Review

ELITE II and Val-HeFT are different trials: together what do they tell us?

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Abstract

The Losartan Heart Failure Survival Study (ELITE II) and the Valsartan Heart Failure Trial (Val-HeFT) both evaluated the efficacy and tolerability of a selective angiotensin II receptor antagonist on morbidity and mortality in patients with symptomatic heart failure. The trials differed, however, in terms of their primary hypothesis, study design, and treatment regimens, and this must be taken into consideration when comparing and interpreting the data from these studies. The data are in many ways complementary, and add to our understanding of the optimal treatment of symptomatic heart failure. Additional studies are needed, however, to fully define the role of angiotensin II receptor antagonists in the management of this very heterogeneous group of patients.

Keywords ACE inhibition, angiotensin receptor antagonism, heart failure, prognosis

Despite progress over recent decades in the prevention and treatment of cardiovascular disease, heart failure continues to place a significant and increasing burden on patients and healthcare systems worldwide. In the USA alone, an estimated four million to five million people suffer from chronic heart failure, where it has an estimated five-year mortality rate of 50% and is the leading cause of hospitalisation in age groups 65 years and older [1,2].

Typically, a patient with heart failure has reduced cardiac output, elevated filling pressures, and increased peripheral vascular resistance. Heart failure is not a homogenous disease process, however, and this makes the study of heart failure potentially complex, and makes the comparison between different patient cohorts in different clinical trials difficult.

Angiotensin-converting enzyme (ACE) inhibitors are the treatment of choice in heart failure, with proven ability to reduce morbidity and mortality [3]. More recently, however, reporting of data from large-scale clinical trials has focused attention on the potential role of angiotensin II antagonists. Two such trials – the Losartan Heart Failure Survival Study (ELITE II) and the Valsartan Heart Failure Trial (Val-HeFT) – are reviewed below.

ELITE II and Val-HeFT: similarities and differences

Both ELITE II [4] and Val-HeFT [5] evaluated the efficacy of a selective angiotensin II receptor antagonist on morbidity and mortality in patients with symptomatic heart failure. There are essential differences however, in the design of these trials that must be taken into consideration when comparing these two studies and interpreting the clinical impact of the results. The bottom line, as detailed in this communication, is that the trials address very different hypotheses and provide complementary but different types of information; too much comparison is simply inappropriate.

The hypotheses

The questions addressed reflect the most essential differences between the two trials. The primary hypothesis in the ELITE II study was that losartan would be superior to capto-

CHARM = Candesartan in Heart Failure to Affect Reduction in Morbidity and Mortality; ELITE = Evaluation of Losartan in the Elderly; ELITE II = Losartan Heart Failure Survival Study; ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; OPTIMAAL = The Optimal Therapy in Myocardial Infarction with the AII Antagonist Losartan; Val-HeFT = Valsartan Heart Failure Trial; VALIANT = Valsartan in Acute Myocardial Infarction Trial.
ACE = angiotensin-converting enzyme; CI = confidence interval; NYHA = New York Heart Association; RR = relative risk.

pril with regard to survival. This was largely based on the unexpectedly favourable results of the first Evaluation of Losartan in the Elderly (ELITE) trial [6]. In ELITE II, the ACE inhibitor captopril was again compared with the angiotensin II antagonist, losartan, so there were two active arms. The study had 90% power to detect a relative 25% difference in total mortality between treatments.

In contrast, the primary hypothesis in Val-HeFT was that valsartan in addition to an ACE inhibitor would improve mortality as compared to placebo (i.e. that the combination with an angiotensin II antagonist would be better than an ACE inhibitor alone). This study had 90% power to detect a relative 20% difference in total mortality between treatments.

Both trials were powered to detect superiority and were event-driven; ELITE II required 510 deaths and Val-HeFT required 906 deaths. ELITE II had a single primary endpoint: all-cause mortality. Val-HeFT had two primary endpoints: all-cause mortality and combined all-cause mortality/morbidity. Morbidity was defined as death, sudden cardiac death with resuscitation, hospitalisation for heart failure, or the need for parenteral inotropic or vasodilator therapy.

Study designs

There were important differences with regard to the details of study design. ELITE II randomised and titrated patients to a relatively low dose of losartan (50 mg, once daily), or captopril (50 mg, three times daily), in ACE-inhibitor-naïve patients. Val-HeFT randomised and titrated patients to placebo or relatively high doses of valsartan (160 mg, twice daily), in patients tolerating chronic treatment with an ACE inhibitor. Both trials included symptomatic patients in New York Heart Association (NYHA) class II–IV, with an ejection fraction $<40\%$ requiring therapy for heart failure. ELITE II, however, restricted inclusion to patients >60 years old. Conventional exclusion criteria were used in both trials. An 'intention-to-treat' approach was utilised for the primary analysis of all efficacy parameters in both trials. Both trials employed a Clinical Endpoint Adjudication Committee.

