

# AT<sub>1</sub> receptor antagonists—beyond blood pressure control: possible place in heart failure treatment

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The renin-angiotensin system (RAS) plays an important role in heart failure, and renin angiotensin aldosterone blockade has been shown to be of benefit in its treatment. The effectiveness of angiotensin converting enzyme (ACE) inhibitors has been well established in major trials including CONSENSUS 1, SOLVD, and V-HeFT-II.<sup>1-3</sup> More recently, the benefits of the aldosterone antagonist spironolactone have been demonstrated in the RALES trial.<sup>4</sup>

RAS blockade has also been of benefit in patients who have sustained a myocardial infarction, complicated by either left ventricular systolic dysfunction or by clinical signs of acute heart failure. This has been well documented in clinical trials, in particular SAVE, AIRE, and TRACE.<sup>5-7</sup>

Given the huge success of ACE inhibitors, it is not surprising that there is hope that angiotensin II type I (AT<sub>1</sub>) receptor antagonists might also have an important role in these patients. In assessing the potential role of AT<sub>1</sub> antagonists there are three questions that need addressing:

- Are AT<sub>1</sub> antagonists better than placebo?
- Are AT<sub>1</sub> antagonists better than ACE inhibitors?
- Should they be used in combination with ACE inhibitors?

## Better than placebo?

No randomised, placebo controlled clinical trial has, to date, prospectively tested the hypothesis that AT<sub>1</sub> antagonists are superior to placebo in terms of morbidity and mortality end points in congestive heart failure (CHF); in reality, this question would have been redundant should AT<sub>1</sub> receptor antagonists have been shown to be superior to ACE inhibitors. However, following the results of the ELITE-II trial (see below) this question has now become an extremely important one to answer.

We do have one study which showed that, compared to placebo, an AT<sub>1</sub> antagonist can improve exercise tolerance in CHF in a dose dependent manner (fig 1).<sup>8</sup> This study randomised men and women with mild to moderately severe heart failure and reduced left ventricular systolic function to either placebo or to different doses of candesartan cilexetil, 4 mg, 8 mg, and 16 mg.

There was an increase in exercise tolerance with active treatment that appears to be dose dependent, with the 16 mg dose significantly improving exercise time, compared to placebo ( $p < 0.05$ ) (fig 1).

There is a need for a large outcomes study that will show that AT<sub>1</sub> antagonists improve

prognosis. Originally designing such a study was seen as an ethical challenge; now in the light of ELITE-II, it is an ethical imperative.

## Better than an ACE inhibitor?

“Better” can mean two things: more efficacious or superior tolerability. These are really two sides of the same coin. A treatment cannot be efficacious if it is not well tolerated and therefore taken by the patient.

### TOLERABILITY

If AT<sub>1</sub> antagonists are as effective as ACE inhibitors and better tolerated, there could be a substantial public health benefit to be gained. AT<sub>1</sub> antagonists do not cause cough and do not seem to cause more of any other adverse effect than ACE inhibitors. They are, therefore, almost certainly better tolerated than ACE inhibitors.

In the ELITE-I study 21% of captopril treated patients discontinued treatment because of an adverse event (excluding death) compared to 12% of losartan treated patients ( $p = 0.002$ ).<sup>9</sup> The results from ELITE-II confirm this finding.<sup>10</sup>

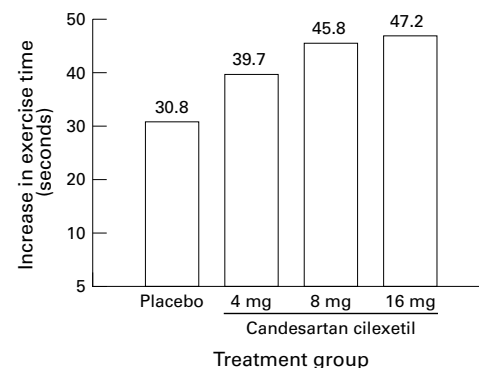


Figure 1 Mean change from baseline to last value in total exercise time (bicycle ergometry) among patients with CHF treated with placebo or candesartan cilexetil 4–16 mg for  $\leq 12$  weeks (intention to treat population,  $n = 807$ ).

