

The Val-HeFT study: *what does it tell us?*

Dr Ken McDonald

Background

The evolution of the neuroendocrine hypothesis marked a watershed in the management of heart failure associated with left ventricular systolic dysfunction. This major leap in the understanding of the pathophysiology of heart failure has led in particular to an increased interest in amelioration of the heightened activity of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. This has resulted in the development of two major strategies to improve prognosis in this syndrome, the use of angiotensin converting enzyme inhibition (ACEI) and beta-adrenergic blockade.

ACEI therapy

The natural history of all phases of left ventricular systolic dysfunction has been favourably influenced by ACEI therapy [1]. It has always been assumed that the major benefit of this intervention has been the reduction in the formation of angiotensin II. This peptide has powerful vasoconstrictor effects, induces harmful myocardial and vascular growth and also stimulates apoptosis [2]. However, some of the benefit of ACEI inhibition may stem from the preservation of bradykinin [3]. Moreover, further investigation of the mechanism of benefit of ACEI therapy has revealed the escape of angiotensin II formation with time, most likely reflecting the activity of non-ACE mediated formation of angiotensin II [4]. Furthermore, the suppression of aldosterone production lessens with chronic ACEI therapy. Questions remain, therefore, regarding the exact mechanism of benefit of ACEI therapy, and certainly suggest that more complete inhibition of angiotensin II could be obtained, and could possibly be beneficial.

ARB

The recent development of angiotensin II type I receptor blockade (ARB) has allowed for more complete inhibition of the effects of angiotensin II than that achieved with ACEI therapy. There are other differences between these compounds, most notably the effect on bradykinin, which may provide an additional benefit with ACEI therapy, but also potentially predisposes to the cough side effect. Furthermore, the blockade of the type I receptor may result in increased levels of circulating angiotensin II, which may act as

the type II receptor. The relevance of this issue remains unclear, but it is thought that the type II receptor may mediate an antiproliferative effect and stimulate vasodilatation. This may accentuate the beneficial effects of ARB therapy at the type I receptor. The above underline the potential for differing clinical effects with these two classes of drug in heart failure, and suggests the potential of a synergistic effect.

To date, two strategies have been tested for the use of ARB in heart failure. Head-to-head comparison was undertaken in the Evaluation of Losartan In The Elderly (ELITE) I and II studies. ELITE I tested comparable tolerability of the two classes and found fewer side effects with losartan compared with captopril. Surprisingly, patients treated with losartan had a better survival rate, though it must be stressed that this initial study was not designed as a mortality trial and was not powered to detect mortality differences. Nonetheless, it did raise the issue as to whether the ARB may be more effective than the ACEI in the management of heart failure. Consequently, the ELITE II study was designed as a mortality trial and failed to define a survival difference [5]. Indeed, the trend favoured captopril, again, fewer side effects were seen than with the ARB.

The Randomised Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial was the first clinical trial to address the beneficial effects of adding ARB to ACEI therapy [6]. The primary endpoint in this trial was remodelling. These data demonstrated that the combination of candesartan and enalapril was more effective than either therapy alone in retarding progressive structural change. This would support the hypothesis that this combination approach may provide a morbidity or mortality benefit.

Val-HeFT

Val-HeFT (Valsartan Heart Failure Trial) is a landmark study in that it is the first mortality trial designed to assess the morbidity and mortality benefit of adding ARB (valsartan) to established optimal therapy, which for the most part included ACEI [7]. In excess of 5,000 patients were randomised. Demographics were typical of heart failure trial patients, with a greater preponderance of men (~80%) and a younger mean age (~63 years) than that seen in the typical