Patient populations

The ELITE II trial included 3152 patients with a mean age of 71.4 years. Of these, 69% were male, the mean ejection fraction for patients was 31%, 80% had a history of ischaemic heart disease, 49% were in NYHA class II and 51% in NYHA III/IV. Overall, 289 sites from 46 countries participated in the ELITE II trial. The Val-HeFT study included 5009 patients with a mean age of 62.7 years. Of these, 80% were male, the mean ejection fraction for patients was 27%, 57% had a history of ischaemic heart disease, 62% were in NYHA class II and 38% in NYHA III/IV. In total, 300 sites from 16 countries participated in the Val-HeFT trial. Although the study populations were similar in most respects, differences were noted with regard to the number of patients treated with an ACE inhibitor (ELITE II 23% [prior to randomisation], Val-HeFT 92%) and with a beta-blocker (ELITE II 22%, Val-HeFT 33%). In both ELITE II and Val-HeFT, patients were stratified according to background beta-blocker therapy. Only in the ELITE II protocol, however, was the proportion of randomised patients taking beta-blockers limited to 25% (although this was not reached in practice). Calculated annualised mortality rates were 11% for ELITE II and 9% for Val-HeFT.

Results

In the ELITE II trial, 79% of patients achieved the target dose of test medication, compared with 80% in the Val-HeFT study. The mean dose of losartan in ELITE II was 44 mg vs 254 mg of valsartan in Val-HeFT. There were 530 deaths in ELITE II and 906 deaths in Val-HeFT. Regarding all-cause mortality/all-cause hospitalisation, there were a total of 1459 events in ELITE II and a total of 1524 events in Val-HeFT. The median follow up was 1.5 years in ELITE II and 1.9 years in Val-HeFT.

There were no significant differences between losartan and captopril in ELITE II for either all-cause mortality or all-cause hospitalisation, although there were, numerically, more deaths in the losartan group. Although there was no significant difference in all-cause mortality in Val-HeFT, there was a significant (13.3%) difference between valsartan and placebo in all-cause mortality/morbidity in favour of valsartan (relative risk [RR] 0.867, 95% confidence interval [CI] 0.784–0.959; $P=0.009$). This difference was almost completely due to a 27.5% reduction in all-cause hospitalisation in the valsartan group (RR 0.725, 95% CI 0.630–0.833; $P=0.00001$). Consistent with the improvement in morbidity were significant ($P<0.05$) improvements in NYHA class, symptoms of heart failure and quality-of-life assessments.

Subgroup analyses

Importantly, a subgroup of 366 (7%) patients included in the Val-HeFT study was not treated with an ACE inhibitor. This permits comparison between valsartan (as monotherapy) and placebo. The results, albeit from a small subgroup of the study population, indicate a highly statistically significant reduction both in all-cause mortality (30% reduction, $P=0.01$) and in all-cause hospitalisation (44.5% reduction, RR 0.560, 95% CI 0.385 to 0.813; $P=0.0002$). Exclusion of the subgroup of patients not receiving an ACE-inhibitor therapy, makes the observed overall reduction in the combined endpoint of mortality and morbidity no longer significant.

Subgroup analysis in ELITE II does not suggest any significant interactions between other concurrent therapy and the effects of losartan or captopril. As stated in the results [4], while there appeared to be an interaction with beta-blocker usage at baseline, this difference was not seen if use was based on concomitant treatment with beta-blockers during the study. Patients on losartan or captopril who also took beta-blockers did better than patients not on such treatment at randomisation.

Table 1

Overview of ongoing angiotensin II antagonist trials in chronic heart failure (CHF) and post-myocardial infarction (post-MI) patients

Study	Patients	Comparators	Size	Status
OPTIMAAL	Post-MI	Losartan vs captopril	$n = 5477$	Recruitment complete; end date 2002
VALIANT	Post-MI	Valsartan vs captopril vs combination	$n = 14500$	Recruitment complete; end date 2003
CHARM	CHF	Candesartan vs placebo	$n = 2548$	Recruitment complete; end date 2003
	CHF (ACE intolerant)	Candesartan vs placebo	$n = 2028$	Recruitment complete
	Diastolic dysfunction	Candesartan vs placebo	$n = 3024$	Recruitment complete

ACE, angiotensin-converting enzyme.

In the Val-HeFT study, in the subgroup ($n = 1606$; 32%) treated with both an ACE inhibitor and a beta-blocker, a trend favouring placebo was observed (risk increase 15% for valsartan versus placebo, RR 1.185, 95% CI 0.969–1.450). A potential negative interaction in patients receiving an angiotensin II antagonist in addition to both an ACE inhibitor and a beta-blocker is biologically unexpected and this subgroup finding should be viewed with caution. Further, this issue is being adequately addressed by the large number of patients receiving beta-blockers for secondary prophylaxis following myocardial infarction, and randomised to the combination arm of valsartan plus captopril in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) [7].

