The role of candesartan in the treatment of chronic heart failure

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Abstract

The renin-angiotensin system (RAS) plays a fundamental role in cardiovascular pathophysiology. In particular, angiotensin II (AII) has been identified as a culprit in endothelial and vascular damage, elevated blood pressure, and cardiac failure. Pharmacological inhibition of this system is available through two mechanisms; the reduction of AII formation by inhibition of angiotensin-converting enzyme (ACE), and by direct blockade of the type 1 angiotensin II receptor by angiotensin II receptor blockers (ARBs).

Angiotensin-converting enzyme (ACE) inhibitors have a proven role in the management of elevated blood pressure and diabetes and may confer specific vascular benefit. In patients with chronic heart failure (CHF) secondary to left ventricular systolic dysfunction (LVSD), there is extensive evidence that, when compared to placebo, ACE inhibitors reduce morbidity and mortality. Randomised placebo controlled trials have also shown ACE inhibitors reduce all-cause mortality and major cardiovascular events after myocardial infarction.

Given the unequivocal benefit of ACE inhibitors, initial studies with ARBs in patients with LV dysfunction (in CHF and following myocardial infarction) have focused on two areas: the role of ARBs when compared with ACE inhibitors, and when combined with ACE inhibitors.

Only recently, with the results of the CHARM study, have the role of ARBs when compared to placebo in a population with CHF been clarified. This study also addressed the benefit of ARBs in patients with heart failure and preserved LV systolic function.

Key words: candesartan, angiotensin II receptor blockers, heart failure, hypertension, diabetes, CHARM trial.

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The role of ARBs in left ventricular dysfunction

CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study)[1] first demonstrated the benefit of the angiotensin-converting enzyme (ACE) inhibitor enalapril, when compared to placebo, in patients with severe (NYHA class IV) heart failure and reduced systolic function. The same drug was subsequently shown to be beneficial in patients with less advanced heart failure in the SOLVD (Studies of Left Ventricular Dysfunction) Treatment trial.[2] These and other trials have shown clearly that ACE inhibitors reduce mortality and morbidity (hospital admissions) in patients with heart failure.

It is well recognised that some patients cannot tolerate ACE inhibitors. Furthermore, even in those who do, prognosis remains poor. This may, in part, be explained by the phenomenon of 'aldosterone escape' whereby, in patients with heart failure on long-term ACE inhibitor treatment, aldosterone values, which initially fall, return to pre-treatment levels. This observation led to suggestions that renin-angiotensin system (RAS) suppression with ACE inhibitors might be incomplete. An attractive hypothesis was that angiotensin II receptor blockers (ARBs) might offer more 'complete' RAS inhibition and thus better outcome.

Safety and efficacy

ELITE-1 (Evaluation of Losartan In The Elderly study)[3] demonstrated in 1997 the comparative tolerability (primarily on renal function) of the ARB losartan compared to captopril in patients

over the age of 65 with chronic heart failure (CHF). A significant reduction in sudden death in the losartan group was an unexpected finding on sub-group analysis. The ELITE II study discussed below was designed to confirm this observation.

In patients with NYHA class II–IV CHF, investigation of clinical surrogates showed no difference in six-minute walk test, ventricular function, NYHA class or quality of life at 18 or 43 weeks among the three groups in patients taking candesartan alone, enalapril alone or candesartan and enalapril combined in the RESOLVD (Randomised Evaluation of Strategies for Left Ventricular Dysfunction) pilot study.[4] The combination of candesartan and enalapril was reported to have greater benefit on left ventricular remodelling than either agent on its own. Follow-up at 43 weeks did not show any significant differences in hospitalisations for CHF or hospitalisations for any cause among the three groups. In contrast to ELITE I there was also no difference in mortality.

