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University Department  
of Clinical,  
Pharmacology and  
Therapeutics,  
Ninewells Hospital and  
Medical School,  
Dundee, DD1 9SY,  
UK.

Correspondence to:  
Dr Colin A J  
Farquharson  
Tel: +44 1382 660111  
ext 33176  
Fax: +44 1382 644972  
Email: c.a.j.  
farquharson@  
dundee.ac.uk

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## Angiotensin II receptor blockers in chronic heart failure - Not as ELITE as expected!

Colin AJ Farquharson, Allan D Struthers

### Introduction

For over a decade angiotensin converting enzyme (ACE) inhibitors have revolutionised the treatment of chronic heart failure, becoming a frontline therapy on the basis of several key randomised controlled trials that have unequivocally demonstrated their clear mortality and morbidity benefits in patients with heart failure secondary to left ventricular systolic dysfunction. However, in the dawning of a new millennium we are in the process of evaluating another class of drug targeting the renin-angiotensin system with regard to long-term outcome in heart failure - the angiotensin (AT<sub>1</sub>) receptor antagonists.

These drugs have been tested extensively in essential hypertension, where they have been found to be efficacious, safe and well tolerated with a better side effect profile than ACE inhibitors. Until recently, however, data on their impact on long-term outcomes in heart failure, compared with the ACE inhibitors, had largely been limited. The first steps in answering these crucial questions have been taken by the results of the ELITE I and II studies,<sup>1,2</sup> discussed below, and will be clarified over the next 3 years by the CHARM, OPTIMAAL, Val-HeFT and VALIANT trials<sup>3,6</sup> (Table 1).

### The ELITE Studies

The ELITE I trial, published in 1997, enrolled 722 patients aged 65 years or more with NYHA Class II-IV heart failure and randomised them to receive either losartan 50 mg once daily or captopril 50 mg thrice daily.<sup>1</sup> The defined primary endpoint had been "tolerability of especially persistent renal dysfunction" (ie. worsening of renal impairment assessed by an increase in serum creatinine) between the two treatments. Over the duration of the study, there was no difference between the treatment groups with regard to this endpoint, but more interestingly, the 352 patients receiving losartan had a 46% lower risk of death from all causes than the 370 patients in the captopril treatment group (p=0.035). This difference was mainly due to a 64% reduction in sudden cardiac deaths in the losartan group (5 vs 14 patients). In addition, losartan was associated with a 26% reduction in all-cause hospitalisation and a 35% reduction in non-cardiovascular mortality. Hospitalisations for heart failure were not different between the two drug classes, but non-fatal adverse events and side effects were significantly lower in the losartan group compared with captopril (p=0.02).

These results were clearly intriguing, albeit viewed with a healthy scepticism given that the study was not primarily designed (nor powered) as a mortality study but rather as a study of safety and tolerability of losartan in an elderly population, and the total number of events observed in both treatment groups was small. Since convincing mortality data for angiotensin II receptor blockers was still essentially lacking, and there were sound theoretical hypotheses to explain the treatment

differential in the ELITE I results, the much larger ELITE II study was undertaken, rechallenging captopril and losartan in a trial powered to look at mortality as a primary endpoint. This study enrolled 3152 patients with clinical NYHA Class II-IV heart failure and confirmed left ventricular systolic dysfunction, again comparing 50 mg losartan daily with 50 mg captopril thrice daily, and the preliminary results were presented at the 72nd annual American Heart Association Scientific Sessions in Atlanta in November 1999.

Surprisingly, ELITE II did not confirm the survival advantage seen for losartan over captopril observed in the earlier ELITE I study. In fact, captopril resulted in a marginally (and non-significantly) lower mortality than losartan (15.9% vs 17.7% respectively; p=0.16) and a lower prevalence of sudden death (7.3% vs 9.0%; p=0.08). Although these trends were not significant, they were in contradistinction to the results of the earlier study. Of particular interest, however, in a subgroup analysis of those taking beta-blockers (approximately a quarter of the patients), there was a larger decrease in mortality (44%) in those taking captopril compared with the patients taking losartan. However, as one would expect, losartan was better tolerated than captopril: withdrawals from the trial due to adverse events were 9.4% and 14.5% respectively (p<0.001).

The above results of the ELITE II study concurred with data from the RESOLVD trial,<sup>6</sup> which was terminated prematurely (after a follow-up period of 43 weeks) because of a higher incidence of cardiovascular events (including mortality) in those receiving candesartan compared with those taking enalapril alone, although these differences did not reach statistical significance. Again, similarly to ELITE, this study was small and not primarily designed as a mortality study, and therefore the role of candesartan alone as a first-line therapy in heart failure remains to be clarified.

