Val-HeFT: changing the heart failure horizon

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The Valsartan Heart Failure Trial (Val-HeFT) established that the angiotensin receptor blocker valsartan is effective for reducing morbidity and slowing the progression of heart failure in patients already taking angiotensin-converting enzymes or beta blockers. In patients not receiving ACE inhibitors, valsartan significantly improves mortality. This review surveys the results from Val-HeFT and makes the point that the concordance between mechanistic data and overall clinical outcomes indicates that neurohormones, echocardiographic data and other parameters might be legitimate surrogate markers in place of clinical outcomes in future heart-failure trials.

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In August 2002, the angiotensin receptor blocker (ARB) valsartan became the first — and thus far the only — drug in this class to receive U.S. Food and Drug Administration (FDA) approval for the indication of heart failure in patients who are intolerant of angiotensin-converting enzyme (ACE) inhibitors. This decision was based on the findings of the Valsartan Heart Failure Trial (Val-HeFT), which was the first long-term, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of an ARB when added to usual prescribed therapy in patients with chronic heart failure.

The trial results have been reported elsewhere. Briefly, 5010 patients (80% male) with heart failure of New York Heart Association (NYHA) class II–IV were randomly assigned to placebo or valsartan titrated to 160 mg twice daily, in addition to their background therapies (ACE inhibitors in 93%, diuretics in 85%, digoxin in 67%, and beta-blockers in 35%). Follow-up averaged 23 months, and the two primary end-points of the study were all-cause mortality, and combined all-cause mortality and morbidity (the latter defined as cardiac arrest with resuscitation, hospital admission for heart failure, or administration of intravenous inotropic or vasodilator drugs for ≥ 4 h without hospital admission). Secondary end-points included hospitalization for heart failure, signs and symptoms of heart failure, change from baseline in NYHA functional class, change from baseline in echocardiographic indices of left ventricular ejection fraction (LVEF) and left ventricular internal diastolic diameter, and quality of life scores.

Mortality was similar in the two treatment groups. The incidence of combined mortality and morbidity was 13.2% lower with valsartan than with placebo [relative risk 0.87, 97.5% confidence interval (CI) 0.77–0.97; P=0.009]. The major effect of valsartan in Val-HeFT was a 27.5% reduction in the incidence of hospitalizations for heart failure (P<0.001), demonstrating that the drug was effective in slowing the progression of disease. An analysis of the primary end-points in subgroups defined according to baseline heart failure therapy showed that valsartan was beneficial in patients receiving either an ACE inhibitor or a beta-blocker, or neither, whereas there was no effect in patients receiving both drug classes.

These positive principal findings were corroborated by statistically significant improvements in many of the secondary end-points in the
valsartan group as compared with the placebo group. The results were further supported by the consistency of the findings for the combined mortality/morbidity end-point in subgroup analyses based on demographical and baseline clinical characteristics (including coexisting diabetes and heart failure disease severity). In addition, morbidity benefits were seen in patients with and without hypertension, confirming that the positive effects from inhibiting the renin–angiotensin–aldosterone system were independent of blood pressure lowering.

The Val-HeFT echocardiographic study, which included all 5010 patients, provides strong evidence that valsartan reverses remodelling in heart failure. In the valsartan group versus placebo, there was a significantly greater reduction in left ventricular internal diastolic diameter (0.12 cm m⁻² versus −0.05 cm m⁻²; \( P<0.001 \)) and a significantly greater increase in LVEF (4.5% versus 3.2%; \( P<0.001 \)). The positive responses observed for both parameters were sustained over the 2 years of the trial and were consistent with the overall trial findings (i.e. the beneficial effects of valsartan on left ventricular structure and function were seen in patients receiving cotreatment with either ACE inhibitors or beta-blockers, or neither drug). Changes in neurohormone levels observed during the trial provide further support for the clinical outcomes. Compared with placebo, valsartan significantly reduced plasma levels of brain natriuretic peptide and attenuated the rise in plasma noradrenaline (norepinephrine). Val-HeFT also provided the first opportunity to examine the long-term effects of ARBs on plasma aldosterone levels in heart failure patients. Compared with placebo, adding valsartan to prescribed therapy resulted in a significant decrease in aldosterone levels that was manifest at 4 months and was sustained throughout the trial. The concordance between the mechanistic data and the overall clinical outcomes in Val-HeFT raises the possibility that neurohormonal and echocardiographic parameters could serve as legitimate surrogate end-points in themselves in future trials, in place of clinical outcomes. In Val-HeFT the annual mortality rate in the group treated with an ACE inhibitor and a beta-blocker at baseline was 6%, as might be anticipated among well treated recruits in a study. With such low mortality rates, to demonstrate statistically significant improvements with an additional drug would require impossibly large trials in the future. The neurohormones in particular may prove to be extremely useful surrogate end-points; analyses from Val-HeFT have shown that plasma brain natriuretic peptide and noradrenaline are independent prognostic markers of clinical outcome in patients with heart failure.

