Which Inhibitor of the Renin–Angiotensin System Should Be Used in Chronic Heart Failure and Acute Myocardial Infarction?

John J.V. McMurray, MD; Marc A. Pfeffer, MD, PhD; Karl Swedberg, MD, PhD; Victor J. Dzau, MD

The value of angiotensin-converting enzyme (ACE) inhibitors in reducing mortality rates and major nonfatal cardiovascular events in patients with chronic heart failure (CHF) caused by left ventricular systolic dysfunction (LVSD) and in those with acute myocardial infarction (AMI) has been established by multiple randomized clinical trials.1–3 Angiotensin II type 1 receptor blockers (ARBs) offer an alternative means of blocking the renin–angiotensin system (RAS).4,5 The hypothetical reasons why an ARB might be more effective or better tolerated (or both) than an ACE inhibitor have been reviewed in detail.6,7 Briefly, angiotensin II is produced by enzymes other than ACE, meaning that ACE inhibitors might be less effective at blocking this peptide than an ARB (Figure 1).8,9 Angiotensin type 1 (AT₁) receptor blockade also makes more angiotensin II available to stimulate the unblocked AT₂ receptor (and perhaps other AT receptor subtypes)10,11 with purported beneficial actions in reducing cardiovascular disease progression.12

Unlike ARBs, ACE (kininase II) inhibitors inhibit bradykinin breakdown. Augmentation of bradykinin may have actions including potentiation of vasodilation, fibrinolytic effects, and inhibition of cellular growth and division, which may contribute to the benefits of ACE inhibitors.6,13,14 Conversely, bradykinin accumulation may cause some of the adverse effects of ACE inhibitors, ie, cough, rash, and angioedema.6,7

The evaluation of the effects of ARBs in CHF and AMI has therefore been challenging because of the incontrovertible role of ACE inhibitors in these conditions, raising questions about trial design, dose selection, statistics, and even ethics.15,16 A particular issue has been the need for direct comparisons, including formally conducted tests for “noninferiority,” with the implications this has for patient selection, choice of ACE inhibitor and dose, sample size, and end points.15–17

The 2 main approaches taken involved either a head-to-head comparison of the 2 types of treatment (1 trial in CHF and 2 in AMI) or a strategy of adding an ARB or placebo to an ACE inhibitor (2 trials in CHF and 1 in AMI). The pharmacological concepts underpinning these 2 approaches are also more complex than they appear at first sight. These alternative approaches view the actions of bradykinin in a contradictory way. The head-to-head comparison approach is based on better tolerability of an ARB because of a lack of bradykinin-mediated adverse effects, coupled with a potentially greater ability of an ARB to more completely block the RAS. Conversely, the add-on strategy assumes that the potential clinical benefits of bradykinin outweigh any adverse effects it might cause and that these might add to potentially more complete blockade of the RAS with an ARB. The add-on approach also results in a different pharmacological effect than when an ARB is used alone.7 With combination therapy, the negative feedback mediated a rise in angiotensin II, which normally occurs with an ARB (and may activate other AT receptors), that is reduced by the ACE inhibitor.

A third trial design was used in one CHF study that compared an ARB with placebo in patients who could not take an ACE inhibitor because of prior intolerance.18 The 3 major ARB trials in CHF with LVSD and the 2 trials in AMI are now completed, and it is unlikely that more will follow. Physicians will therefore have to decide how to use ACE inhibitors and ARBs, alone or in combination, in these conditions on the basis of the recently completed trials.