### Potential mechanisms

The impact of the activated renin-angiotensin-aldosterone system on the natural history of chronic heart failure is well established, and in theoretical terms the angiotensin II receptor blockers address potential shortcomings of ACE inhibition. Angiotensin II formation from angiotensin I is suppressed only partially by ACE inhibitors.<sup>7</sup> There is also evidence to suggest that angiotensin II can be formed by enzymes other than ACE such as chymase, cathepsin G and CAGE,<sup>8</sup> and therefore even with complete ACE inhibition angiotensin II can be formed and exert its harmful effects. All of angiotensin II's currently known detrimental effects are mediated via the AT<sub>1</sub>-receptor; blockade of that receptor would thus allow more effective blockade of the renin-angiotensin system than is possible with ACE inhibition alone. By acting only on the AT<sub>1</sub>-receptor, angiotensin receptor antagonists do not alter bradykinin metabolism, unlike the ACE inhibitors which

**Table 1** Ongoing mortality trials evaluating angiotensin II receptor antagonists in patients with chronic heart failure

Study	Drug evaluated	Comparison	Study population	Expected conclusion
CHARM	Candesartan	Placebo (± open-label ACEI)	Symptomatic CHF (NYHA II-IV) ● LVEF <40% in ACEI-intolerant arm ● LVEF <40% in ACEI+angiotensin receptor antagonist arm ● LVEF >40% in angiotensin receptor antagonist alone arm n=6500	2002
OPTIMAAL	Losartan	Captopril	Anterior Q-wave MI or new LBBB or signs of CHF or LVSD n=5476	2000
Val-HeFT	Valsartan (& open-label ACEI)	Placebo (& open-label ACEI)	NYHA Class II-IV CHF ● LVEF <40% and LVDD>2.9cm/m <sup>2</sup> ● Usual therapy including open-label ACEI n=5009	2002
VALIANT	Valsartan & Captopril Valsartan	Captopril alone Captopril	Heart failure ± LVSD post MI n=14,500	2003

cause accumulation of bradykinin through reduced breakdown via ACE.

There are a number of potential mechanisms that may have contributed to a lack of differential effect seen between captopril and losartan in the ELITE II study. First, it is possible that the bradykinin-mediated beneficial effects produced by ACE inhibitors provide a more substantial advantage in heart failure than previously thought. Increased bradykinin is likely to stimulate release of nitric oxide and prostacyclin, leading to improvement in endothelial function and contributing to an antiatherosclerotic effect. On the other hand, bradykinin has been shown experimentally to release norepinephrine from sympathetic nerves in ischaemic myocardium<sup>9,10</sup> that would potentially offset its advantageous effect on nitric oxide. It is fascinating that the ELITE II study showed a significant survival benefit over losartan in those taking both ACE inhibition and beta-blockade, as this therapeutic combination would provide all of the beneficial effects of bradykinin on nitric oxide whilst negating its adverse effects on norepinephrine release. In addition, it is possible that the non-ACE pathways generating angiotensin II in chronic heart failure are perhaps not as important as currently thought, and that the potentiation of bradykinin by captopril has a greater impact than blocking angiotensin II from non-ACE pathways by losartan.

Another possibility could be that the unopposed stimulation of the AT<sub>2</sub>-receptor by increased levels of angiotensin II during long-term AT<sub>1</sub>-receptor blockade may actually have unknown harmful effects rather than the beneficial ones elucidated by current short-term experimental data. This would be somewhat of a paradigm shift, and clearly requires further assessment as such harmful effects (if any are present) could potentially be overcome by combined AT<sub>1</sub>/AT<sub>2</sub> blockade. Alternatively, combined ACE inhibitor/AT<sub>1</sub>-receptor antagonist therapy would lead to less angiotensin II, in turn causing less AT<sub>2</sub>-receptor stimulation than AT<sub>1</sub>-receptor blockade alone. Also, it is possible that completely unrelated and as of yet unknown mechanisms have confounded the differential effects of ACE inhibitors and angiotensin receptor antagonists.

### Conclusions

As with many large-scale long-term outcome trials, more questions have been posed than answered regarding

the potential role of angiotensin II receptor blockers as first-line agents in chronic heart failure. Given the present data, in patients with left ventricular systolic dysfunction, ACE inhibitors must remain the treatment of choice, owing to the large body of data supporting their use in this clinical syndrome. However, ARBs seems a reasonable alternative for renin-angiotensin axis blockade in the significant number of heart failure patients who are genuinely intolerant of ACE inhibitors.

The pendulum has now swung back in favour of ACE inhibition for chronic heart failure, although one can only await with great expectation the results of the ongoing trials comparing not only angiotensin II receptor blockers with ACE inhibitors but a combination of the two with regards tolerability and survival. Whether this potentially useful class of drugs will ultimately become the cornerstone of heart failure therapy in place of, or in addition to, ACE inhibitors is still in debate, but hopefully we should not have to wait too long for the definitive answers.

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