Clinical Update: The Role of Angiotensin II Receptor Blockers in Patients with Left Ventricular Dysfunction (Part II of II)

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Summary

Almost 5 million individuals in the United States have chronic heart failure (HF), which is increasing in prevalence. Angiotensin-converting enzyme (ACE) inhibitors are standard therapies for HF, although more than 10% of patients with HF are unable to tolerate these agents. Furthermore, ACE inhibitors may not provide complete blockade of the renin-angiotensin system (RAS) in the long term. Because angiotensin II receptor blockers (ARBs) may block the RAS more completely than ACE inhibitors and are better tolerated, several large-scale ARB trials have been performed exploring their potential role in treating patients with symptomatic HF and left ventricular systolic dysfunction. The Losartan Heart Failure Survival Study (ELITE II) demonstrated no significant differences in morbidity and mortality between the ARB losartan and the ACE inhibitor captopril among elderly patients with HF. The Valsartan Heart Failure Trial (Val-HeFT) demonstrated reductions in hospitalizations for HF with the ARB valsartan when added to standard HF therapy, with no effect on mortality. Both trials suggested a potential negative interaction between ARB and beta-blocker therapy. The Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program demonstrated significant reductions in morbidity and mortality with the ARB candesartan in patients with HF due to systolic dysfunction, with or without

ACE inhibitors and with or without beta blockers. Thus, the addition of ARBs to the treatment regimen of patients with symptomatic HF should be strongly considered.

Key words: heart failure, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers

Introduction

Approximately 5 million Americans have been diagnosed with chronic heart failure (HF), with associated high rates of morbidity, disability, and mortality.¹ Angiotensin-converting enzyme (ACE) inhibitors, which inhibit the renin-angiotensin system (RAS), are strongly recommended as standard therapies to slow the progression of HF.² Yet, recent epidemiologic studies indicate that mortality rates in this disease remain unacceptably high, at 25% after 1 year and 50% within 5 years of diagnosis.^{3,4} In addition, up to 10% of patients with HF are unable to tolerate ACE inhibitors, often due to persistent dry cough.⁵ Angiotensin-converting enzyme inhibitor therapy may also not provide optimal long-term blockade of the RAS.^{6,7}

Alternative, improved therapies for HF are thus greatly needed. Angiotensin II receptor blockers (ARBs) provide a theoretically more complete mode of RAS blockade and have better tolerability than ACE inhibitors. It has therefore been hypothesized that ARBs could provide similar and potentially additive clinical benefits to ACE-inhibitor therapy among patients with HF. Several large-scale HF trials have therefore been conducted with ARBs.^{8–10} The study designs, results, and implications of these trials with regard to the potential role of ARBs in the management of HF are reviewed in this article.

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ELITE II

The first large-scale ARB trial to be completed was the Losartan Heart Failure Survival Study (ELITE II), in which the ARB losartan (titrated to 50 mg once daily) was directly compared with the ACE inhibitor captopril (titrated to 50 mg 3 times daily) in 3,152 patients, aged ≥ 60 years, with HF and

left ventricular ejection fraction (LVEF) $\leq 40\%$.⁸ After a median follow-up of 555 days, there were no significant differences in morbidity or mortality between the treatment groups (Fig. 1), although trends in the primary and major secondary endpoints favored captopril. Losartan was well tolerated, with significantly fewer discontinuations for adverse events compared with captopril (9.7 vs. 14.7%; $p < 0.001$). However, compared with captopril, losartan demonstrated a significant increase in mortality in patients who were prescribed beta-blocker therapy at the time of randomization (22% of the study population), suggesting a possible negative interaction between losartan and beta blockers.

Val-HeFT

In the Valsartan Heart Failure Trial (Val-HeFT), 5,010 patients with HF and LVEF $< 40\%$ were randomized to the ARB valsartan (titrated to 160 mg twice daily) or placebo, on top of conventional HF therapy, including ACE inhibitors.⁹ Mean follow-up was 23 months. Approximately 93% of the subjects received ACE-inhibitor therapy and 35% received a beta blocker. Valsartan significantly reduced the combined endpoint of cardiovascular morbidity and mortality (cardiac arrest with resuscitation, hospitalization for HF, or administration of intravenous inotropic or vasodilator therapy for at least 4 h; $p = 0.009$), compared with placebo, due mainly to a 24% reduction in HF hospitalizations. No effect on mortality was observed with valsartan (Fig. 1). Furthermore, most of the clinical benefit obtained with valsartan appeared to occur among the 7% of the patients who were not receiving ACE-inhibitor therapy ($n = 366$), raising the question as to whether adding an ARB to an ACE inhibitor provided incremental clinical benefit. Of major concern is that fact that the addition of valsartan to patients who were receiving both ACE inhibitor- and beta-blocker therapy concomitantly ($n = 1,610$) significantly increased overall mortality, compared with placebo, suggesting a potentially deleterious interaction between valsartan and concomitant ACE inhibitor-beta-blocker therapy.