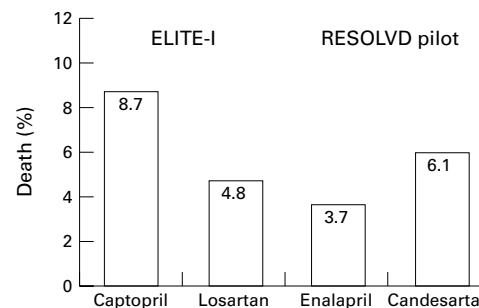


Figure 2 Mortality results from ELITE-I and RESOLVD pilot appear to be contradictory.

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Table 1 Losartan heart failure survival study: ELITE-II study end point summary

	Crude rate		Adjusted hazards ratio (95% CI)	p Value
	Captopril (n=1574)	Losartan (n=1578)		
Primary end point				
All cause mortality	250 (15.9%)	280 (17.7%)	0.88 (0.75 to 1.05)	0.16
Secondary end point				
Sudden death/resusc arrest	115 (7.3%)	142 (9.0%)	0.80 (0.63 to 1.03)	0.08
Tertiary end points				
All cause mortality/hospitalisation	707 (44.9%)	752 (47.7%)	0.94 (0.85 to 1.04)	0.21
Withdrawal for adverse experience	228 (14.5%)	149 (9.4%)		< 0.001

In addition, the SPICE trial found that candesartan cilexetil was well tolerated by heart failure patients who were ACE inhibitor intolerant.<sup>11</sup> Eighty three per cent of patients remained on active treatment at 12 weeks compared to 87% of placebo assigned patients (difference not significant).

#### EFFICACY

In theory, AT<sub>1</sub> antagonists may be more efficacious than ACE inhibitors as they will block the action of angiotensin II generated through non-ACE pathways. In addition, there may be potential benefits of hyperstimulating the unblocked AT<sub>2</sub> receptor.

However, unlike AT<sub>1</sub> antagonists, ACE inhibitors increase bradykinin. For some time the effects of bradykinin have been considered to be negative; it produces cough and may enhance noradrenaline (norepinephrine) release, but there are reasons to believe that bradykinin may also have positive effects. It increases vasodilation, promotes the release of fibrinolytic factors and leads to growth inhibition.

#### ELITE-I and RESOLVD

Until very recently, there were only two small studies that came to very different conclusions regarding the comparative efficacies of ACE inhibitors and AT<sub>1</sub> antagonists: the ELITE-I trial, comparing losartan and captopril; and the RESOLVD pilot trials, comparing candesartan cilexetil to enalapril.<sup>9, 12</sup> The ELITE-I study reported that CHF patients treated with losartan had a lower mortality than patients treated with captopril. The RESOLVD study did not support these findings (fig 2). These contradictory results can be explained by the fact that these two trials were designed to examine tolerability rather than mortality and were not large enough to prove, with confidence, whether AT<sub>1</sub> antagonists have superior efficacy to ACE inhibitors.

#### ELITE-II

Recently data have become available from ELITE-II, the first large, definitive study which explores the effect of angiotensin receptor antagonists on outcome in patients with heart failure.<sup>10</sup> ELITE-II was designed to confirm the finding of ELITE-I that losartan was more effective than captopril. The patients in the study were an average of 71 years old, with mild to moderate heart failure, reduced ejection fractions (average 31%), receiving standard

treatment with diuretics, digoxin and, in up to 25% of cases,  $\beta$  blockers.

Over 3000 patients were randomised to the same treatments as in ELITE-I: captopril 50 mg three times daily or losartan 50 mg daily. It was an event driven trial with a target number of deaths of 510. The anticipated follow up was two years, although it was one and a half in practice. The primary end point was all cause mortality and the secondary end point was sudden death or resuscitation from cardiac arrest. The principal tertiary end point was all cause death or all cause hospitalisation.

There was no significant difference in all cause mortality between the two groups (table 1). The hazard ratio was 0.88 in favour of captopril, and there was approximately 12% risk reduction in all cause mortality in the captopril group compared to the losartan group, although this was not significant ( $p = 0.16$ ).