The SPICE pilot study for the CHARM (Candesartan Heart Failure – Assessment of Reduction in Mortality and morbidity) programme compared the ARB candesartan with placebo and found it was well tolerated in 270 patients with CHF intolerant of ACE inhibitors because of adverse effects.[5]

Outcome trials comparing ARB and ACE inhibitors

ELITE II,[6] which reported in 2000, was the first major ARB mortality and morbidity trial in CHF. The study, in effect, repeated the design of ELITE I but with sufficient numbers and power to detect a difference (but not equivalence) in mortality between losartan 50 mg daily and captopril 50 mg t.d.s. in patients over the age of 65, with NYHA class II–IV CHF. All-cause mortality with losartan was 17.7% compared with 15.9% for captopril (p=0.16). Losartan was, however, better tolerated. It has subsequently been argued that the dose of losartan used was too low.

Outcome trials combining ARBs and ACE inhibitors in CHF

Whilst small-scale trials of combined therapy had indicated lack of harm (e.g. RESOLVD) there remained the issue of adequacy of RAS inhibition. The possibility that optimal clinical outcome with RAS inhibition required a combination ACE inhibitor and ARB was tested in Val-HeFT (Valsartan Heart Failure Trial).[7]

This was the second major trial of ARBs in CHF and investigated whether adding a maximal dose of valsartan (up to 160 mg b.d.) to standard therapy in 5,010 patients with NYHA class II–IV heart failure, would reduce all-cause mortality when compared to usual treatment plus placebo. In this study 93% of patients were taking ACE inhibitors and 35% beta blockers, representing optimal CHF therapy at that time. After 23 months, all-cause mortality was no different (19.7% *vs.* 19.4% for valsartan and placebo respectively). Hospitalisation for heart failure was significantly reduced with valsartan (13.8% *vs.* 18.2%, p<0.001). The mean achieved dose of valsartan was 254 mg.

The trial added a caveat. Post-hoc analysis showed that valsartan had an adverse effect when given to the 1,610 patients already taking both ACE inhibitors and beta blockers. At the time, fears were raised that the combination of 'complete' RAS inhibition combined with beta blockade might reflect excessive neuro-hormonal inhibition.

Outcome trials of ARBs and ACE inhibitors post-MI

Two studies have investigated the role of ARBs in patients with LV dysfunction following myocardial infarction (MI). The first study to report in 2002, OPTIMAAL (Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan),[8] followed a similar design to ELITE II and compared the effect of losartan 50 mg daily with captopril 50 mg t.d.s. on all-cause mortality in over 5,000 patients following MI. After a mean follow-up of 2.7 years there was a non-significant excess of all-cause death in the losartan group (499 [18%] *vs.* 447 [16%], p=0.07). No difference was observed in all-cause hospital rates. Losartan was significantly better tolerated (discontinuations 17% *vs.* 23%, p<0.0001).

The VALIANT (Valsartan in Acute Myocardial Infarction) trial,[9] which reported in 2003, studied the effect of three treatment groups (captopril, valsartan and their combination) on all-cause mortality in 14,000 patients following MI. At 24.7 months, 979 (19.9%) of patients in the valsartan group had died, compared to 958 (19.5%) in the captopril group and 941(19.3%) in the combination group. Statistical analysis confirmed non-inferiority for valsartan versus captopril (p=0.004). Combining valsartan with captopril increased the rate of adverse events without improving survival.

Unanswered questions

Prior to the publication of the CHARM studies, several questions regarding the role of ARBs in CHF remained:

- The question of whether ARBs were better than placebo was unanswered. For all-cause mortality, ARBs appeared to be no worse than ACE inhibitors when given alone and thus served as an alternative in patients intolerant of ACE inhibitors.
- The use of an ACE inhibitor/ARB combination was more difficult to discern, with a potential benefit in improving symptoms and reducing hospitalisations. Whether this combination was safe was uncertain. The expanding evidence base for benefit with beta blockade when added to ACE inhibition suggested that the ACE inhibitor/ARB combination might best be reserved for patients who could not tolerate a beta blocker.
- It had been increasingly recognised that many cases of heart failure occur in patients in whom there is no evidence of significant systolic LV dysfunction. The role of ARBs in the management of heart failure with preserved left ventricular systolic function remained unknown.