Tolerability

Treatment with an angiotensin II antagonist was extraordinarily well tolerated in both trials. In ELITE II, 14.5% of patients on captopril, vs 9.4% on losartan, discontinued taking the study medication due to adverse experiences ($P < 0.001$). In the Val-HeFT study, 9.9% of patients on valsartan, vs 7.2% on placebo, discontinued taking the study medication due to adverse experiences ($P < 0.05$). The data with valsartan are particularly encouraging. The target dose in the Val-HeFT study (320 mg) was reasonably high, and yet could still be combined with an ACE inhibitor and tolerated well by patients. Clearly, the two trials provide different information with regard to tolerability. ELITE II compared losartan to captopril in mainly ACE inhibitor naïve patients whereas Val-HeFT compared valsartan to placebo in patients tolerating long-term treatment with an ACE inhibitor.

Clinical implications

What are the major clinical implications of these two studies? The results from the ELITE II trial suggest that treatment with losartan (50 mg daily) is not superior to treatment with captopril (50 mg three times daily) but is significantly better tolerated. Considering the extensive documentation confirming the efficacy of ACE inhibitors in patients with heart failure [3], these agents should remain the treatment of choice. Because no significant differences regarding mortality or morbidity were observed between losartan and captopril, losartan would be an appropriate choice in patients intolerant of ACE inhibitors.

The Val-HeFT study suggests that valsartan added to an ACE inhibitor does not improve survival. Therapy with valsartan added to an ACE inhibitor, however, did significantly reduce hospitalisation in the entire cohort, so that the second primary hypothesis (i.e. reduction in the combined endpoint of all-cause mortality/morbidity) was supported. Importantly, valsartan markedly improved survival and reduced hospitalisation in the subgroup of patients who were not treated with an ACE inhibitor. These findings in the subgroup without ACE inhibitor treatment may well represent the strongest evidence to date that angiotensin II antagonists are comparable in efficacy to ACE inhibitors with regards to mortality and morbidity. Some caution should be exercised when interpreting the data, however, since a proportion of the patients enrolled in the Val-HeFT study are likely to have been ACE-inhibitor intolerant and, as such, may differ from the heart failure population in general.

The near future

There are currently three large ongoing trials in patients with heart failure or left ventricular dysfunction (Table 1). These studies, however, again address different hypotheses in special populations and will not necessarily clearly define the role of angiotensin II antagonists in the management of the heterogeneous group of patients with chronic heart failure. The Optimal Therapy in Myocardial Infarction with the AII Antagonist Losartan (OPTIMAAL) study [8] compares losartan to captopril in patients with left ventricular dysfunction following myocardial infarction ($n = 5477$), and is due to be completed during the first quarter of 2002. VALIANT [7] compares valsartan, captopril, and the combination (i.e. three arms) in a similar population with left ventricular dysfunction following myocardial infarction ($n = 14{,}500$), and the investigators plan to report their findings in 2003. Both of these post-infarction trials have prospectively included a noninferiority hypothesis [9].

The Candesartan in Heart Failure to Affect Reduction in Morbidity and Mortality (CHARM) study [10] is targeting

three different populations and compares candesartan to placebo as add-on therapy in patients on chronic ACE inhibitor therapy (arm 1, $n = 2548$), candesartan to placebo in ACE inhibitor intolerant patients (arm 2, $n = 2028$), and also candesartan to placebo in patients with symptomatic heart failure and preserved systolic function (ejection fraction >40%) (arm 3, $n = 3024$). CHARM will, therefore, provide important information in three populations and will specifically, along with a more detailed analysis of Val-HeFT, determine the future role of combination therapy in clinical research and practice.

A fourth trial – the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) – is also in progress (personal communication). This study, which will compare an ACE inhibitor (ramipril) with an angiotensin II antagonist (telmisartan), both alone and in combination, will enrol an estimated 30,000 patients at high risk of cardiovascular disease. It will not add to our understanding of treatment options in heart failure, however, since patients with symptomatic heart failure or decreased ejection fraction will be excluded from the trial.

Investigators and clinicians involved in the management of patients with heart failure must carefully digest the available data in order to interpret better the results of the ongoing trials. Selective angiotensin II receptor antagonists have a multitude of theoretical benefits [11] and a side-effect profile similar to placebo [12]. This makes their use attractive in this syndrome in which therapy has become increasingly complex and in which the target population is still inadequately treated [13]. Their excellent tolerance would make angiotensin II antagonists formidable contenders.

An unequivocal demonstration of efficacy comparable to ACE inhibitors on both mortality and morbidity, however, is essential if these agents are to attain first-line status. As placebo-controlled trials without ACE inhibitors are clearly unethical, the most appropriate way forward would appear to be a large, three-arm trial powered to detect both superiority and equivalence, comparing an ACE inhibitor vs an angiotensin II antagonist versus the combination on mortality and morbidity in patients with heart failure. That would be ethical, feasible, and clinically relevant, but very expensive. Any takers?

Competing interests

None declared.

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