The secondary end point also showed no significant difference between the two groups. Similarly, the tertiary end point also revealed no significant difference between the two treatments with a hazard ratio of 0.94 ( $p = 0.21$ ).

The only significant difference in outcome between the two groups was that more patients had to be withdrawn from captopril treatment because of adverse effects. The ELITE-II investigators concluded that losartan was clearly not superior to captopril and that ACE inhibitors should therefore remain the first line treatment of choice for patients with chronic heart failure. Indeed, comparison of ELITE-II with historical data from a trial comparing an ACE inhibitor with placebo (and therefore, indirectly, allowing us to compare losartan with placebo) shows that ELITE-II cannot even confirm that losartan is superior to placebo (table 2).

#### In combination with ACE inhibitors?

There are theoretical reasons to suggest that ACE inhibitors and AT<sub>1</sub> antagonists should be used in combination. If angiotensin receptor antagonists give better and more complete RAS blockade, and there are positive non-angiotensin II effects of ACE inhibitors, the optimum treatment may be to use both treatments together.

In a small study, 33 patients with severely symptomatic heart failure who were receiving full conventional treatment, including a large dose of ACE inhibitor,<sup>13</sup> were randomised to receive either placebo or losartan on top of full conventional treatment, for six months. The two primary end points were improvement in exercise time, and improvement in New York Heart Association (NYHA) functional class.

The results showed that adding an angiotensin receptor antagonist to an ACE inhibitor significantly improved exercise tolerance in these patients ( $p < 0.02$ ) (fig 3). In addition, NYHA classification also showed a significant improvement with the addition of losartan ( $p < 0.01$ ). Clearly, this improvement will make patients feel much better and will improve their clinical status.

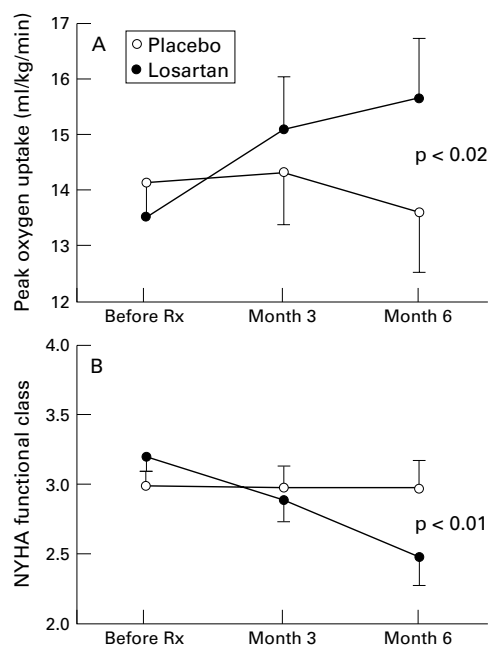


Figure 3 Effect of combination treatment with an ACE inhibitor plus losartan on exercise tolerance and NYHA functional class.

#### RESOLVD PILOT

The RESOLVD pilot study explored the effect of combination treatment on left ventricular remodelling.<sup>12</sup> Patients with heart failure tend to show progressive left ventricular enlargement, which correlates with a poor outcome. Patients received either combination treatment with candesartan cilexetil and enalapril, or enalapril or candesartan monotherapy.

Left ventricular enlargement occurred in the enalapril group. In the combination treatment groups progressive left ventricular enlargement was retarded or even reversed. However, there was no significant difference in mortality between the two groups. A sufficiently large trial is needed to provide definitive data on morbidity and mortality.

#### NORMAL LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Patients with heart failure and normal left ventricular dysfunction are generally neglected. There may also be an important role for RAS blockade in these patients who tend to be hypertensive, often have diabetes, and fre-

quently have ventricular hypertrophy. It is hoped that RAS blockade would improve the outcome for this type of patients.

#### Ongoing studies

It is hoped that many of the remaining questions regarding the role of AT<sub>1</sub> receptor antagonists in the management of cardiovascular disease will be answered by a number of ongoing studies.