The CHARM programme

The CHARM programme was designed as three parallel, independent, integrated trials comparing candesartan with placebo in three distinct but complementary populations of patients with

Table 1. Results from the CHARM-Alternative trial

	Candesartan n=1,013	Placebo n=1,015	Adjusted hazard ratio	p
CV death or hospitalisation for CHF	334 (33%)	406 (40%)	0.70	<0.0001
CV death	219 (22%)	252 (25%)	0.80	0.02
Hospitalisation for CHF	207 (20%)	286 (28%)	0.61	<0.0001
CV death, hospitalisation, MI, stroke, revascularisation	396 (39%)	456 (45%)	0.76	<0.0001
Deaths any cause	265 (26%)	296 (29%)	0.83	0.033

Key: CV = cardiovascular; CHF = chronic heart failure; MI = myocardial infarction

Table 2. Results from the CHARM-Added trial

	Candesartan n=1,276	Placebo n=1,272	Adjusted hazard ratio	p
CV death or hospitalisation for CHF	483 (38%)	538 (42%)	0.83	0.01
CV death	302 (24%)	347 (27%)	0.83	0.021
Hospitalisation for CHF	309 (24%)	356 (28%)	0.83	0.018
CV death, hospitalisation, MI, stroke, revascularisation	548 (43%)	596 (47%)	0.87	0.018
Deaths any cause	377 (30%)	412 (32%)	0.89	0.105

Key: CV = cardiovascular; CHF = chronic heart failure; MI = myocardial infarction

symptomatic heart failure.[10] Results from the CHARM programme were presented at the European Society of Cardiology in September 2003 and published in the *Lancet.*

The CHARM-Alternative trial[11] set out to examine the effects of candesartan in patients with heart failure and reduced left ventricular systolic function, who were intolerant of ACE inhibitors. The CHARM-Added trial[12] investigated whether combining candesartan with ACE inhibition would affect clinical outcome. The CHARM-Preserved trial[13] was designed to examine the effects of candesartan on cardiovascular mortality and hospitalisation for management of CHF in patients with preserved left ventricular ejection fraction (LVEF). The three groups were then included in a predetermined analysis presented as CHARM-Overall.[14] In all studies the target dose of candesartan was 32 mg daily.

CHARM-Alternative

This trial included patients with symptomatic heart failure and an ejection fraction of < 0.40, who had ACE inhibitor treatment discontinued by a physician because of drug intolerance. The most common manifestations of ACE inhibitor intolerance before study entry were cough (72%), symptomatic hypotension (13%) and renal dysfunction (12%). Patients were randomised to candesartan or placebo. At baseline, 55% of patients were taking beta blockers and 24% spironolactone. A total of 2,028 patients with a mean ejection fraction of 30% were followed for 33.7 months. Study drug discontinuation rates were similar at 30% for candesartan and 29% in the placebo group.

Results are summarised in table 1. Candesartan significantly reduced both cardiovascular death and hospitalisation for heart failure. Candesartan was well tolerated with a mean dose at six months of 23 mg/day compared to 27 mg/day for placebo. Although patients with previous ACE inhibitor discontinuation because of renal insufficiency and hypotension were more likely to have a recurrence while taking candesartan than placebo, most patients with these histories tolerated candesartan. Three cases of angioedema occurred with candesartan (0 with placebo). None required hospital admission; all occurred in patients who had experienced angioedema with ACE inhibitors (of whom there were 39 in total).

Importantly this study addresses one of the key outstanding questions regarding ARBs in CHF. When compared to placebo, the 23% reduction in cardiovascular mortality and hospital admission in the candesartan group is similar to the 26% relative reduction seen with enalapril in the SOLVD treatment trial. It must be noted that the benefit seen with candesartan is on top of current therapy with far wider use of beta blockade than in earlier studies with ACE inhibitors. This study suggests, though does not prove, that candesartan may be as effective as an ACE inhibitor in patients with LVSD.