FIG. 1 A significant reduction in all-cause mortality was seen with candesartan in a combined analysis of the two CHARM trials in patients with low left ventricular ejection fraction (LVEF). No significant reduction in mortality was seen in ELITE II or Val-HeFT. ELITE II = Losartan Heart Failure Survival Study, Val-HeFT = Valsartan Heart Failure Trial, CHARM = Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity, ARB = angiotensin II receptor blocker, HR = hazard ratio.

The CHARM Program

The Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program was conducted to investigate potential clinical benefits with the ARB candesartan across a wide spectrum of patients with symptomatic HF.¹⁰ The program included two randomized, double-blind, placebo-controlled clinical trials comparing candesartan (titrated to 32 mg once daily) with placebo in patients with symptomatic HF and reduced LV systolic function:

CHARM-Alternative: Patients with LVEF $\leq 40\%$ not receiving ACE-inhibitor therapy due to previous intolerance ($n = 2,028$); CHARM-Added: Patients with LVEF $\leq 40\%$ who were receiving ACE inhibitors ($n = 2,548$).

The primary outcome for each of these trials was cardiovascular death or hospital admission for worsening HF.

The CHARM-Alternative trial addressed the issue of whether ARBs provide clinical benefits among patients with HF, in the absence of ACE-inhibitor therapy.¹¹ The most common reason cited for prior ACE-inhibitor intolerance was cough (72%), followed by symptomatic hypotension (13%), renal dysfunction (12%), and angioedema (4%). Approximately 55% of patients received beta-blocker therapy and 24% received spironolactone.

After a median follow-up of 33.7 months in CHARM-Alternative, the primary endpoint of cardiovascular death or hospital admission for HF occurred in 33% of patients in the candesartan group compared with 40% with placebo, a significant 23% relative risk reduction with candesartan ($p = 0.0004$) (Fig. 2). Risk reductions for the individual components of the primary endpoint were consistent with the primary results (15% risk reduction in cardiovascular death, $p = 0.07$; 32% risk reduction in hospital admission for HF, $p < 0.0001$). The clinical benefits demonstrated in CHARM-Alternative were simi-

Numbers at risk:
Candesartan 1013 929 831 434 122
Placebo 1015 887 798 427 126

FIG. 2 In CHARM-Alternative, candesartan significantly reduced the primary endpoint of cardiovascular (CV) death or hospital admission for heart failure (HF), compared with placebo, in patients with HF with previous intolerance to angiotensin-converting enzyme inhibitors. CI = confidence interval. Other abbreviations as in Figure 1. Reprinted from Ref. No. 11 with permission.

lar to those observed with ACE-inhibitor therapy in the Studies of Left Ventricular Dysfunction (SOLVD) trial (a 26% reduction in all-cause mortality or hospitalization for HF).¹²

Candesartan was generally well tolerated in these patients with prior ACE-inhibitor intolerance, with similar discontinuation rates in the candesartan (30%) and placebo (29%) groups over the median 2.8 years of follow-up. Most patients with prior ACE-inhibitor intolerance due to hypotension, renal dysfunction, or hyperkalemia were able to tolerate candesartan therapy without recurrence of these same adverse events. Among the 39 patients in the candesartan group with a history of angioedema on ACE-inhibitor therapy, angioedema recurred in 3 patients; none of the cases was considered life threatening or led to hospital admission, and permanent discontinuation of study drug occurred in only one patient.

The specific goal of CHARM-Added was to evaluate whether, compared with placebo, ARB therapy with candesartan would improve clinical outcomes when added to ACE-inhibitor therapy in patients with symptomatic HF and LVEF $\leq 40\%$ ($n = 2,548$).¹³ Most patients enrolled (73%) were classified as New York Heart Association class III HF. While all patients in CHARM-Added were receiving ACE inhibitors, 55% were also being treated with beta blockers and 17% with spironolactone. According to the study investigators, 96% of patients were receiving optimum ACE-inhibitor doses at randomization.

