Haemodynamic and neurohormonal effects of AT₁-receptor blockers

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AT₁-receptor blockers offer potential advantages in the management of heart failure, since they selectively block AT₁-receptor activation, independent of the source of angiotensin II, while preserving the potentially beneficial effects of AT₂-receptor activation. In placebo-controlled trials, these agents have been shown to have beneficial effects on haemodynamics and clinical status. Comparative studies, including the RESOLVD Pilot Study with candesartan, have shown that AT₁-receptor blockers and angiotensin-converting-enzyme (ACE) inhibitors produce comparable changes in haemodynamics, neurohormones, cardiac function, and heart-failure symptoms. The RESOLVD Pilot Study also showed that the combination of candesartan and enalapril produced a significantly greater improvement in left-ventricular ejection fraction (LVEF) than either agent alone, consistent with the finding in the CHARM-Added study that the combination of candesartan and an ACE inhibitor significantly reduced cardiovascular mortality and morbidity, compared with ACE inhibition alone. Moreover, in the RESOLVD Pilot Study, triple combination therapy with candesartan, enalapril and metoprolol controlled release resulted in significantly improved LVEF and reductions in cardiac volumes, suggesting a favourable effect on cardiac function and remodelling, compared with dual neurohormonal blockade. By contrast, no such improvements in cardiac function were seen with valsartan in patients who were also receiving an ACE inhibitor and a β-blocker in the Val-HeFT echocardiographic substudy. In conclusion, mechanistic studies suggest that AT₁-receptor blockers have a valuable role in the management of heart failure.

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Introduction

Despite the proven benefits of neurohormonal blockade with angiotensin-converting-enzyme (ACE) inhibitors, β-blockers and aldosterone antagonists in reducing mortality and morbidity in patients with heart failure, mortality remains high, particularly in the oldest patients. Data from the Swedish Hospital Discharge Registry, for example, show that although 1-year mortality rates after a first hospitalization for heart failure declined between 1988 and 2000, they still vary from approximately 9% in individuals aged 45-54 years to 35% in those aged 75-84 years¹. Moreover, a significant number of patients are unable to tolerate ACE inhibitors because of adverse effects; data from the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) registry, for example, showed that 9% of patients were unable to tolerate ACE inhibitors, making intolerance the principal reason for non-use of these agents². Clearly, scope remains for the improvement of neurohormonal blockade in patients with heart failure, and there is a particular need for alternative therapies in patients who are unable to tolerate ACE inhibitors. The use of AT₁-receptor blockers may provide a means of fulfilling these needs.
Rationale for the use of AT₁-receptor blockers in heart failure

Angiotensin II can be produced both through the action of ACE on angiotensin I and through ACE-independent pathways that are not affected by ACE inhibitors. As a result, during long-term ACE-inhibitor therapy, plasma concentrations of angiotensin II eventually return to pre-treatment levels in many patients. Moreover, since ACE inhibitors act by reducing angiotensin-II formation, they unselectively inhibit both the deleterious effects of AT₁-receptor activation and the potentially beneficial effects of AT₂-receptor activation. By contrast, AT₁-receptor blockers offer the advantage of selective blockade of AT₁-receptor activation, independent of the source of angiotensin II, while allowing stimulation of AT₂ receptors. Another difference is that AT₁-receptor blockers, in contrast to ACE inhibitors, do not increase bradykinin levels. This may lead to a tolerability advantage of AT₁-receptor blockers over ACE inhibitors. However, bradykinin also has potentially beneficial vasodilator effects, indicating that the optimal treatment for many patients may be the combination of an ACE inhibitor (leading to bradykinin potentiation) and an AT₁-receptor blocker (ensuring complete blockade of angiotensin II at the AT₁ receptor).

The introduction of AT₁-receptor blockers into the treatment of heart failure required that three criteria be met. First, it was necessary to show that these agents are more effective than placebo; second, it was important to determine whether AT₁-receptor blockers are as effective as ACE inhibitors in reducing neurohormonal activation and improving heart-failure symptoms; third, it was important to assess whether AT₁-receptor blockers are effective and safe when combined with ACE inhibitors to provide more complete blockade of the renin-angiotensin system.