CHARM-Added

This trial included patients with functional NYHA class II–IV heart failure and an ejection fraction of < 0.40, who were being treated with ACE inhibitors. Enalapril, lisinopril, captopril and ramipril were the commonly used ACE inhibitors in the study patients, together accounting for 74% of all ACE inhibitors used. The mean daily dosage of ACE inhibitor reflected optimum clinical practice in the view of the investigator, with 17 mg, 18 mg, 82 mg and 7 mg prescribed per day respectively. At baseline, 55% of patients were being treated with beta blockers and 17% with spironolactone.

A total of 2,548 patients with a mean ejection fraction of 28% were followed for 41 months. Overall 24% of patients in the candesartan group and 18% in the placebo group permanently discontinued study medication for adverse events or abnormal laboratory values (p=0.0003). There were higher rates of discontinuation for renal dysfunction and elevated serum potassium in the candesartan group. Among patients taking spironolactone, serum creatinine at least doubled in eight of 71

patients (11%) in the candesartan group and three of 71 (4%) in the placebo group (p=0.21).

A summary of the results in the CHARM-Added trial can be seen in table 2. Addition of candesartan to optimal treatment significantly reduced the risk of both cardiovascular death and hospitalisation for heart failure. The achieved ACE inhibitor dose of 17 mg of enalapril equates to an achieved dose of 16.6 mg in the SOLVD study and 17 mg in Val-HeFT. This benefit was seen in all pre-defined subgroups including patients taking both beta blockers and ACE inhibitors. Of these patients, 175 (25%) of 702 died in the candesartan group versus 195 (27%) of 711 in the placebo group (hazard ratio 0.88, p=0.22).

The trial results appear to conflict with those from Val-HeFT, in which a worse outcome was observed in the 35% of patients in whom valsartan was added to both beta blockers and ACE inhibitors. The differences between the results may be explained by the type or dose of ARB used, or by underpowered analyses of small subgroups in Val-HeFT.

RALES (Randomised Aldactone Evaluation Study)[15] investigated the benefit of spironolactone in patients with LVSD and NYHA class III or IV symptoms already taking ACE inhibitors (95% of patients) and beta blockers (11% of patients). The study was discontinued early following the finding of a 30% reduction in all-cause mortality and a 35% reduction in hospitalisation for heart failure (p<0.001 for both). NYHA class also improved significantly (p<0.001).

Both CHARM-Added and RALES lend credence to the view that a more 'complete' RAS inhibition with combined ACE inhibition and angiotensin II receptor blockade is advantageous in patients on optimal treatment with ACE inhibitors and beta blockers who still have symptoms. In the 'added' study, 17% of patients in the candesartan group were, in effect, on a 'quadruple therapy' of ACE inhibitors, ARBs, beta blockers and spironolactone.

CHARM-Preserved

Although patients with heart failure and reduced LVEF have worse outcomes than those with preserved ejection fraction, the latter group still has high rates of mortality and hospital admission for heart failure. Few treatments have been specifically assessed in patients with preserved ejection fraction. Current guidelines for treatment extrapolate recommendations from other patient groups. The CHARM-Preserved trial was designed to examine the effects of candesartan on cardiovascular mortality and hospitalisation in patients with NYHA class II–IV CHF and an ejection fraction higher than 0.40. A total of 3,025 patients with a mean ejection fraction of 54% were followed for 37 months. The achieved dosage was 25 mg and 28 mg for the candesartan and placebo groups respectively.

By the end of the study drug discontinuation rates were 22% for candesartan and 18% for placebo. In the candesartan group 18% of patients and 14% in the placebo group permanently discontinued study medication for adverse events or abnormal laboratory values (p=0.001). In 6% of patients taking candesartan, creatinine at least doubled compared to 3% of placebo (p=0.007).

