EDITORIAL COMMENT

Angiotensin Receptor Blockers in Heart Failure: A Work in Progress*

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The concept that the renin–angiotensin system (RAS) plays a major role in the development, progression and clinical manifestations of heart failure has become widely accepted over the past several decades. The importance of the angiotensin (Ang) II Type 1 (AT₁) receptor in mediating most of the pathophysiologic effects of Ang II has also been well established. Nonetheless, finding a role for the angiotensin receptor blockers (ARBs) in the treatment of heart failure has not been an easy task, nor is it by any means complete at this time. Much of the difficulty is related to the fact that by the time the ARBs became available in clinical practice, a substantial body of evidence demonstrating that the angiotensin-converting enzyme inhibitors (ACEIs) improved the natural history of patients with heart failure had already been accumulated (1). Based on the consistency of beneficial effects that were seen in clinical trials encompassing a broad spectrum of patients ranging from individuals with asymptomatic left ventricular dysfunction to those with advanced symptoms, the ACEIs emerged as a cornerstone of therapy for heart failure (2). The ACEIs also have been shown to reduce mortality and progression to heart failure in myocardial infarction survivors (3,4). More recently, the results of the Heart Outcomes Prevention Evaluation (HOPE) study indicate that their clinical benefits (including prevention of heart failure) extend to patients with evidence of (or risk factors for) atherosclerotic vascular disease (5). So persuasive is the evidence of the efficacy of the ACEIs that their prescription is used as a quality indicator for the management of heart failure.

Thus, studies evaluating the effects of ARBs have had to be designed with the recognition that ACEIs are considered to be effective in improving the clinical course in virtually all stages of heart failure resulting from systolic dysfunction. This has posed a problem because a major effect of both classes of agents is to limit the interaction of Ang II with the AT₁ receptor, the ACEIs by blocking Ang II generation and the ARBs by competing with the peptide for receptor occupancy. Thus, despite important pharmacologic differences between these classes of drugs, including the ability of the ARBs to directly block the effects of Ang II regardless of how it is generated (thereby affording protection against Ang II that is generated within tissue through nonangiotensin-converting enzyme pathways using enzymes such as chymase [6]), the ARBs failed to demonstrate superiority to the ACEIs in improving the clinical course of heart failure patients (7), nor do they reduce the incidence of worrisome increases in renal function tests in the heart failure population compared with the ACEIs (8). However, there is evidence that the ARBs are clearly better tolerated by patients than the ACEIs in treating both heart failure and hypertension (7–10). When added to standard therapy (that included ACEIs in most patients) in theValsartan Heart Failure Trial (Val-HeFT), an ARB was shown to have essentially no effect on mortality, although there was a significant improvement in morbidity mainly because of a reduction in heart failure hospitalizations (11). Even this piece of good news for the ARBs, however, has been tempered by the observation that patients who were receiving beta-blockers in addition to an ACEI in Val-HeFT experienced an increased risk for morbidity and mortality when the ARB was introduced. This finding has raised the possibility that the combination of an ACEI, ARB and beta-blocker may have unexpected deleterious consequences in the heart failure population.

With the ACEIs so well established as a therapy for heart failure, an important issue that has faced clinicians is whether or not ARBs by themselves improve survival and reduce morbidity in heart failure patients. Thus, the post hoc analysis of the patients not receiving an ACEI who were included in Val-HeFT that is reported in this issue of the Journal is a welcome and interesting addition to the medical literature (12). In Val-HeFT, 366 patients (7% of the study population) were not, for one reason or another, on an ACEI at the time that they were randomized to either valsartan or placebo. The investigators found that the addition of the ARB to these patients was associated with significant reductions in the mortality and combined morbidity and mortality end points that were used in the main trial. In contrast, only the latter end point was significantly improved by the addition of valsartan in the entire 5,010-patient Val-HeFT study population. Moreover, the 33% reduction in mortality with the ARB in patients not receiving an ACEI was of the magnitude that one might have expected to see with an ACEI in this population, and the substantial 53% risk reduction for heart failure hospitalization is very relevant clinically. Changes in secondary end points, though small in magnitude, were generally in the favor of a beneficial effect of the ARB. These findings provide evidence of physiologic benefits that help support and explain the clinical ones that were seen in this analysis. Also encouraging was the fact that there was no evidence of a reversal of these favorable effects in the patient group that

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was receiving a beta-blocking agent when the ARB was added.

These results, although encouraging, need to be interpreted with caution. As wisely pointed out by the authors, the results of this post-hoc analysis do not carry nearly the same weight as would the results of a clinical trial that was specifically designed and adequately powered to assess the effects of the ARBs on clinical end points in a population not receiving an ACEI. The number of patients included in the present subgroup analysis was relatively small and several characteristics of the selected population were significantly different from the general study population, including the fact that the patients not receiving an ACEI when the trial began were older, more likely to be female, had more advanced symptoms and had a greater likelihood of having an ischemic etiology of their heart failure. They also had higher average ejection fraction and systolic blood pressure rates than did the rest of the study population. Other more subtle and/or not reported differences between the non-ACEI subgroup and the other patients that could have influenced the outcome may also have been present. At the least, these concerns limit the generalizability of the findings in the present report to the broader universe of heart failure patients.

Even more important is the fact that considerable past experience with heart failure trials that were not adequately powered has taught us the lesson that the beneficial effects that such trials purport to show may simply be the result of the play of chance. The danger in accepting results from underpowered trials (or subgroups of larger studies) no matter how sizable the effects (or what p value was reached) has become apparent when the results of adequately powered trials demonstrated either lack of benefit or even harmful effects of a promising new therapy (7,8,13,14). Fortunately, more definitive information about the efficacy of ARBs in ACEI-intolerant patients will be available when the results of one of the arms of the CHARM study that is specifically designed and adequately powered to assess this issue is reported (15).

Finally, small subgroup analyses such as this one derived from Val-HeFT offer little or no insight into the characteristics of the patients that might be more (or less) likely to benefit from treatment with an ARB, nor are we able to discern the optimal dose of valsartan for treating patients with heart failure. Additional questions regarding the efficacy of ARBs other than valsartan in this population also remain unanswered. Given the differences between the various ARBs in the characteristics of their antagonism of Ang II at the AT1 receptor site (16) and in other properties of the individual molecules (17,18) that could be relevant in treating heart failure patients, this question is of more than passing interest.

Although the ACEIs have been shown to benefit patients with heart failure, there is information that up to 20% of patients may not be receiving them because of real or perceived side effects (19,20). What then is the best approach to treating these patients with the evidence that is currently available? First, it would be important to determine if the reason for excluding the ACEI is due to actual side effects such as cough or angioedema. If it is not, efforts should be made to re-initiate therapy with an ACEI. For patients who cannot be started or maintained on an ACEI; however, the use of an ARB is warranted. This is based on the known role of Ang II in the pathogenesis of heart failure and it is supported by the present results of the Val-HeFT subgroup analysis of patients not receiving an ACEI. As with the ACEIs, a beta-blocker should also be given unless there is a specific contraindication to the administration of drugs in this class.

These recommendations, of course, await the results of CHARM to substantiate, refute or further modify them. It is also worth considering at this moment in time what the current recommendations might be if it had been the ARBs rather than the ACEIs that were the first class of drugs introduced to interfere with the RAS and to treat heart failure. What then might we be saying today about the role of the ACEIs in the management of patients with heart failure and what difficulties might there be in finding their appropriate place in the therapeutic regimen?

**References**