After a median follow-up of 41 months, the addition of candesartan to ACE inhibitor-therapy demonstrated a significant 15% risk reduction in the primary endpoint of cardiovascular death or HF hospitalization, compared with placebo (38 vs. 42%, respectively; $p = 0.011$) (Fig. 3). Candesartan also significantly reduced each component of the primary outcome (16% risk reduction in cardiovascular death, $p = 0.029$; 17% risk reduction in hospital admission for HF, $p = 0.014$).

FIG. 3 In CHARM-Added, candesartan significantly reduced the primary endpoint of cardiovascular (CV) death or heart failure (HF) hospitalization, compared with placebo, when added to angiotensin-converting enzyme inhibitor therapy. Abbreviations as in Figures 1 and 2. Reprinted from Ref. No. 13 with permission.

Candesartan reduced the primary outcome in all predefined subgroups, including patients taking a recommended dose of ACE inhibitor and patients treated with both ACE inhibitors and beta blockers concomitantly. Thus, there was no evidence of any negative interaction between candesartan and beta-blocker therapy.

Candesartan was generally well tolerated; 24% of patients in the candesartan group and 18% of the patients in the placebo group permanently discontinued study drug because of an adverse event or laboratory abnormality over the median 3.4 years of follow-up ($p = 0.0003$), which was most commonly related to increases in serum creatinine or potassium levels, or hypotension. Two cases of angioedema in the candesartan group and three cases in the placebo group were reported (all affected subjects were receiving an ACE inhibitor at the time).

In a predefined analysis combining CHARM-Alternative and CHARM-Added, the two trials in patients with LVEF $\leq 40\%$, candesartan demonstrated a significant 12% reduction in all-cause mortality ($p = 0.018$) (Fig. 1) and a significant 16% reduction in cardiovascular mortality ($p = 0.005$).¹⁰

Potential Differences among Angiotensin II Receptor Blockers

Several inconsistencies across the ARB trials described above in patients with HF and LV systolic dysfunction have raised some doubt that ARBs share a “class effect” in HF. Following completion of ELITE II,⁸ concern was raised that ARBs may not be as effective as ACE inhibitors in patients with chronic HF. However, it is also possible that losartan provides less protection against cardiovascular outcomes compared with other ARBs, or that the dose of losartan used in ELITE II (50 mg once daily) was subtherapeutic (leaving the question of the optimal dose of losartan for HF management unanswered). Similarly confusing is the possibility of a negative interaction between ARBs and beta blockers, suggested by both the ELITE II⁸ and Val-HeFT⁹ results, but not seen in CHARM-Added.¹³ Finally, the question of whether incremental clinical benefit can be gained by adding an ARB to ACE-inhibitor therapy appeared to be answered with a “no” with valsartan therapy in Val-HeFT, since the major benefit in the trial was observed in patients not receiving ACE-inhibitor therapy,⁹ but with a strong “yes” with candesartan therapy in CHARM.¹³

Although all ARBs work by inhibiting the effects of angiotensin II at the site of the angiotensin II type 1 (AT_1) receptor, they vary in important pharmacologic properties, which may bear on their efficacy in lowering blood pressure and providing target-organ protection.¹⁴ For example, one study in rabbit and rat aortas found that candesartan demonstrated long-lasting inhibition of angiotensin II binding, consistent with insurmountable blockade, whereas irbesartan and losartan provided angiotensin II blockade of shorter duration, indicative of surmountable blockade.¹⁵ In addition, differences in antihypertensive efficacy have been observed in multiple head-to-head comparison trials of various ARBs.^{16–19} It is therefore not

unreasonable to question whether different ARBs may have differing effects on long-term clinical outcomes.

Conclusion

In patients with chronic HF, ARBs appear to be as effective as ACE inhibitors, reducing morbidity and mortality in patients with ACE-inhibitor intolerance, and, in the case of candesartan, provide incremental clinical benefit when used in addition to ACE-inhibitor therapy. However, some unanticipated differences among some of these trial results were also observed, casting doubt on the widely held belief in an ARB class effect with regard to safety and clinical outcomes. In the management of patients with HF due to LV systolic dysfunction, clinicians would be well advised to prescribe only those ARBs shown to reduce clinical outcomes in these patient populations, at their clinically proven doses.

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