

## Perspective for Angiotensin Receptor Blockers in Heart Failure — The Importance of CHARM

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### BACKGROUND

Heart failure is a common disease in the population and despite modern medical therapy, continues to have a high mortality and morbidity. Heart failure is the most common cause of admission to hospital in patients over the age of 65 and is a common cause of unplanned recurrent admissions. Mortality in the recent COMET Trial was over 30% at five years.

Despite treatment with angiotensin converting enzymes (ACE) inhibitors, diuretics, beta blockers, spiro lactone and digoxin, we are still searching for additional therapies to reduce both mortality and morbidity.

Blockade of the renin angiotensin system with ACE inhibitors has been shown to reduce both symptoms and mortality in patients with heart failure. The inhibition of the ACE enzyme reduces plasma angiotensin II concentrations and thus stimulation of the AT<sub>1</sub> receptor. It has, however, been shown recently that with time, other pathways for the conversion of angiotensin to angiotensin II take over and angiotensin II will steadily rise. ACE inhibitors also have other actions, including inhibition of the breakdown of bradykinin resulting in elevated levels of bradykinin. Bradykinin is responsible for some of the unwanted effects of ACE inhibitors, such as cough and angio-oedema, but may also be responsible for some of the benefits.

The rationale for the use of angiotensin receptor blockers (ARBs) in heart failure is that they can be used either alone instead of an ACE inhibitor or in combination with an ACE inhibitor. As ARBs provide greater AT<sub>1</sub> receptor inhibition. If that was thought to be the main action of the ACE inhibitors, then ARBs would be a better substitute for ACE inhibitor. A number of trials have been done comparing ARBs

alone with ACE inhibitors alone. If, however, the other actions of ACE inhibition, particularly the elevation of bradykinin, is important, this provides a good rationale for using a combination of ARBs with an ACE inhibitor.

ARBs have been tried in a number of areas of cardiovascular medicine. In the area of heart failure, they have been tested in the ELITE II Trial with Losartan, the ValHeFT Trial with Valsartan and the CHARM Trial with Candesartan.<sup>1-3</sup> There are ongoing studies with other ARBs. There have been two major trials of patients post myocardial infarction with impaired left ventricular function — the OPTIMAAL Study with Losartan and the VALIANT Study with Valsartan — which are similar but by no means identical to patients with chronic heart failure.<sup>4-5</sup>

### CANDESARTAN IN HEART FAILURE — ASSESSMENT OF REDUCTION IN MORTALITY AND MORBIDITY (CHARM) PROGRAMME

The CHARM programme had three component trials which compared Candesartan to placebo in patients with symptomatic heart failure. The first arm was the CHARM Alternative trial, which included patients with symptomatic heart failure, a low ejection fraction (<40%) and who were thought by their physician to be ACE inhibitor intolerant. It is important to note that intolerance was a clinical decision and there was no formal challenge. These patients were not taking an ACE inhibitor at the time of entry into the trial. The second arm of the programme, CHARM Added, included patients with heart failure and a low ejection fraction (<40%), but who were on an ACE inhibitor at the time. This, therefore, tested the hypothesis that the addition of an ARB to an ACE inhibitor would improve outcomes. The third arm, CHARM-Preserved,

studied a unique group of patients not previously investigated. These patients had symptomatic heart failure and “a normal ejection fraction over 40%”. Initially, these patients were not allowed to be on an ACE inhibitor but following the publication of the HOPE Study, the caring physicians could initiate an ACE inhibitor if they wished. About 20% of these patients were on ACE inhibition.

The criteria for entry into the study were above 18 years of age and symptomatic heart failure. The major exclusions included abnormal renal function, although a creatinine of up to approximately 250 $\mu$ mol/L was acceptable. A serum potassium up to 5.5mmol/L was acceptable. The trial was a worldwide investigation of over 7,600 patients. Out of which, 62 patients were from Singapore, 140 were from Malaysia and 227 were from Australia.