The most striking benefits of valsartan were seen in patients who were not taking an ACE inhibitor \((n=366)\), and it was an analysis of this subgroup that provided the basis for the U.S. FDA approval of valsartan for the indication heart failure. In patients not receiving an ACE inhibitor, both the primary end-points of all-cause mortality and combined mortality/morbidity were significantly reduced with valsartan (Fig. 1). Comparing the valsartan group with the placebo group, the
relative risks were as follows: all-cause mortality 0.67 (95% CI 0.42—1.06; \( P = 0.017 \)); combined mortality/morbidity 0.56 (95% CI 0.39—0.81; \( P < 0.001 \)); and rate of first hospitalization for heart failure 0.47 (95% CI 0.29—0.78; \( P = 0.006 \)). As with the trial population as a whole, positive effects of valsartan on secondary outcomes, including left ventricular structure and function, neurohormones, quality of life and exercise capacity, were in full accordance with the clinical findings.\(^8\) It is quite remarkable for the FDA to base an approval on data from a subgroup; however, it is noteworthy that the sample size in this group was larger than the entire cohort (\( n = 253 \)) in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).\(^9\)

The FDA approval cites even greater reductions in risk for clinical outcomes with valsartan in this non-ACE inhibitor subgroup than those reported by the investigators. This reflects the decision by the FDA to use relative risks from unadjusted regression analyses, rather than the relative risks published by the investigators, which controlled for pre-specified baseline covariates (NYHA class, LVEF, cause of heart failure, age and beta-blocker use or non-use). The FDA approval therefore cites risk reductions of 41% for all-cause mortality and 49% for combined mortality/morbidity, as compared with the (more circumspect) published figures of 33% and 44%, respectively.

The findings of Val-HeFT indicate that there is no additional benefit to be gained from giving an ARB to patients who are already being treated with both an ACE inhibitor and a beta-blocker, suggesting that there is little scope for achieving further blockade of the renin—angiotensin—aldosterone system in these patients. Beta-blockers in particular are powerful inhibitors of plasma renin activity, and previous studies have demonstrated marked reductions in both angiotensin I and II levels in patients treated with both drugs, as compared with patients on ACE inhibitors alone.\(^10\) Nevertheless, Val-HeFT is only one study and cannot provide all of the answers. Other large trials that are due to report within the next few years will shed further light on the benefits or otherwise of combining ARBs with ACE inhibitors in therapy for heart failure. The adverse effect of triple therapy with a combination of ARB, ACE inhibitor and beta-blocker suggested by the subgroup analysis in Val-HeFT might have been a statistical anomaly. The Candesartan in Heart failure — Assessment of Reduction in Mortality and morbidity (CHARM) trial\(^11\) and the post-myocardial infarction trial VALIANT (VALsartan In Acute myocardial iNfarction Trial)\(^12\) both contain triple therapy arms. Those arms have not been stopped, which indicates that there are no adverse effects from this combination.

Val-HeFT has established that valsartan is an effective drug for reducing morbidity and slowing the progression of heart failure and, in patients not receiving treatment with an ACE inhibitor, increasing survival markedly. The 33% reduction in risk for all-cause mortality in patients not treated with an ACE inhibitor who were randomized to valsartan compares favourably with the 27% reduction in risk seen in the enalapril group in CONSENSUS.\(^9\)

The role for valsartan in heart failure is probably greater in clinical practice than indicated by the percentage of patients not on ACE inhibitors in Val-HeFT. Despite the fact that ACE inhibitors are first-line therapy for heart failure, substantial numbers of patients are not taking them. Reports indicate that between 24% and 66% of heart failure patients are not receiving ACE inhibitors.\(^13—17\) Some community-based data indicate extremely low use, with only 10—36% of such patients receiving prescriptions.\(^14\) In the International Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) registry,\(^18\) 20% of patients diagnosed with left ventricular dysfunction were not prescribed ACE inhibitors. There is also evidence that elderly patients\(^19\) and those residing in nursing homes\(^20\) are less likely to receive ACE inhibitors than are younger and ambulatory patients. Among patients who are receiving ACE inhibitors, target doses for effective inhibition of the renin—angiotensin—aldosterone system may not be readily achieved. One recent report showed that 22% of patients hospitalized for HF were unable to reach 50% of their target dose.\(^21\) How much of the poor uptake of ACE inhibitors is due to drug intolerance is unclear, but the emergence of ARBs as a possible alternative for heart failure patients is a major new development in treatment options. Studies have consistently demonstrated the superior tolerability of ARBs, which is also reflected in greater adherence to therapy as compared with other drug classes.\(^22,23\) and Val-HeFT has shown that adherence to the maximum recommended dose of valsartan over 2 years is excellent.\(^1,8\)

In summary, the U.S. FDA approval for an extended indication establishes a central role for valsartan in the polypharmacy required for the management of chronic heart failure. Given the evidence for widespread under-use of ACE inhibitors, this new heart failure indication could have profound implications for the treatment of patients in clinical practice. The findings of Val-HeFT suggest that valsartan can safely and
effectively substitute for ACE inhibitors in long-term patient care.

References


