



## Editorial

# Angiotensin receptor blockers and heart failure: still CHARMing after VALIANT?

Karl Swedberg<sup>a,\*</sup>, John J.V. McMurray<sup>b</sup>

<sup>a</sup> Department of Medicine, Sahlgrenska University Hospital, Östra, SE 416 85 Göteborg, Sweden

<sup>b</sup> University of Glasgow, Glasgow, UK

Received 19 December 2003; accepted 31 December 2003

The effects of ACE-inhibitors have been documented extensively during the last 15 years. They offer wide benefits to patients with cardiovascular disease. Their effects are most prominent in patients with chronic activation of the renin–angiotensin–aldosterone system (RAAS) as are those of aldosterone receptor blockade. However, adverse effects are not uncommon. Antagonism of the actions of both angiotensin II and aldosterone can lead to deterioration in renal function. Notably, ACE-inhibitors also cause cough. Alternative approaches to inhibition of the RAAS are therefore important, particularly for patients who are intolerant of an ACE-inhibitor.

Angiotensin receptor blockers (ARBs) provide a unique pharmacological mechanism for inhibiting the RAS and they have demonstrated high tolerability in large trials. However, their efficacy has been uncertain, in comparison with ACE-inhibitors. Actually, two large trials (one in heart failure and one in myocardial infarction) suggested that the ARB losartan was not as effective as a proven dose of captopril.<sup>1,2</sup>

Recently, we have seen the publication of two new randomised clinical trials, where the efficacy of an ARB was evaluated in chronic heart failure (CHF) and after a recent myocardial infarction.

In the CHARM programme (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), 7601 patients with symptomatic CHF were recruited.<sup>3</sup> They were allocated to placebo or candesartan, titrated to a target dose of 32 mg (average dose 24 mg daily), and followed in average 38 months. Moreover, this programme included three parallel component trials (CHARM-alternative, CHARM-added and CHARM-preserved), each with its composite outcome of cardiovascular mortality or CHF hospitalisation.<sup>4,5,6</sup> In two of these, patients with CHF and reduced left ventricular

systolic function were recruited. In CHARM-alternative 2028 patients intolerant to an ACE-inhibitor were included, in CHARM-added 2576 patients already on optimal treatment with an ACE-inhibitor were randomised. In CHARM-preserved, 3028 with CHF and a left ventricular ejection fraction >40% were enrolled. The results showed that **candesartan reduced the composite outcomes, cardiovascular mortality, hospital admissions for heart failure and all cause mortality, particularly among patients with reduced left ventricular systolic function. Furthermore and importantly, in CHARM-added, these benefits were achieved on top of all other life saving therapies including ACE-inhibitors,  $\beta$ -blockers (in 55% of patients) and spironolactone (in 17%).**

The important new trial in acute myocardial infarction is VALIANT (VALsartan In Acute myocardial infarction), where 14703 patients were recruited within 0.5–10 days after an acute myocardial infarction.<sup>7</sup> They were randomised to one of three treatment arms, captopril in a target dose of 50 mg tid, valsartan target dose 160 mg bid or the combination of captopril 50 mg tid and valsartan 80 mg bid. The follow-up was for 25 months. In this trial, valsartan was demonstrated to be as effective as a proven dose of captopril in reducing mortality as well as cardiovascular events including myocardial infarction. Indeed, in an imputed placebo analysis, valsartan, was shown to preserve 99.6% of the mortality benefit of captopril. However, there was **no further reduction in the primary mortality outcome (or secondary composite outcomes) when valsartan was added to captopril. On the contrary, adverse effects, including hypotension and increased serum creatinine, were more common with the combination therapy.**

How can we interpret and understand the similarities and apparent differences between CHARM and VALIANT (and between these new ARB trials and the older ones)?