Table 3. Results from the CHARM-Preserved trial

	Candesartan n=1,514	Placebo n=1,519	Adjusted hazard ratio	p
CV death or hospitalisation for CHF	333 (22%)	366 (24%)	0.86	0.051
CV death	170 (11%)	170 (11%)	0.95	0.635
Hospitalisation for CHF	241 (16%)	276 (18%)	0.84	0.047
CV death, hospitalisation, MI, stroke, revascularisation	460 (31%)	497 (33%)	0.87	0.130
Deaths any cause	244 (16%)	237 (16%)	Not given	Not given

Key: CV = cardiovascular; CHF = chronic heart failure; MI = myocardial infarction

The composite end point just failed to reach significance at 0.051 (see table 3). Cardiovascular death did not differ between the two groups. There were fewer first admissions to hospital for CHF in the candesartan group.

Post-hoc analysis of all hospital admissions for CHF showed significant benefit with candesartan (402 *vs.* 566, p=0.014).

Compared with the 'added' and 'alternative' trials, patients in the 'preserved' trials were older (mean age 64.0, 66.5 and 67.2 years respectively) and there were more women (40%). Patients were also more likely to have a history of hypertension and less likely to have had a prior MI. It is of note that, in a population of whom 65% were reported to have hypertension, there was a 6.9/2.9 mmHg difference in blood pressure at six months.

This study is the first in a heart failure population to demonstrate a significant reduction in the development of diabetes. Compared with the placebo group 40% fewer individuals in the candesartan group developed diabetes (77 *vs.* 44, p=0.005).

Given the known lesser mortality in patients with heart failure and preserved LV function (when compared with systolic LV dysfunction) the trial may have been underpowered to show benefit given that follow-up was of similar duration to the systolic groups.

CHARM-Overall

As part of the CHARM programme, pre-specified analysis was performed on the combined groups and published as a separate paper alongside the three studies. Overall, 3,803 patients were assigned to candesartan and 3,796 to placebo. The median duration of follow-up was 37.7 months.

There was no overall difference in the primary outcome of all-cause death: 886 (23%) patients in the candesartan group and 945 (25%) in the placebo group died (unadjusted; 0.91, p=0.055, co-variate adjusted 0.90, p=0.032), with fewer cardiovascular deaths (691 [18%] *vs.* 769 [20%], 0.87, p=0.006) and hospitalisations for heart failure (757 [20%] *vs.* 918 [24%],

p=0.0001) respectively. The failure to achieve overall reduction in all-cause death was primarily driven by the inclusion of the 'preserved' group.

The treatment difference in cardiovascular mortality was most striking in the first year and was then maintained without additional divergence. There were slightly more non-cardiovascular deaths in the candesartan group (195 [5%] *vs.*176 [5%]; p=0.45), which was due to a difference in cancer deaths (86 [2.3%] *vs.* 59 [1.6%], p=0.038). The incidence of non-fatal neoplasms was similar at 185 *vs.* 194 (p=0.49). Overall more patients discontinued candesartan because of concerns about renal function, hypotension and hyperkalaemia.

The reduction in risk of cardiovascular death or CHF hospitalisations with candesartan was similar in men and women, in patients above and below the age of 75 years, and across the NYHA classes. Candesartan was similarly effective in patients with LVEF above and below 40%. Similar benefits were seen whether or not ACE inhibitors, beta blockers, spironolactone, any diuretic, digoxin, aspirin or lipid-lowering drugs were used at baseline.

The validity of the overall analysis remains uncertain insofar as the 'preserved' trial may be investigating a different pathological entity to the established systolic LV dysfunction seen in the 'added' and 'alternative' studies. It has been suggested that the population in the 'preserved' trial may have more in common with recent studies investigating the role of ARBs in hypertension. This comparison is difficult to make. The LIFE study,[16] which investigated the benefit of blood pressure lowering in patients with elevated blood pressure and left ventricular hypertrophy (but excluded patients with heart failure), observed a cardiovascular mortality rate of 10.6 per 1,000 patient years and a stroke rate 14.5 per 1,000 years in the placebo group. In CHARM-Preserved, the cardiovascular mortality rate was approximately 37 per 1,000 patient years, although the placebo stroke rate was similar at approximately 13.7 per 1,000 patient years. As in other areas of cardiovascular disease, it appears that the development of overt heart failure indicates a discontinuity in the pathological process with a dramatic increase in mortality.