Placebo-controlled studies with AT₁-receptor blockers

Placebo-controlled studies have consistently shown that AT₁-receptor blockers significantly improve cardiac haemodynamics in patients with heart failure. In one such study, 218 patients with New York Heart Association (NYHA) Class II-IV heart failure were randomized to receive irbesartan 12.5 mg, 37.5 mg, 75 mg, 150 mg, or placebo, after which cardiac haemodynamics were measured. After the first dose of study medication, placebo-treated patients were re-randomized to one of the four doses of irbesartan, after which treatment was continued for 12 weeks, and the haemodynamic measurements repeated. Irbesartan produced dose-dependent reductions in pulmonary capillary wedge pressure, mean pulmonary arterial pressure, and mean systemic arterial pressure without causing reflex tachycardia. Left-ventricular ejection fraction tended to increase in a dose-dependent manner. The effects of irbesartan on neurohormones were inconsistent and not statistically significant, however.

In a second study, 134 patients received losartan 2.5 mg, 5 mg, 10 mg, 25 mg or 50 mg, or placebo once daily for 12 weeks. Losartan 50 mg was associated with a significant decrease in systemic vascular resistance, compared with placebo, and a non-significant decrease in pulmonary capillary wedge pressure. The cardiac index was significantly greater with losartan 50 mg than with placebo. Heart rate was reduced with all losartan doses, compared with placebo.

A further study investigated the effect of candesartan 2-16 mg on haemodynamics, neurohormones and heart-failure symptoms in 218 patients with NYHA Class II-III heart failure. Treatment with candesartan for 12 weeks produced significant, dose-dependent, reductions in pulmonary capillary wedge pressure and mean pulmonary arterial pressure, compared with placebo, and a trend towards a reduction in systemic vascular resistance. Plasma renin activity and angiotensin-II concentrations increased during candesartan treatment, while the concentrations of aldosterone and atrial natriuretic peptide (ANP) decreased. Significant improvements in heart-failure symptoms were seen in patients receiving candesartan at doses of 4 mg and above.

The effects of candesartan on exercise capacity and heart-failure symptoms were investigated in a randomized, double-blind, placebo-controlled study involving 844 patients with NYHA Class II-III heart failure. After a 4-week placebo run-in period, patients were randomized to receive candesartan 4 mg, 8 mg or 16 mg, once daily, or placebo for 12 weeks. Exercise capacity was measured by bicycle ergometry at least twice during the placebo run-in period, and after 6 and 12 weeks of treatment. Candesartan 16 mg produced a significantly greater increase in exercise capacity than placebo (Fig. 1), and all doses of candesartan produced significant improvements in the Dyspnoea Fatigue Index score. Candesartan 8 mg and 16 mg was associated with significant increases in plasma renin activity and angiotensin-II concentrations, and decreases in aldosterone concentrations, compared with placebo. NYHA class improved more often in candesartan-treated patients than in those receiving placebo, but the

Fig. 1. Change in exercise capacity in patients with NYHA Class II-III heart failure treated with candesartan 4 mg, 8 mg or 16 mg once daily, or placebo for 12 weeks. *P < 0.05. Reproduced from Riegger et al. 1999 with the permission of Lippincott Williams & Wilkins.
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There were no significant differences between the effects of candesartan and enalapril monotherapies on exercise capacity or ventricular volumes (Fig. 2), or on heart rate or blood pressure. As expected, plasma levels of angiotensin II increased in candesartan-treated patients and decreased in enalapril-treated patients, but there were no significant differences in changes in aldosterone concentrations between the two treatments. Plasma levels of brain natriuretic peptide (BNP) tended to increase with both agents, but there were no significant differences between the two monotherapy groups.

Comparative studies with AT$_1$-receptor blockers and ACE inhibitors

Most studies comparing ACE inhibitors and AT$_1$-receptor blockers have been performed by withdrawing ACE-inhibitor therapy from previously treated patients and then randomizing them to one or the other of the therapies. In one such study$^{10}$, 116 patients with NYHA Class II-IV heart failure and left-ventricular ejection fractions of 45% or below were randomized to receive losartan 25 mg or 50 mg, or enalapril 20 mg, for 12 weeks. Exercise capacity, assessed by means of a treadmill test and the 6-minute walk test, did not change significantly after replacement of ACE-inhibitor therapy with losartan. Similarly, there were no significant differences in changes in dyspnoea fatigue index or left-ventricular ejection fraction between the losartan and enalapril groups.

