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

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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 aldosterone 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, β-blockers (in 55% of patients) and spironolactone (in 17%).

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The important new trial in acute myocardial infarction is VALIANT (VALsartan In Acute myocardial iNFarc-Tion), where 14703 patients were recruited within 0.5–10 days after an acute myocardial infarction. 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
Studies recruited different patient populations and treatment was used in a different way. In CHARMM, patients with CHF on optimal background therapy were randomised into a placebo-controlled trial. Importantly, many of the patients who were randomised into CHARMM-added were those who retained symptoms 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 CHARMM 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 CHARMM-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 CHARMM are consistent with those of Val-HeFT, where valsartan in a target dose of 160 mg bid was used in patients with left ventricular systolic dysfunction. The CHARMM 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, β-blockers and ARB has been removed by CHARMM and VALIANT as no such interaction was observed in these trials.

The most important similarity between (and message from) CHARMM 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 β-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