Angiotensin II receptor antagonists in the treatment of heart failure: background to and design of the CHARM study

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Abstract

While angiotensin-converting enzyme (ACE) inhibitors are established agents for the treatment of hypertension and heart failure, in contrast the angiotensin II receptor antagonists (AIIRAs) have failed to demonstrate more than equivalence in randomised clinical trials. Trials such as ELITE II are criticised on the grounds that the dose used of losartan (50 mg) may have been sub-optimal. In ValHeFT, valsartan was shown to be superior to placebo only in patients who did not also receive a beta blocker. The ambiguity of response of AIIRAs in such trials will hopefully be clarified in CHARM, a large, placebo-controlled study which will assess the effects of candesartan in heart failure patients with either reduced ejection fractions in addition to an ACE inhibitor, and in those intolerant to an ACE inhibitor, as well as in patients with preserved ventricular function (diastolic heart failure) not on an ACE inhibitor. The design of the study is discussed.

Key words: angiotensin II receptor antagonists (AIIRAs), heart failure, losartan, valsartan, candesartan, CHARM.

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Introduction

In the treatment of heart failure, the path to proving the role for angiotensin II receptor antagonists (AIIRAs) is a continuing frustration. Whilst angiotensin-converting enzyme (ACE) inhibitors clearly improve both symptoms and survival in heart failure,[1,2] the situation for the AIIRAs is less clear.

At first sight, the AIIRAs appear an obvious choice as an alternative therapy to ACE inhibitors in heart failure. The rationale for this arises from several observations. ACE inhibitors do not always suppress concentrations of angiotensin II in patients with heart failure;[3] presumably a reflection of the existence of other enzyme pathways that escape ACE inhibition.[4] In addition, if higher doses of ACE inhibitors are significantly better than low doses in reducing mortality and symptoms for heart failure (ATLAS study),[5] then the attraction of a product that would occupy the vasoactive angiotensin AT_1 receptor seems obvious. The haemodynamic data for the AIIRAs are almost identical to those of the ACE inhibitors,[6-8] and have a side effect profile comparable to placebo. Moreover, in the majority of patients with heart failure that can tolerate an ACE inhibitor, concomitant therapy with an AIIRA might reasonably be assumed to be of greater benefit than either as monotherapy. Despite theoretical optimism, the mortality for patients in heart failure treated with AIIRAs, either as monotherapy or combined with an ACE inhibitor, is disappointing.[9-12]

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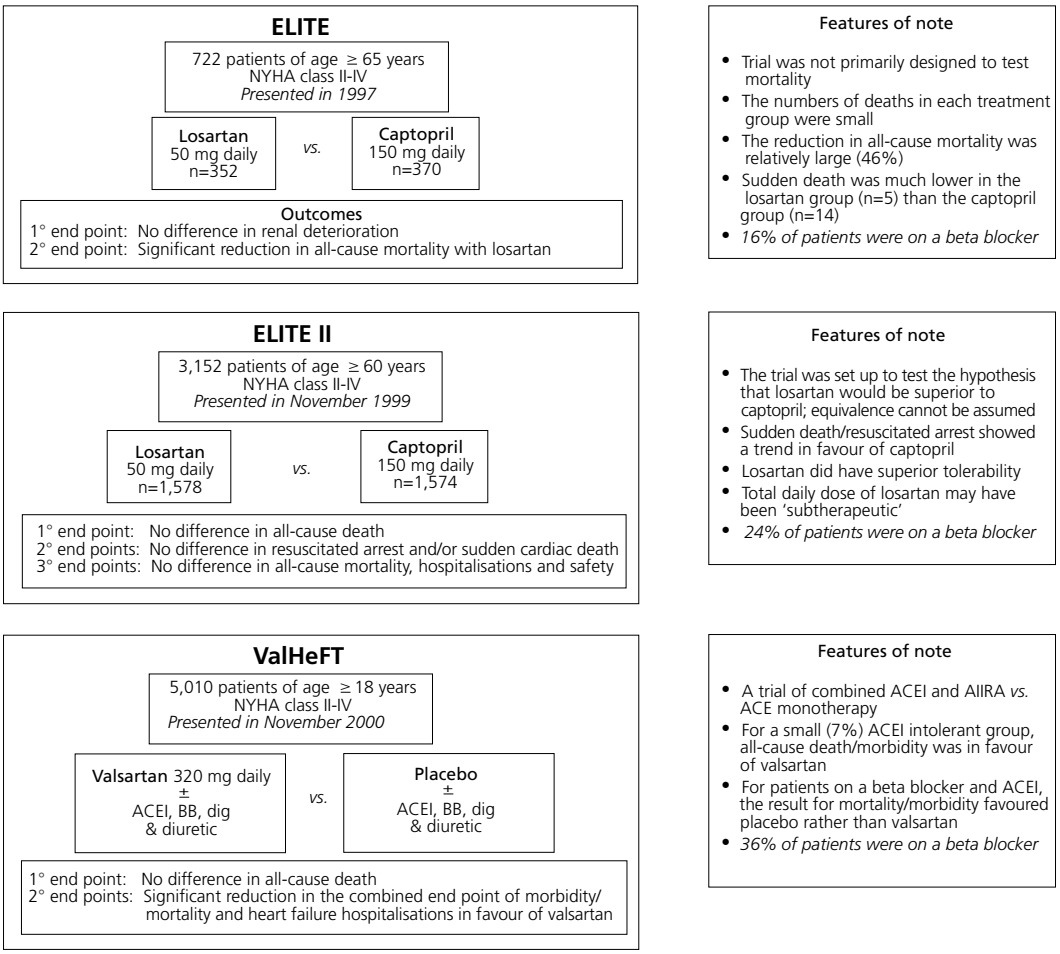
Background