The main discrepancy is between CHARM-added and the combination treatment arm of VALIANT. There are a number of potential explanations. Firstly, the two

\* Correspondence to: Tel.: +46-313434000; fax: +46-312-589-33.  
E-mail address: karl.swedberg@hjl.gu.se (K. Swedberg).

studies recruited different patient populations and treatment was used in a different way. In CHARM, patients with CHF on optimal background therapy were randomised into a placebo-controlled trial. Importantly, many of the patients who were randomised into CHARM-added were those who remained symptomatic despite treatment with what the treating physician had determined to be an optimal, individualised, dose of an ACE-inhibitor, that is they had failed on this important treatment. These patients may have the most marked, chronic, neurohormonal activation. Moreover, during ACE-inhibitor treatment "ACE-escape" can occur in these patients, with increasing levels of angiotensin II over time. An ARB was added to established, long-standing, ACE-inhibitor therapy. In contrast, VALIANT-patients with a recent myocardial infarction were randomised into one of three active treatment arms. Only 14% of these patients had previous CHF. Many may have had only short-lived activation of the RAAS. In the combination arm, an ACE-inhibitor and ARB were started simultaneously in this acute setting. The patients in these studies also faced different risks. In CHF the major risk is death or a hospitalisation for worsening heart failure while in patients with a recent myocardial infarction, the risk of a reinfarction, relatively, is much higher (this outcome is not very common among CHF patients).

Second, the differences in the doses of both ARB and ACE-inhibitor used in these trials may have been important. In VALIANT, a proven, high, dose of ACE inhibitor was mandated by the study protocol whereas in CHARM the dose of the ACE-inhibitor was chosen by the investigator. Conversely, in the combination arm of VALIANT, the dose of valsartan was half that used in the valsartan monotherapy arm and in Val-HeFT (the mean dose of captopril taken was also lower in this arm). It is unlikely that this lower dose of valsartan was equivalent to the large dose of candesartan used in CHARM-added.

The other apparent difference is between VALIANT and OPTIMAAL where losartan was not as effective as captopril. Here the dose of ARB might be the most important consideration. In OPTIMAAL (and ELITE 2) the dose of losartan used was 50 mg daily while that in the LIFE-trial was 100 mg. It has been argued that a much higher dose should be used in the CHF and AMI trials and this discussion has led to the initiation of a CHF outcome trial, where losartan 50 mg is being compared to 150 mg daily.

There are also similarities between the ARB trials. In chronic heart failure, the findings of CHARM are consistent with those of Val-HeFT,<sup>8</sup> where valsartan in a target dose of 160 mg bid was used in patients with left ventricular systolic dysfunction. The CHARM results demonstrate an effect on mortality in addition to hospitalisations, but these patients were sicker with more events over a longer follow up time than the Val-HeFT population. The previous concern about "triple neurohormonal blockade" by combining ACE-inhibitors,  $\beta$ -blockers and ARB has been

removed by CHARM and VALIANT as no such interaction was observed in these trials.

The most important similarity between (and message from) CHARM and VALIANT is that neurohormonal antagonism, using a new pharmacological approach, has once again been shown to provide additional clinical benefits in cardiovascular disease. Physicians have to realise the public health importance of this concept. Over the last 10–15 years, major achievements have been accomplished in the treatment of myocardial infarction, CHF with depressed left ventricular systolic function and in patients with vascular disease. The success of the combination of ACE-inhibitors and  $\beta$ -blockers with reduction of mortality and morbidity outcomes in CHF in addition to symptomatic benefits has few, if any, similar achievements in modern medicine. The next step in the progress of CHF management is to have this message accepted widely and then to get the medical community to realise that we have more to offer. For patients with heart failure soon after a myocardial infarction, an ARB, valsartan, is effective. For patients with symptoms due to chronic heart failure, addition of another ARB, candesartan, offers important additional and incremental clinical benefits.

## References

1. Pitt B, Poole-Wilson P, Segal R et al. Effects of losartan versus captopril on mortality in patients with symptomatic heart failure: rationale, design, and baseline characteristics of patients in the losartan heart failure survival study – ELITE II. *J Cardiac Failure* 1999;5:146–54.
2. Dickstein K, Kjeksus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal trial in myocardial infarction with angiotensin II antagonist losartan. *Lancet* 2002;360(9335):752–60.
3. Pfeffer MA, Swedberg K, Granger CB et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. *Lancet* 2003;362(9386):759–66.
4. Granger CB, McMurray JJ, Yusuf S et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-alternative trial. *Lancet* 2003;362(9386):772–6.
5. McMurray JJ, Ostergren J, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-added trial. *Lancet* 2003;362(9386):767–71.
6. Yusuf S, Pfeffer MA, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-preserved trial. *Lancet* 2003;362(9386):777–81.
7. Pfeffer MA, McMurray JJ, Velazquez EJ et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349(20):1893–906.
8. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345(23):1667–75.