CHF With Reduced Left Ventricular Systolic Function

ACE Inhibitor–ARB Head-to-Head Comparison
The Evaluation of Losartan in the Elderly (ELITE; n=722) study compared the tolerability of losartan 50 mg once daily and captopril 50 mg thrice daily over a period of 48 weeks (Table 1). There were 17 (4.8%) in the losartan group and 32 (8.7%) in the captopril group (relative risk reduction, 46%; 95% CI, 5 to 69; P=0.035).19 Because this finding was unexpected, the investigators properly designed ELITE 2 (n=3159), which compared the effect of these 2 treatments on all-cause mortality, prospectively.20 With a 17.7% mortality in the losartan group and 15.9% in the captopril group (hazard ratio, 1.13; 95.7% CI, 0.95 to 1.35; P=0.16), losartan was not better than captopril. ELITE-2 was not powered to test for noninferiority. However, because an ACE inhibitor has been compared with placebo in CHF and losartan has been compared with an ACE inhibitor in ELITE 2, an indirect comparison between losartan and placebo is possible (im-
puted placebo analysis). In this analysis, losartan 50 mg once daily could not be shown to be better than placebo. Concern that the dose of losartan was too low in this trial (and in another trial in AMI) led to a further large outcome trial with losartan in CHF. The Heart Failure Endpoint Evaluation With the Angiotensin II Antagonist Losartan (HEAAL) study is comparing 50 mg of losartan once daily to 150 mg once daily in patients intolerant of an ACE inhibitor.

Combination ARB–ACE Inhibitor Treatment
In the Valsartan Heart Failure Trial (Val-HeFT; n=5010), placebo or valsartan 160 mg twice daily was added to standard treatment that included, in 93% of patients, an ACE inhibitor (Table 1). Although there was no reduction in mortality, valsartan significantly reduced the risk of the coprimary end point (death, admission to hospital with heart failure, ≥4 hours of intravenous treatment for heart failure without admission or cardiac arrest with resuscitation) by 13.2%. This was due mainly to a 27.5% reduction in the risk of hospitalization for CHF. Two subgroup analyses, however, detracted attention from this overall positive effect. One suggested that most benefit was concentrated in the minority (7%) of patients not taking an ACE inhibitor. The other suggested that patients taking both an ACE inhibitor and a β-blocker at baseline (optimal treatment) did worse when valsartan was added. Consequently, the Food and Drug Administration (FDA) and international guidelines recommended avoidance of “triple therapy” (the combination of an ACE inhibitor, β-blocker, and ARB) because of this apparent risk. The FDA did, however, approve valsartan for use in patients intolerant of an ACE inhibitor.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program (n=7601) consisted of 3 independent but linked trials, 2 of which randomized patients with LVSD (Table 1). In CHARM-Added (n=2548), patients taking an ACE inhibitor (in more than half of the patients, a β-blocker also) were randomized to either placebo or a target dose of candesartan 32 mg once daily. The risk of the primary outcome in this trial, death from a cardiovascular cause or hospitalization for worsening CHF, was reduced significantly by 15% with candesartan. Candesartan led to a prominent reduction in investigator-reported hospitalizations for worsening CHF. The effectiveness of candesartan was not altered by baseline use of a β-blocker in addition to an ACE inhibitor. Indeed, those receiving triple therapy had similar incremental reductions in cardiovascular deaths and heart failure hospitalizations.

Placebo–ARB Comparison in Patients Intolerant of an ACE Inhibitor
In CHARM-Alternative (n=2028), patients with prior intolerance of an ACE inhibitor were randomized to either placebo or candesartan (Table 1). The risk of death from a cardiovascular cause or hospitalization for worsening CHF

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<th>TABLE 1. ARB Trials in Patients With Heart Failure and Reduced Left Ventricular Systolic Function</th>
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<td><strong>ELITE-2 (n=3152)</strong></td>
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LVEF indicates left ventricular ejection fraction; NA, not applicable because of study design; and NR, not reported.
was reduced significantly by 23% with candesartan. Closer examination of the other outcomes of this study suggests that candesartan had clinical benefits of a magnitude similar to an ACE inhibitor from previous trials in patients with CHF and LVSD.1

Clinical Questions Arising From the Completed ARB Trials in CHF

Is an ARB an Alternative to an ACE inhibitor in CHF With LVSD?