Several small, randomised studies of patients with mild to severe heart failure have shown similar effects on haemodynamics, improvement in symptoms and exercise capacity, with both AIIRAs and ACE inhibitors.[13-18] The first study to suggest a mortality advantage for an AIIRA was the ELITE study (figure 1),[9] although this lacked statistical power. When losartan was compared against captopril in a much larger study (ELITE II),[10] (figure 1), investigators were alarmed to find no difference in mortality. It has been suggested that the responsibility for this result may lie in the fact that the dose of losartan (50 mg daily) may not have been optimal.

Figure 1. Design, outcomes and points to note in the three major trials of angiotensin receptor antagonists compared to other ACE inhibitors (ELITE, ELITE II) or as combination therapy (ValHeFT) in heart failure



Key: NYHA = New York Heart Association; 1° = primary; 2° = secondary; 3° = tertiary; ACEI = angiotensin-converting enzyme inhibitor; BB = beta blocker; dig = digoxin; AIIRA = angiotensin II receptor antagonist

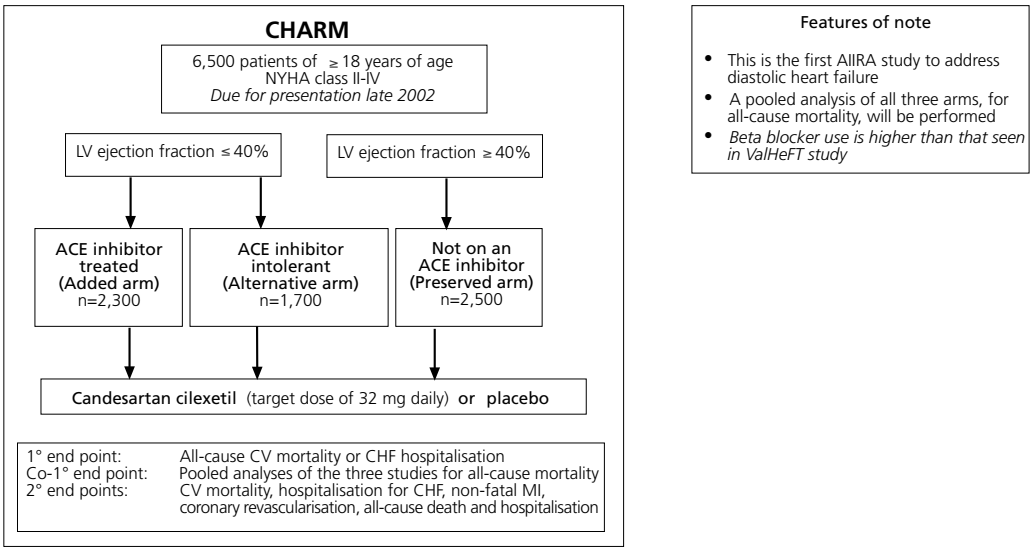
This early disappointment was further compounded by the result of the RESOLVD study.[11] RESOLVD was the first study to compare an AIIRA (candesartan) alone with the combination of candesartan and an ACE inhibitor (enalapril) and enalapril alone in congestive heart failure. In this study, the AIIRA appeared to confer a higher mortality when used alone or in combination with enalapril when compared to enalapril alone. However, the combination of candesartan and enalapril was more beneficial in preventing left ventricular dilatation and suppressing neurohormonal activation than either product alone. This result led to the development of the much larger CHARM trial which could assess major clinical outcomes.[19]