In a further study, 166 patients with NYHA Class III-IV heart failure and left-ventricular ejection fractions of 35% or less underwent a 3-week stabilization period of optimal therapy, including digitalis, diuretics and an ACE inhibitor, after which they were randomized to receive losartan 25 mg or 50 mg, or enalapril 20 mg, for 8 weeks$^{11}$. There were no significant differences between the effects of losartan and enalapril on exercise capacity in the 6-minute walk test, dyspnoea fatigue index, or neurohormonal activation, as assessed by plasma noradrenaline and N-terminal atrial natriuretic factor concentrations.

The effects of candesartan and enalapril in patients with heart failure were compared in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study$^{12}$. In this study, 768 patients with NYHA Class II-IV heart failure and left-ventricular ejection fractions below 40% were randomized to receive candesartan 4 mg, 8 mg or 16 mg alone, candesartan 4 mg or 8 mg plus enalapril 20 mg, or enalapril 20 mg alone, for 43 weeks. Endpoints included exercise capacity, measured by the 6-minute walk test, ejection fraction and ventricular volumes, measured by radionuclide angiography, neurohormone levels and NYHA functional class.

There were no significant differences between the effects of candesartan and enalapril monotherapies on ejection fraction or ventricular volumes (Fig. 2), or on heart rate or blood pressure. As expected, plasma levels of angiotensin II increased in candesartan-treated patients and decreased in enalapril-treated patients, but there were no significant differences in changes in aldosterone concentrations between the two treatments. Plasma levels of brain natriuretic peptide (BNP) tended to increase with both agents, but there were no significant differences between the two monotherapy groups.

Fig. 2. Changes in left-ventricular ejection fraction, end-diastolic volume (EDV) and end-systolic volume (ESV) in patients with NYHA Class II-IV heart failure treated for 43 weeks with candesartan 4 mg, 8 mg or 16 mg, or enalapril 20 mg, in the RESOLVD Pilot Study$^{12}$. Reproduced from McKelvie et al. 1999$^{12}$ with the permission of Lippincott, Williams & Wilkins.
Fig. 3. Mean changes in ejection fraction, end-systolic volume (ESV) and end-diastolic volume (EDV) in patients receiving candesartan or enalapril, alone or in combination, in the RESOLVD Pilot Study. *P < 0.05, 0.01 vs. baseline; †P < 0.05, 0.01 versus enalapril. Reproduced from McKelvie et al. 1999 with the permission of Lippincott, Williams & Wilkins.

Studies with AT₁-receptor blockers in combination with ACE inhibitors

Incomplete blockade of the renin-angiotensin system during long-term ACE-inhibitor therapy may contribute to symptomatic deterioration in patients with heart failure, and hence the possibility of combining an AT₁-receptor blocker with an ACE inhibitor to achieve maximal blockade has attracted interest. The possibility that some of the beneficial effects of an ACE inhibitor are due to prevention of the degradation of bradykinin by ACE provides a further rationale for combining an AT₁-receptor blocker with an ACE inhibitor. In one study, 33 patients with severe heart failure despite treatment with maximal doses of ACE inhibitors were randomized to receive losartan 50 mg or placebo in addition to their usual therapy. The addition of losartan resulted in a significant increase in exercise capacity, compared with placebo. Moreover, functional status improved by at least one NYHA class in 9 of 16 losartan-treated patients, compared with 1 of 17 patients in the placebo group.

In a further study, 109 patients with NYHA Class II-III heart failure received irbesartan, titrated to 150 mg/day, or placebo in addition to standard therapy with ACE inhibitors and diuretics. Exercise capacity and left-ventricular ejection fraction tended to improve in patients receiving irbesartan, compared with the placebo group, and the combination of an AT₁-receptor blocker and an ACE inhibitor was well tolerated.

The effects of valsartan 80 mg twice daily and 160 mg twice daily, in combination with long-term ACE-inhibitor therapy, were investigated in a randomized, placebo-controlled trial involving 83 patients with stable symptomatic (NYHA Class II-IV) heart failure. Compared with placebo, valsartan 160 mg twice daily produced significantly greater reductions in systolic blood pressure, pulmonary capillary wedge pressure, and pulmonary artery diastolic pressure. Valsartan-treated patients also showed a significant decrease in plasma aldosterone from baseline, whereas aldosterone concentrations did not change significantly in placebo-treated patients.