There has only been one head-to-head comparison of an ACE inhibitor and ARB (ELITE 2), in which the 2 agents (perhaps because of an inadequate dose of the ARB) were not shown to be equivalent.20 This finding and other considerations such as cost and the length and breadth of clinical experience in using ACE inhibitors in these patients indicate that ACE inhibitors should remain the preferred initial antagonist of the RAS.

Should an ARB Be Used in a Patient Intolerant of an ACE Inhibitor?

The CHARM-Alternative trial (and, to a lesser extent, the subgroup analysis of patients not taking an ACE inhibitor in Val-HeFT) showed that these 2 ARBs and dosing regimens are beneficial in CHF and are treatment alternatives for patients intolerant of an ACE inhibitor (Figure 2).18–24 The clearest indication of intolerance is a cough or angioedema because they do not seem to be caused by an ARB. Effective doses of ARBs almost certainly cause as much hypotension and renal dysfunction as an ACE inhibitor.18 Consequently, careful monitoring of patients previously withdrawn from an ACE inhibitor for these adverse effects is merited when an ARB is used.

Should an ARB Be Added to an ACE Inhibitor (and β-Blocker) in CHF?

With a greater proportion of patients on both an ACE inhibitor and β-blocker and a longer-term follow-up, CHARM-Added had more events and therefore greater statistical power than Val-HeFT to test the hypothesis that adding an ARB to standard treatment would be of incremental benefit.23,29 The improvement in outcomes with triple therapy in CHARM-Added is consistent with other evidence of greater neurohumoral suppression,20–33 improved symptoms, and increased exercise tolerance.34 There is, however, conflicting information about “reverse remodeling” of the left ventricle. Val-HeFT showed no further favorable change when valsartan was added to background treatment with both an ACE inhibitor and a β-blocker.35 Conversely, in the Randomized Evaluation of Strategies of Left Ventricular Dysfunction (RESOLVD; n=768) pilot study, triple therapy resulted in the greatest reverse remodeling, perhaps reflecting the different design of this study.36 In our view, there is now strong evidence that ARBs should be used in CHF patients with LVSD in addition to other standard, lifesaving treatments in patients who remain symptomatic (Figure 2) to reduce risk of cardiovascular death, heart failure hospitalization, and other indexes of disease progression.

Which Should Be Added, an ARB or Spironolactone?

The Randomized Aldactone Evaluation Study (RALES; n=1663) showed that low-dose spironolactone reduced mortality by 30% in patients with severe CHF (currently or recently in NYHA functional class IV).37 Most patients (94%) in RALES were taking an ACE inhibitor, but only 10.5% were treated with a β-blocker. Therefore, RALES differed greatly from CHARM-Added and Val-HeFT in terms of patient severity and background β-blocker use, making comparison difficult. Clearly, the substantial mortality benefit of spironolactone argues strongly for use of this treatment in patients with severe CHF (Figure 2). This is supported by the effectiveness of another aldosterone antagonist, eplerenone, after AMI (see below).38 Conversely, although the effects of spironolactone in less severe CHF have not been quantified, those of ARBs have. The most difficult question is whether all 3 inhibitors of the RAS (or “quadruple therapy”: an ACE inhibitor, a β-blocker, spironolactone, and an ARB) are the most effective (but also safe). Because “aldosterone escape” occurs even in patients taking both an ACE inhibitor and an ARB, there is a theoretical reason to use all 3 inhibitors of the renin–angiotensin–aldosterone-system together.31,33 CHARM-Added, with 17% of patients taking spironolactone at baseline, currently provides the firmest data with which to answer this question. The beneficial effects of candesartan in this trial did not appear to be influenced by background spironolactone treatment. There was, however, more renal dysfunction and hyperkalemia when candesartan was added in patients taking an ACE inhibitor and spironolactone at baseline compared with those taking only an ACE inhibitor. Therefore, use of all 3 RAS inhibitors mandates even more careful monitoring of blood chemistry.