An important part of the design of the trial was the attempt to maximise the dose of Candesartan. The aim was to reach 32mg. The drug was titrated every two weeks, starting in some patients with 4mg and others with 8mg, with the aim of reaching a maximum of 32mg. The increase was occasionally delayed for a further fortnight, following which an attempt was made to increase the dosage. It is worth noting that at the end of the trial, the average dose was 24mg — half the patients were on 32mg while half were on 16mg. When one utilises a treatment based on a clinical trial, it is important to use the dosage regime used in the trial. Thus, for patients with heart failure, it is important to aim for a high dose — 16 or 32mg — of Candesartan.

It is also of note that these patients were on good treatment for heart failure. Over 50% of the patients were on a beta blocker at the beginning of the trial while 17% were on Spironolactone.

## TRIAL RESULTS

### *Comparison of an Angiotensin Receptor Blocker with Placebo*

The CHARM Alternative Trial was the first trial to directly address this question. In the ValHeFT Trial, there was a small subgroup of 366 patients who were not taking an ACE inhibitor, but the ValHeFT Trial was not specifically designed to address this question. In the CHARM Study, the addition of Candesartan reduced the incidence of cardiovascular death or congestive heart failure hospitalisations (the primary outcome) from 40 to 33%, or 7% in absolute terms, with a risk reduction of 23% relatively and a p value of  $p=0.004$ . In terms of hospitalisation, the event rate was reduced by 32%.

The majority of patients (around 70%) were deemed ACE inhibitor intolerant because of cough. In 13% of patients, ACE inhibitor was stopped due to hypotension while in around 12%, due to renal dysfunction. There was a small number, 4% of patients, who had had angio-oedema or anaphylaxis. Despite this intolerance, the majority of patients tolerated an ARB. During the course of the trial, 21.5% of the patients on Candesartan ceased therapy compared to 19.3% on placebo i.e. only a 2% incidence of excess withdrawals due to the drug therapy. Of particular note, less than 0.5% of patients appeared to develop a cough on Candesartan. If we were to review the reasons for stopping Candesartan relative to the reason for stopping ACE inhibitor, we would see that the most common reason was worsening renal function. Thus, it is important that renal function is monitored closely. However, the majority of patients who had ceased an ACE inhibitor because of abnormal renal function were able to tolerate the Candesartan. This may reflect the trial review where patients are monitored more carefully and drug doses made more regularly. It is also worth noting that only one patient out of 39 with angio-oedema on an ACE inhibitor got angio-oedema when rechallenged with Candesartan and this was mild. It would therefore appear to be safe to re-challenge these patients with an ARB and obtain the benefits of blockade of the renin angiotensin system in cases of heart failure.

As mentioned above, the ValHeFT study had a small subgroup of patients who were not taking an ACE inhibitor but received the ARB, and who clearly benefited.

Based primarily on the CHARM Trial but also on this subgroup of the ValHeFT study, I think we can now clearly recommend that all patients with symptomatic heart failure with a low ejection fraction and intolerance to ACE inhibitor should be on an ARB. One could expect the vast majority of patients to tolerate the treatment well.

### *Trials of Angiotensin Receptor Blockade vs ACE Inhibitor*

The ELITE II Trial compared Captopril with Losartan 50mg, the expectation being that Losartan would be better based on the previous trial, ELITE I.

At the end of the trial, there was no statistical difference between patients treated with Losartan and those treated with Captopril. In fact, the point estimates and confidence limits tended to favour Captopril. Based on this trial, it was not possible to conclude that Losartan was better than placebo.

Further, it did not suggest, based on the statistics, that Losartan was non-inferior to Captopril. The VALIANT Trial, although in a somewhat different population of patients post-myocardial infarction with low ejection fraction or symptoms of heart failure, compared Captopril with Valsartan in a large dose of 160mg BD. Again, there was no statistical benefit in favour of Valsartan but on this occasion and as pre-designed in the study, Valsartan was demonstrated to be non-inferior to Captopril, suggesting that one could be substituted for the other.

The messages that can be derived from the data from these two trials are firstly, not all ARBs have the same effect — the drug and dose used would be important. Secondly, it is important to use the appropriate dose, which should be the one that has been tested in trials. An ARB used in an appropriate dose may have the same effect as an ACE inhibitor, however at this time, I strongly believe ACE inhibitors should remain the first line treatment for heart failure rather than ARB.