Combination therapy with candesartan and enalapril was compared with the respective monotherapies in the RESOLVD Pilot Study. Left-ventricular end-systolic and end-diastolic volumes increased to a significantly (P < 0.01) lesser extent in patients receiving combination therapy than in either of the monotherapy groups (Fig. 3). The blood-pressure reductions achieved with combination therapy, although modest, were significantly greater than those achieved with either agent alone. Despite the modest reduction in blood pressure found with the combination therapy, there was no increase in the heart rate. The addition of enalapril significantly attenuated the increase in plasma angiotensin-II concentrations seen in candesartan-treated patients, and plasma concentrations of BNP were significantly (P < 0.01) lower with combination therapy than with either candesartan or enalapril monotherapy.

AT₁-receptor blockers and ACE inhibitors in combination with ß-blockers

Patients in the RESOLVD Pilot Study who were eligible for ß-blocker therapy (n=426) were further randomized after 19 weeks to receive metoprolol controlled release (CR) or placebo in addition to their previous study medication. Triple neurohormonal blockade with candesartan, enalapril and metoprolol CR resulted in a significant increase in left-ventricular ejection fraction (LVEF) and reductions in end-systolic and end-diastolic volumes, compared with dual neurohormonal blockade (P < 0.01) (Fig. 4). These findings show that the combination of candesartan, enalapril and metoprolol CR has a beneficial effect on cardiac function and remodelling in patients with heart failure. They thus support the results of the CHARM-Added study.
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Fig. 4. Mean changes in left-ventricular end-systolic volume (ESV), end-diastolic volume (EDV) and ejection fraction (LVEF) in patients receiving candesartan or enalapril, alone or in combination, with or without metoprolol CR in the RESOLVD Study. *P<0.01 vs. baseline and either monotherapy; **P<0.001 vs. baseline and either monotherapy, P<0.01 vs. combination therapy; ***P<0.0001 vs. baseline, P<0.01 vs. combination therapy, P<0.001 vs. either monotherapy.

Fig. 5. Effects of valsartan on left-ventricular ejection fraction (EF) and internal diastolic diameter (LVIDd) in patients treated with ACE inhibitors (ACEI) or β-blockers (BB), alone or in combination, in the Val-HeFT Study. Reproduced from Wong et al. 2002, copyright 2002, with permission from Excerpta Medica.

which showed that the addition of candesartan to treatment with ACE inhibitors and β-blockers reduced the incidence of cardiovascular death or hospitalization for heart failure by approximately 15% compared with placebo. This presumably reflects the improvement in survival associated with smaller cardiac volumes.

The findings with triple neurohormonal blockade in the RESOLVD Pilot Study contrast with the results of the Valsartan Heart Failure Trial (Val-HeFT) echocardiographic substudy. As in the RESOLVD Pilot Study, Val-HeFT found that the addition of an AT₁-receptor blocker to ACE-inhibitor therapy resulted in improvements in left-ventricular ejection fraction and neurohormones. However, in this study, the addition of valsartan to treatment with an ACE inhibitor plus a β-blocker had no effect on ejection fraction or end-diastolic volume (Fig. 5). This is consistent with the finding in Val-HeFT that the addition of valsartan to an ACE inhibitor and a β-blocker did not improve clinical outcome. These apparent differences between RESOLVD and Val-HeFT could be due to differences in patient characteristics and study design, but could also reflect differences between candesartan and valsartan, and the extent of AT₁-receptor blockade achieved with the doses used.
The good tolerability of triple combination therapy with AT1-receptor blockers, ACE inhibitors and β-blockers is illustrated by the finding in the RESOLVD Study that there were no significant differences in changes in blood pressure between the treatment groups. As would be expected, heart rate decreased significantly in metoprolol-treated patients, but there was no significant difference in the incidence of hyperkalaemia or increases in serum creatinine between the groups.

Conclusions
Mechanistic studies of haemodynamics, neurohormones and functional capacity have shown that AT1-receptor blockers have beneficial effects on these endpoints, compared with placebo. AT1-receptor blockers are at least as effective as ACE inhibitors, and can safely be combined with ACE inhibitors to achieve enhanced blockade of the renin-angiotensin system. Moreover, the RESOLVD Pilot Study has shown that the combination of candesartan with ACE inhibitors and β-blockers has a favourable effect on cardiac remodelling, which may be one of the reasons for the significant reductions in cardiovascular mortality and morbidity seen in the CHARM-Added Study. AT1-receptor blockers, therefore, have a valuable role in the management of heart failure.

References