In November 2000, the ValHeFT (Valsartan and Heart Failure) trial reported.[12] This study recruited over 5,000 patients and compared a high dose of valsartan to placebo (figure 1). ValHeFT showed no difference in all-cause mortality between the two arms (valsartan group 19.7%, placebo group 19.4%). However, there was a significant (13%) reduction in the composite end point of mortality and heart failure hospitalisation. A surprising result was that the benefit of valsartan was only seen in patients who did not receive beta adrenergic receptor blockers (beta blockers) and in those not receiving an ACE inhibitor. The overall results suggest that valsartan and an ACE inhibitor, in combination, might benefit patients largely by a reduction in heart failure admissions and an improvement in New York Heart Association (NYHA) class and quality of life, but with no reduction in mortality.

The CHARM study

CHARM will be the largest study to-date of an AIIRA in patients with heart failure. It will recruit 6,500 patients with symptomatic heart failure from 26 countries in Europe, the United States, Canada, South Africa and Australia. The study is unique in having three arms (figure 2). Each one of these arms will address the

Figure 2. Design, end points and features of note in the CHARM study that will compare the angiotensin receptor antagonist, candesartan, with placebo, an ACE inhibitor or as a combination therapy



Key: NYHA = New York Heart Association; LV = left ventricular; ACE = angiotensin-converting enzyme; CV = cardiovascular; 1° = primary; 2° = secondary; AIIRA = angiotensin II receptor antagonist; CHF = congestive heart failure; MI = myocardial infarction

issues that are faced in the 'everyday world' of treating patients with heart failure. They are as follows:

- An 'alternative' arm consisting of patients who are intolerant to ACE inhibitors
- An 'added' arm in whom patients already on an ACE inhibitor are prescribed candesartan in addition
- A 'preserved' arm consisting of patients, who in broad terms, have diastolic heart failure.

The follow-up period is for a minimum of two years and the results are expected at the end of 2002.

The alternative arm of CHARM

The alternative arm will consist of candesartan as monotherapy compared to placebo in patients who are intolerant of an ACE inhibitor. Intolerance of an ACE inhibitor will be defined as a physician's decision to discontinue ACE inhibitor therapy due to drug-related adverse events, including angioedema, anaphylaxis, cough, symptomatic hypotension, renal dysfunction, taste disturbance, neutropenia, rash or gastrointestinal upset. The 1,700 patients in this group will have a left ventricular ejection fraction of < 40%. One of the more interesting results to emerge from the ValHeFT study was the data on those patients who were intolerant of an ACE inhibitor and were prescribed valsartan as monotherapy.[12] Despite small numbers in this subanalysis (7% of study population), the result showed a 45% reduction in the combined mortality/morbidity outcome in favour of valsartan. In the case of candesartan, a previous, smaller study (SPICE) has shown that patients with heart failure and intolerant of ACE inhibitors can tolerate and do benefit from candesartan as an alternative therapy.[18]

The added arm of CHARM

In this arm, the choice of ACE inhibitor therapy is at the discretion of the investigator and no dose is specified. It is mandatory that this group of patients have been on an ACE inhibitor for a minimum of 30 days before randomisation. Patients treated with an ACE inhibitor will be randomised to candesartan or placebo. This is perhaps the most poignant of the groups to be randomised, particularly as even more patients will be on beta blockers. One downside to the ValHeFT results was a trend to an unfavourable interaction when AIIRAs, ACE inhibitors and beta blockers were used in combination.