#### ***Trials of Angiotensin Receptor Blockade Combined with an ACE Inhibitor vs an ACE Inhibitor***

The first trial to assess this was the ValHeFT Study, which showed no benefit in terms of mortality from the addition of Valsartan, although there was a small risk reduction (13.2%) in terms of mortality and morbidity. There has been debate about the clinical significance of this small risk reduction. The most discussed element of the ValHeFT Study was the subgroup finding that patients on a beta blocker, comprising 35% of the patients, appeared to do worse than those who were not taking beta blocker. This suggested that triple neuro-hormonal blockade — ACE inhibitor, ARB and a beta blocker — were potentially harmful.

The CHARM Added Study addressed the question of the addition of Candesartan to standard treatment including an ACE inhibitor.

Patients were on a reasonable dose of ACE inhibitor, around 17mg per day for Enalapril and Lisinopril and 82mg a day for Captopril. The addition of Candesartan reduced the incidence of cardiovascular death or hospitalisation from 42.3 to 37.9%, a 15% relative reduction with a statistical significance of  $p=0.011$ . Looking at secondary outcomes, there was a reduction in both cardiovascular death and cardiovascular hospitalisations of around 15%. Of particular note was that in the beta blocker subgroup, there was no difference whether a patient was on a beta blocker or not. The trend, if anything, was in favour of patients being on all three agents.

It is of note that in the recent VALIANT Study (a combination of Valsartan and Captopril vs Captopril alone), there was again no indication that putting patients on triple therapy was harmful. Thus, I think it is now safe to conclude that the subgroup analysis from ValHeFT was just that, a subgroup analysis, which is hypothesis generating and not definitive and when tested in these latter two trials, triple neuro-hormonal therapy has been proven to be safe.

Of concern is the multiple medications that many of these patients were on. In patients who had Candesartan added to all therapies, there was a 24% withdrawal rate. There was, however, an 18% withdrawal rate in those on placebo. The 6% difference in withdrawal rate was due to patients being on Candesartan, with the majority of withdrawals being related to increased creatinine, increased potassium or hypotension. This further supports the fact that these patients need to be closely monitored, particularly soon after the introduction of the drug.

The conclusion from this arm of CHARM is that the addition of Candesartan to an ACE inhibitor and beta blocker leads to a further and clinically important reduction in cardiovascular mortality and morbidity.

#### ***How Should the ARB be Added to the ACE Inhibitor?***

The recent VALIANT Trial demonstrated no benefit in using the combination of Valsartan and Captopril against Captopril alone when the two agents were started simultaneously. This is different to the findings in ValHeFT with the same agent (though at a higher dose) and CHARM with Candesartan. One explanation may well be that in the latter trials, the ARB was started after some significant period of time on treatment with the ACE inhibitor.

At this time, I would therefore not recommend the use of an ARB early in the treatment of heart failure but would reserve it when there is breakthrough of symptoms after initial treatment with an ACE inhibitor, diuretic and beta blocker.

#### **CHARM PRESERVED**

A few words about CHARM Preserved. The interesting group of patients with heart failure and a relatively normal ejection fraction has not been well studied. They tend to represent people with multiple risk factors — elderly, female, diabetic, hypertensive — but also incorporate people with coronary artery disease and true diastolic dysfunction.

The results of the trial with Candesartan were somewhat disappointing and there was no clear statistical benefit in terms of cardiovascular death or hospitalisation. The overall event rate was 24% in the placebo arm i.e. nearly half that in the patients with low ejection fraction. An interesting feature that came out of the trial was that the development of new diabetes was significantly reduced as in the other two arms of the trial and in other studies. This arm of the study has not demonstrated clear benefits in patients with heart failure, but because of its beneficial effect on diabetes and its control of blood pressure, I would have a low threshold for starting an ARB or an ACE inhibitor in these patients.

### **THE IMPORTANCE OF CHARM**

CHARM has demonstrated the conclusive role of Candesartan in the ACE inhibitor intolerant patient — it is both efficacious and well tolerated. It has confirmed the role of Candesartan and other ARBs in symptomatic patients with a low ejection fraction who are already on an ACE inhibitor. It has laid to rest concerns about triple neuro-hormonal therapy in this group.

It has provided the first data on patients with heart failure and normal ejection fraction and confirmed the beneficial effect of Candesartan on the development of diabetes.

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