#### HEART FAILURE STUDIES

There is a programme of three trials called CHARM.<sup>14</sup> The first of these is a study looking at patients with heart failure, who have a low left ventricular ejection fraction and who are intolerant of ACE inhibitors. These patients are randomised to placebo or to candesartan cilexetil. This component of the CHARM programme is particularly important as it is the only remaining trial that will explore whether there is a role for angiotensin receptor antagonist monotherapy in patients with heart failure. As a result of its increased importance in defining the place of this new class of drugs in heart failure, the sample size of this component trial has recently been increased.

There are also two large studies designed to address the issue of combination treatment in heart failure: Val-HeFT<sup>15</sup> and the second of the three trials in the CHARM programme. The final study in CHARM will compare candesartan cilexetil and placebo in heart failure patients with normal systolic function.

#### POST-MYOCARDIAL INFARCTION STUDIES

There are also two large ongoing postinfarction trials looking at the effectiveness of angiotensin receptor antagonists: OPTIMAAL and VALIANT.<sup>16,17</sup> OPTIMAAL compares losartan and captopril in over 5000 high risk, post-myocardial infarction patients. The VALIANT trial has three treatment groups: valsartan monotherapy, captopril monotherapy and a combination arm. Importantly, the study is powered to test for both superiority of one treatment over another, and to identify non-inferiority. That means that it will be possible to say whether the AT<sub>1</sub> antagonist is more effective or as effective as the ACE inhibitor.

I would like to thank Dr John Norrie and Dr Colin Berry for the analysis in table 2.

Table 2 Comparison of ACE inhibitor (ACE-I) and AT<sub>1</sub>-receptor blocker (ARB) trials in heart failure/left ventricular dysfunction

Trial/comparison (average follow up)	Placebo group	ACE-I group*	ARB group*	Odds ratio (95% CI)
SOLVD-T (52 weeks)	201/1284	159/1285	—	ACE-I/placebo: 0.76 (0.61 to 0.95)
SOLVD-T (104 weeks)	344/1284	277/1285	—	ACE-I/placebo: 0.75 (0.63 to 0.90)
ELITE (48 weeks)	—	32/370	17/352	—
RESOLVD pilot (43 weeks)	—	4/109	20/327	—
ELITE-2 (79 weeks)	—	250/1574	280/1578	ACE-I/ARB: 0.88 (0.73 to 1.06)
Combined ARB trials	—	286/2053	317/2275	ACE-I/ARB: 0.93 (0.77 to 1.10)
Imputed placebo†—ELITE 2	—	—	—	ARB/placebo: 0.87 (0.65 to 1.16)‡
Imputed placebo†—combined ARB trials	—	—	—	ARB/placebo: 0.82 (0.62 to 1.09)§

\*Deaths/randomised patients.

†Using SOLVD-T 52 week results.

‡Using SOLVD-T 104 week results: 0.86 (0.66 to 1.11).

§Using SOLVD-T 104 week results: 0.81 (0.63 to 1.04).

SOLVD-T, treatment arm of the studies of left ventricular dysfunction<sup>2</sup>; ELITE, evaluation of losartan in the elderly trial<sup>9</sup>; RESOLVD, randomized evaluation of strategies for left ventricular dysfunction trial.<sup>12</sup>

**Trial acronyms**

AIRE: Acute Infarction Ramipril Efficacy

CHARM: Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity

CONSENSUS-1: Cooperative North Scandinavian Enalapril Survival Study

ELITE: Evaluation of Losartan In The Elderly

OPTIMAAL: Optimal Therapy In Myocardial infarction with Angiotensin II Antagonist Losartan

RALES: Randomised Aldactone Evaluation Study

RESOLVD: Randomised Evaluation Of Strategies for Left Ventricular Dysfunction

SAVE: Survival And Ventricular Enlargement

SOLVD-T: Studies of Left Ventricular Dysfunction-Treatment

SPICE: Study of Patients Intolerant of Converting Enzyme inhibitors

TRACE: Trandolapril Cardiac Evaluation VALIANT: Valsartan In Acute Myocardial Infarction

Val-HeFT: Valsartan in Heart Failure Trial V-HeFT-II: Vasodilator Heart Failure Trial II

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