Recently, a pre-specified analysis in the group of CHARM patients with heart failure and reduced LVEF (n=4,576; LVEF ≤ 40%) was presented at the European Society of Cardiology Congress 2004 meeting in Munich, Germany (28th August to 1st September 2004).[17] This demonstrated a 12% relative risk reduction in all-cause mortality (p=0.018) and a 16% relative risk reduction in cardiovascular deaths (p=0.005) when candesartan was added to standard treatment.[17] This new analysis also shows a 24% relative risk reduction in heart failure hospital admissions. The effect of treatment with candesartan was similar irrespective of background medication with ACE inhibitors, beta blockers or spironolactone. Such findings have reinforced the benefit of candesartan in patients with left ventricular systolic dysfunction.

Conclusion

So what are the clinical implications of the CHARM programme? Firstly, the ARB candesartan (at a target dose of 32 mg daily) is highly effective in patients with LVSD when ACE inhibition is not tolerated. There is now no question that all patients with LVSD who do not tolerate ACE inhibitors should be given an ARB.

Secondly, should ARBs be used first line in heart failure? It appears likely, but cannot be proved by the CHARM study, that candesartan is as effective as an ACE inhibitor in patients with LVSD. Without a head-to-head study of ACE inhibition versus angiotensin II receptor blockade in LVSD (which is unlikely to happen), this question will remain open to debate. There is no evidence that ARBs are superior but they are better tolerated than ACE inhibitors. If two medications are equivalent in clinical efficacy but one is better tolerated, then it could be argued that the better-tolerated agent is the drug of choice.

Thirdly, what should be done with patients who are taking and ACE inhibitor and a beta blocker? The 'added' study included patients who remained symptomatic (24% NYHA class II, 73% NYHA class III heart failure). In these patients both cardiovascular death and admission for heart failure was reduced by candesartan. Whilst a small but significant improvement in NYHA class across the three studies overall, was reported at the American College of Cardiology in March 2004, the degree of symptomatic improvement in the 'added' group is not yet known. Where patients remain asymptomatic the decision is less clear, although the reduction in multiple admission suggests that patients with a prior history of repeated hospitalisation might benefit.

The concerns raised in the Val-HeFT study over excessive neuro-hormonal blockade were not substantiated in the CHARM-Added study. The choice of whether to add spironolactone or an ARB remains uncertain. The greater usage of both ACE inhibitors and beta blockers in the CHARM study, compared to RALES, more closely reflects current practice and treatment

Key messages

- In patients with left ventricular systolic dysfunction, ARBs (at optimal dose) should be given if ACE inhibition is not tolerated
- Angiotensin receptor blockade may be considered first-line therapy for systolic heart failure, since efficacy appears comparable to ACE inhibition with better tolerability
- The addition of an ARB in patients already on optimal treatment with ACE inhibitors and beta blockers reduces events in symptomatic patients with left ventricular systolic dysfunction
- Candesartan is the first ARB in the UK to be granted a license for use in patients with left ventricular systolic dysfunction
- Use of an ARB in patients with symptomatic heart failure and preserved LV function may decrease morbidity

recommendations. It is possible that disease markers such as brain natriuretic peptide may have a role in guiding these complex treatment decisions in the future.

Finally, there remains the problem of treating heart failure in patients with preserved systolic function. The CHARM-Preserved study takes us a step closer by showing a decrease in admissions with candesartan. Forthcoming studies will provide more information.

Conflict of interest

HFM has received financial support for speaker meetings, consultancy and research from pharmaceutical companies marketing angiotensin II receptor blockers, including AstraZeneca, Merck Sharp & Dohme, Novartis and Takeda.

Editors' note

It has been recently announced that candesartan is the first ARB to receive UK approval for the treatment of heart failure and impaired LVSD. It can be included as an effective additional treatment in those patients already taking a comprehensive range of drugs and also be given as an alternative to an ACE inhibitor in those patients who have developed ACE inhibitor intolerance.

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