Is There a Role for ARBs in Patients With CHF With Preserved Systolic Function?

The role of ARBs in this important and neglected type of CHF is uncertain, and no ARB has yet been approved to treat these patients. In CHARM-Preserved (n=3025), candesartan did not lead to a statistically significant reduction in the
primary outcome of the trial, although there was a substantial and significant reduction in heart failure hospitalization and no evidence for heterogeneity of the candesartan benefit across the 3 trials. The Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) study is an ongoing placebo-controlled outcome study in this important group of patients testing irbesartan 300 mg once daily.

**Acute Myocardial Infarction**

**ACE Inhibitor–ARB Head-To-Head Comparison**

Two outcome studies have compared an ARB to a dose of captopril (50 mg thrice daily) proven to be effective in an earlier mortality trial (Table 2). The Optimal Therapy in Myocardial Infarction With the Angiotensin II Antagonist Losartan (OPTIMAAL; \( n = 5477 \)) trial used the ARB regimen tested in CHF in ELITE-2 (losartan 50 mg once daily). The Valsartan in Acute Myocardial Infarction (VALIANT; \( n = 14,703 \)) trial used the valsartan regimen studied in CHF in Val-HeFT (valsartan 160 mg twice daily). Both trials selected high-risk survivors of AMI because these patients had been shown to obtain the greatest benefits from ACE inhibitors. The inclusion criteria, however, differed between the 2 trials. VALIANT randomized patients with evidence of reduced LVSD, clinical or radiographic evidence of acute heart failure, or both to reflect closely the patients studied in the key prior long-term treatment ACE inhibitor trials. The use of a “reference” ACE inhibitor (and reference dosing regimen) and the inclusion and exclusion criteria from the reference trials were part of the strict noninferiority design of VALIANT. Both trials selected high-risk survivors of AMI because these patients had been shown to obtain the greatest benefits from ACE inhibitors. The inclusion criteria, however, differed between the 2 trials. VALIANT randomized patients with evidence of reduced LVSD, clinical or radiographic evidence of acute heart failure, or both to reflect closely the patients studied in the key prior long-term treatment ACE inhibitor trials. The inclusion criteria for OPTIMAAL were broader than for VALIANT (Figure 3). The primary aim of both OPTIMAAL and VALIANT was to test for superiority of the ARB over captopril (titrated to 50 mg thrice daily) in terms of all-cause mortality, although each trial was also designed to test for noninferiority if the ARB is not found to be found superior to captopril.

In OPTIMAAL, there was a trend toward superiority of captopril over losartan for the outcome of all-cause mortality, and noninferiority could not be shown. In contrast, in VALIANT, valsartan was found to be as effective as captopril. This was confirmed by formal noninferiority analysis and an imputed-placebo analysis, which showed that valsartan preserved the mortality and other cardiovascular mortality and morbidity benefits of captopril. The pattern of adverse events differed between captopril (more cough, rash, and taste disturbance) and valsartan (more hypotension and renal

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<td>Captopril + valsartan</td>
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*Also 15% primary percutaneous coronary intervention.*
abnormalities), although the proportion of patients who stopped treatment for any reason did not differ between the 2 treatments. On the basis of these findings, valsartan (titrated to 160 mg twice daily) is an alternative to an ACE inhibitor in these high-risk AMI patients (Figure 4).

**Combination ACE Inhibitor–ARB Treatment**

VALIANT is the only trial that reported survival and other outcomes after an MI in patients given an ARB and an ACE inhibitor compared with those given an ACE inhibitor alone.\(^1\) VALIANT, by design, also ensured that patients taking combination therapy received the proven dose of a proven ACE inhibitor. Patients randomized to combination treatment were titrated to valsartan (80 mg twice daily), added to captopril 50 mg thrice daily. This contrasts to the 2 CHF trials, Val-HeFT and CHARM, in which both the choice of ACE inhibitor and its dose were at the discretion of the investigator.

