous start of ACE inhibition and AT_1 blockade may have prevented the potential benefit expected with starting an ARB during non-ACE production of AT-II. At this time, there is no sufficient evidence to support the addition of an ARB to ACE inhibition in the acute setting of postischemic heart failure.

Conclusions

Angiotensin-converting enzyme inhibitors should remain the first choice in the attempt to achieve RAS blockade in heart failure patients.

Main Points

- Treatment with angiotensin-converting enzyme (ACE) inhibitors, despite strong clinical grounds, appears to be less capable over time of achieving a favorable neurohormonal profile. Angiotensin receptor blockers (ARBs) selectively block angiotensin II (AT-II) type 1 receptors and thus provide a more distal inhibition of the renin-angiotensin system (RAS).
- In heart failure patients, the production of AT-II takes place despite the use of maximal recommended doses of ACE inhibitors. Adding ARBs to ACE inhibitors may help block harmful effects of progressive AT-II production through the ACE-escape mechanism.
- Overall, the decrease in morbidity and the rate of hospitalization seen with dual RAS inhibition is not in itself a bad therapeutic outcome as it is the basis for digoxin use, which has a neutral effect on survival in heart failure patients. Given, however, the results of the ATLAS trial, it is hard at this time to recommend adding ARBs to the therapy of stable heart failure patients before the simple titration of ACE inhibitors.
- Clinical benefits seen with combination therapy in stable heart failure were lacking after complicated myocardial infarction and suggest that combination therapy should not be started simultaneously in this population.

The addition of ARBs to symptomatic mild to moderate heart failure patients should follow titration of ACE inhibitors to the recommended doses by outcome trials. The increase of adverse events seen with combination therapy necessitates careful monitoring of renal function and serum potassium. Clinical benefits seen with combination therapy in stable heart failure were lacking after complicated myocardial infarction and suggest that combination therapy should not be started simultaneously in this population. ■

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