The 'preserved' systolic function arm of CHARM

Diastolic heart failure accounts for 40–50% of all cases of heart failure;[20,21] to-date there are no proven therapies for this form of the disease. Evidence is emerging that AIIRAs might be as effective as the ACE inhibitors in patients with diastolic heart failure.[22] An interesting patient group in the CHARM study will be the 'preserved' group in whom left ventricular systolic function is greater than 40%. These patients have a history of having been hospitalised for a cardiac reason and have had signs and symptoms of cardiac failure. Patients in this group will not receive an ACE inhibitor and will be randomised to either candesartan or placebo. As might be predicted, between a third to half of these patients have recognised precursors of diastolic heart failure, including hypertension, left ventricular hypertrophy, diabetes and ischaemia.

The primary end point will be assessing whether candesartan, compared with placebo, will reduce the combined end point of

Table 1. Major ongoing clinical trials (> 1,000 patients) of the angiotensin II receptor antagonists in patients with heart failure

Drug	Name of study	Patient numbers	Basic design, aims and outcomes
Candesartan	CHARM	6,500	Heart failure (systolic and diastolic arms) mortality Candesartan alone or with an ACE inhibitor *vs.* placebo
Irbesartan	I-PRESERVE	3,600	Diastolic heart failure study. Mortality and hospitalisations Irbesartan *vs*. placebo

cardiovascular death or hospitalisation for heart failure. In addition, a pooled analysis of all three study arms will examine all-cause mortality.

Other trials of AIIRAs

In addition to the CHARM study, several other studies are recruiting patients either with heart failure (table 1) or with a cardiovascular risk profile (renal impairment, diabetes, hypertension and post-myocardial infarction) in whom heart failure will be included as an end point (table 2). The reason for including the latter type of studies, which relate to disease precursors of heart failure, is illustrated by the recent results of the RENAAL study.[23] Despite being a study of losartan versus placebo in patients with renal impairment, a secondary end point of a 32% reduction in hospitalisation for heart failure was seen. Hence, some very useful information is likely to emerge from a host of AIIRA studies currently underway.

Randomised, controlled studies on diastolic heart failure are rare. Aside from CHARM, a large study of 3,600 patients is about to start recruitment and will test the AIIRA, irbesartan, against placebo (I-PRESERVE). The I-PRESERVE study will include patients of NYHA class II to IV with left ventricular ejection fractions of > 45%. The estimated treatment period is four years and the study will report in 2006. The only other large study on diastolic heart failure involves the ACE inhibitor, perindopril, (PEP-CHF).[24] PEP-CHF is a placebo-controlled study of 1,000 patients greater than 70 years of age, and will hopefully report in early 2004.

Discussion

A recent meta-analysis of 16 randomised, clinical trials with a total of 12,433 patients, comparing AIIRAs, ACE inhibitors and placebo in heart failure, found that AIIRAs – when compared to ACE inhibitors – did not reduce mortality or hospitalisation. The combination of an AIIRA and an ACE inhibitor was superior to ACE alone in reducing hospitalisation but not mortality.[25] An additional confounding factor in these studies has been the increasing use of beta blockers as concomitant therapy for heart failure. Beta blockers not only have a substantial body of evidence of improvement in morbidity and mortality for this condition, but have also been shown to achieve a reduction in angiotensin II levels.[26] This might explain why patients treated

Table 2. Major clinical trials (> 1,000 patients) of the angiotensin II receptor antagonists in which heart failure is an outcome measure