Mortality (and other prespecified secondary clinical outcomes) was not reduced by combination valsartan and captopril treatment compared with the proven dose of captopril (although combination treatment did increase the rate of adverse events and lower blood pressure more than captopril).

**Clinical Questions Arising From the ARB Trials in AMI**

**Is an ARB an Alternative to an ACE Inhibitor in a Patient With LVSD, Acute Heart Failure, or Both After AMI?**

VALIANT shows that valsartan 160 mg twice daily is as good as a proven dose of a proven ACE inhibitor in reducing risk of death and other major cardiovascular outcomes. This valsartan regimen is therefore an effective alternative, although the choice between these agents will be influenced by cost, tolerability, and prior clinical experience (Figure 4).

**Why Did Combination ACE Inhibitor and ARB Treatment Not Improve Outcome After AMI When It Did in CHF?**

There are several possible explanations for this apparent discrepancy.

- **Differences between AMI and CHF.** Although patients may have been included in OPTIMAAL and VALIANT because of acute “heart failure,” LVSD, or both, the time course and type of subsequent clinical events in these 2 different disease states (CHF and AMI) are dissimilar. After AMI, the rate of clinical events is much higher in the first 6 months than subsequently, whereas in stable CHF, there is a more linear rate of adverse outcomes. Patients with AMI are also relatively more likely to have further acute coronary events, whereas patients with CHF are more likely to experience worsening heart failure leading to hospitalization. However, in a post hoc analysis of VALIANT, valsartan added to captopril actually led to a greater reduction both in the number of patients admitted to hospital with an MI and in the total number of MIs than in hospitalization for heart failure.\(^1\)
  
- **Time course and degree of RAS activation: implications for treatment tolerability.** Although CHF is associated with long-term but modest activation of the RAS, AMI causes short-lived but intense acute neuroendocrine activation, with plasma concentrations of angiotensin II peaking after ≈3 days.\(^41,42\) Initiation of 2 inhibitors of the RAS at this time may not be as well tolerated in this acute, relatively unstable setting as in CHF.\(^43\)
  
- **RAS escape and implications for effect of dual ACE inhibitor–ARB treatment.** In Val-HeFT and especially CHARM-Added (76% patients in NYHA functional class III/IV compared with 38% in Val-HeFT), ARB treatment was started in patients who were persistently symptomatic despite receiving long-term ACE inhibitor treatment (and who probably had chronic activation of the RAS). During long-term treatment with an ACE inhibitor, RAS escape can occur, possibly because of induction of ACE, conversion of angiotensin II from angiotensin I through enzymatic pathways other than ACE eg, chymase (Figure 1), or both.\(^8,9,44,45\) Consequently, adding an ARB to an ACE inhibitor might bring about incremental clinical benefit. In contrast, in VALIANT, patients with acute and in many cases transient activation of the RAS were started simultaneously on both an ACE inhibitor and an ARB. In this acute setting in which RAS escape has not yet occurred (and where RAS activation may not persist), addition of an ARB to an ACE inhibitor may have less beneficial effects (and be less well tolerated), as was the case. Furthermore, after the early, transient activation of the RAS subsides, one inhibitor may be sufficient to fully suppress the system.
  
- **Dose of background ACE inhibitor treatment.** VALIANT, by design, ensured that patients received a proven dose of a proven ACE inhibitor to which valsartan was added. In contrast, the ACE inhibitor and its dose were chosen by the investigator in Val-HeFT and CHARM-Added. The mean dose of captopril in those taking this ACE inhibitor at baseline was ≈80 mg in these 2 CHF trials\(^23,29\) compared with 107 mg in the combination arm of VALIANT (at 1 year).\(^17\) Although this could be an important difference between the trials, the prespecified “recommended dose of ACE inhibitor” subgroup analysis of CHARM-Added appears to show clear efficacy of candesartan even when large doses of ACE inhibitor were taken\(^29;\) however, in Val-HeFT, greater effectiveness of the ARB was reported in those on the lower ACE inhibitor dose at baseline.\(^46\)
  
- **Dose of valsartan added to captopril.** Whereas valsartan 160 mg twice daily was added to background treatment in CHF in Val-HeFT, only 80 mg twice daily was added to captopril in VALIANT in AMI.\(^17,23\) Although in theory a
larger dose of valsartan might have led to clinical benefit, in practice the greater treatment withdrawal as a result of adverse effects seen within the combination arm of VALIANT would likely make a higher-dose valsartan strategy impractical.