Drug	Name of study	Patient numbers	Basic design, aims and outcomes
Losartan	OPTIMAAL	5,477	Post-myocardial infarction mortality study Losartan *vs.* captopril
	LIFE*	9,194	Hypertension mortality study Losartan *vs*. atenolol-based regimes
	RENAAL*	1,500	Non-insulin dependent diabetic patients, renal function Losartan *vs.* 'usual renal care'
Candesartan	SCOPE	5,000	Hypertensive patients and cardiovascular end points Candesartan *vs*. placebo
Valsartan	VALUE	14,500	Hypertension mortality study Valsartan *vs*. amlodipine
	VALIANT	14,500	Post-myocardial infarction mortality study Valsartan *vs*. captopril
Irbesartan	IDNT	1,600	Non-insulin dependent diabetic patients, renal function Irbesartan *vs*. amlodipine and 'usual therapy'
Telmisartan	ONTARGET	23,400	High cardiac risk profile patients - global cardiovascular outcomes Telmisartan alone or with ramipril *vs*. ramipril alone
	TRANSCEND	5,000	High cardiac risk profile patients - global cardiovascular outcomes Telmisartan *vs*. placebo

Key: * studies which have reported

with ACE inhibitors and beta blockers, where the angiotensin II levels are markedly suppressed, see little additional benefit from the addition of an AT_2 receptor.

Potential explanations of the variable results with AIIRAs and ACE inhibitors *per se* are several fold. They may lie in the fact that the mechanism of angiotensin II receptor blockade has several differences to that which occurs with ACE inhibitors. ACE is physiologically involved in the degradation of bradykinin – its inhibition by an ACE inhibitor will lead to local accumulation and vasodilatation. Bradykinin is a peptide that can trigger the release of nitric oxide and prostacyclin from the endothelium and, by this mechanism, cause vasodilatation. Thus, a blood pressure-lowering and haemodynamic off-loading by the ACE inhibitors may in part be due to an accumulation of bradykinin. Recent evidence has also shown that bradykinin might be protective against left ventricular hypertrophy.[27] The well-recognised association between left ventricular hypertrophy and sudden death or cardiovascular sequelae might explain how ACE inhibitors, through an elevation in bradykinin, could offer a survival advantage when compared to AIIRAs.[28]

Secondly, in ACE inhibition of the renin-angiotensin system, there is an almost complete removal of angiotensin II from the circulation; in AIIRA use there is a reactive hyper-reninaemia and

Key messages

- ACE inhibitors have established benefits in heart failure
- AIIRAs have not shown superiority to ACE inhibition in heart failure trials
- Heart failure trials with AIIRAs are criticised and findings are ambiguous
- CHARM is a large trial which will address and, ideally, clarify the role of AIIRAs in heart failure

increased circulating levels of angiotensin II. Angiotensin II will interact with the sympathetic nervous system, specifically the brain stem cardiovascular centres and, hence, will influence neurogenic control of the vascular system. It has been suggested that the profound blockade of the sympathetic nervous system by triple neurohormonal therapy (ACE inhibitor, AIIRA and beta blocker) will result in significant loss of sympathetic tone and a disruption of cardiac autonomic innervation. This might explain the adverse outcome to such patients in the recent ValHeFT study. An alternative explanation might be that such triple neurohormonal blockade might induce a harmful reduction in blood pressure, particularly in patients with an ischaemic aetiology to their heart failure.

The function of the angiotensin AT_2 receptor is also unclear, although stimulation of these receptors in humans has no discernible cardiovascular action. A comprehensive review of the angiotensin II receptors and antagonists can be found in the recent article by Burnier and Brunner.[29]

Currently, no AIIRA is licensed for use in heart failure in the UK. In the United States, the Food and Drug Administration are divided on whether to pass valsartan as a result of the ValHeFT study. A recent *Drug and Therapeutics Bulletin* publication stated that "whether they (AIIRAs) should be used in preference to, or in addition to, ACE inhibitors for heart failure is not clear on available evidence. They may have a role in patients who develop intolerable unwanted effects with an ACE inhibitor…".[30]

AIIRAs currently occupy the sixth position in the cascade of treatment for heart failure after ACE inhibitors, beta blockers, diuretics, digoxin and spironolactone. In order to gain a higher position or to share first place, a number of questions need to be answered. The CHARM study is likely to provide these answers and to clarify the role for AIIRAs in heart failure.

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