It is important to state, however, that even in VALIANT there was some evidence of an additional biological effect of adding an ARB to full-dose ACE inhibitor. Arterial pressure was reduced slightly but significantly more with the combination, and there was a modest and statistically significant reduction in cumulative hospitalizations for CHF and AMI in the combination compared with captopril group. One further trial is testing the possible benefit of combination ACE inhibitor and ARB treatment in patients with cardiovascular disease but preserved left ventricular systolic function.

Should an ARB or Aldosterone Blocker Be Used After AMI? The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy SURVIVAL Study (EPHESUS; n=6642) compared placebo with eplerenone 25 to 50 mg once daily added to background ACE inhibitor (agent and dose determined by investigator) and, in most, β-blocker treatment. Patients had LVSD and clinical or radiographic evidence of acute heart failure (or diabetes mellitus); ie, they were a subset of those randomized in OPTIMAAL and VALIANT (Figure 3). Eplerenone reduced mortality by 15% (P=0.008) and the coprimary outcome of death from a cardiovascular cause or hospitalization for a cardiovascular cause by 13% (P=0.002). Consequently, EPHESUS strongly supports the strategy of adding eplerenone to an ACE inhibitor or ARB. As in CHF, this makes sense from a pathophysiological standpoint because aldosterone is regulated independently of angiotensin II and escapes during long-term ACE inhibitor treatment. Aldosterone blockade is therefore a complementary rather than competing treatment for these survivors of AMI remaining at high risk (Figure 4). Again, the importance of monitoring for hyperkalemia must be underscored.

Summary and Conclusions

With the major trials of ARBs in patients with CHF and LVSD and in patients with high-risk AMI completed, physicians now must incorporate the information they provide into rational treatment plans. We believe that the available trial data provide clear evidence that certain ARBs, when used at the clinically effective dose (titration of either valsartan to 160 mg twice daily or candesartan to 32 mg daily), can reduce cardiovascular morbidity and mortality. When an ACE inhibitor is not being used in patients with CHF or a high-risk AMI, these ARB regimens will lead to reductions in the risk of death and other cardiovascular events that are comparable to those obtained with a proven dose of a proven ACE inhibitor. In patients with CHF, additive clinical benefits have been shown with these ARBs used in combination with ACE inhibitor in both the presence and absence of β-blocker therapy. Therefore, in CHF, ARBs provide a clear advance, offering an additional opportunity to further reduce cardiovascular morbidity and mortality when used concomitantly with both a β-blocker and ACE inhibitor (Figure 5). In AMI complicated by LVSD, acute heart failure, or both, the combination of an ARB with a proven dose of an ACE inhibitor does not result in incremental clinical benefits, although a proven dose of a proven ARB is as effective as an ACE inhibitor. However, even in this acute setting, demonstration of the comparable effectiveness of an ARB (used in the appropriate dose) and ACE inhibitor provides clinicians with an additional tool with which to obtain the lifesaving benefits of RAS blockade in these patients. A consistent finding from all the major trials is that effective doses of these ARBs lead to hypotension and increases in creatinine and potassium. The effort and cost of the additional monitoring needed to detect and manage these generally transient adverse effects are likely offset by the improvements in prognosis that the judicious use of ARBs can produce. Through these recent international clinical trials, ARBs have now earned their position on the short list of treatments that can save lives and reduce cardiovascular morbidity in patients with CHF and high-risk AMI.
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