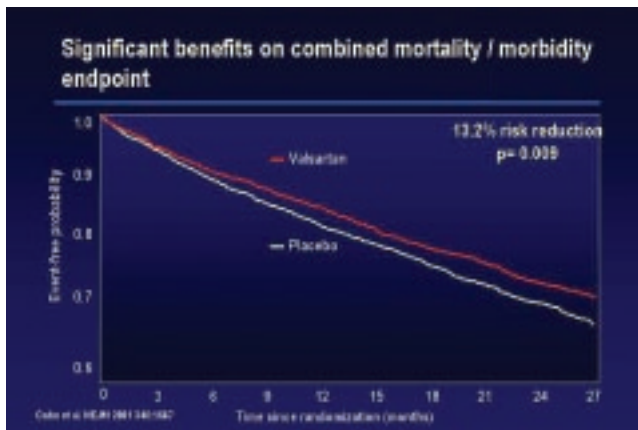


Figure 1.

community heart failure population. The majority were in NYHA class II with the remainder almost exclusively in class III. Mean ejection fraction was <30%, with the majority receiving ACEI (~92%) and ~35% prescribed beta blockade. Patients were stratified as to whether they were or were not on beta blockade and subsequently randomised one-to-one to valsartan, titrated to 160mg BID, or to placebo. There was a co-primary endpoint of all-cause mortality and a combined endpoint of mortality and morbidity, the latter defined as heart failure hospitalisation, use of intravenous inotropic or vasodilator therapy for >4 hours without admission, or resuscitated cardiac arrest. Patients were followed for a mean period of ~24 months.

There was no mortality difference between the two groups. However, the combined endpoint of mortality and morbidity was significantly reduced by valsartan from an absolute value of 32.1% to 28.8% (a 13.2% reduction) (Figure 1). This was predominantly due to a reduction in heart failure-related hospitalisation (27.5% decrease from 1189 to 923 events in the valsartan-treated group) (Figure 2).

Analyses demonstrated that the above results were seen among the predefined subgroups, including young and old (>65 years), male and female, presence or absence of diabetes and ejection fraction, though it did appear that the benefits were more marked in the non-ischaemic population.

Subgroups

Assessment of background therapy with neurohormonal inhibitors brought up some interesting observations. Separation of patients into four groups based on the use or non-use of ACEI or beta-blockers demonstrated a mortality benefit for valsartan in patients who were not on either neurohormonal inhibitor. There was a very significant reduction in morbidity in all subgroups, with the exception of the group receiving beta blockers and ACEI. This subgroup also demonstrated an increase in mortality indicating a potential hazard with what has been referred to as 'triple neurohormonal blockade'. As yet, there is no clear explanation for this observation. We await further information on this issue from the ongoing CHARM study program, which contains an arm where ARB therapy has been added to ACEI and beta blockade. For the present,

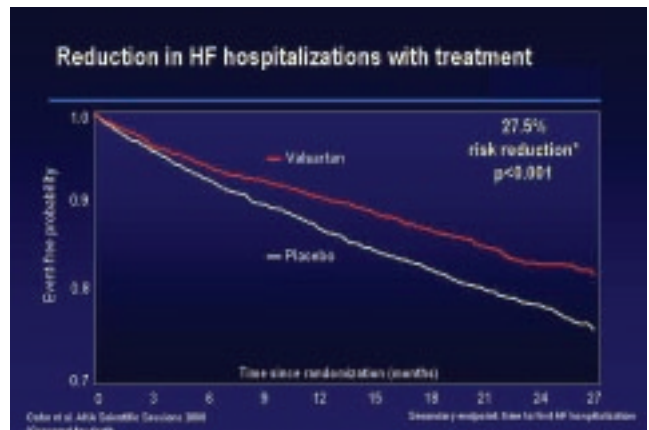


Figure 2.

however, it seems prudent to avoid the concomitant use of all three agents until this issue has been clarified.

Conclusions

The Val-HeFT data represent a landmark study for several reasons. It is the largest trial to date where ARB therapy has been added to standard neurohormonal blockade in systolic dysfunction heart failure. It is the first trial to demonstrate a significant morbidity benefit, and it is of importance that the parameter that was most significantly influenced by valsartan was hospitalisation for heart failure. This is a robust and important endpoint in a syndrome where hospital utilisation is far too frequent, consuming two-thirds of the economic costs of this syndrome. As a result of these data, the addition of valsartan to either ACEI or beta blockade (but not to both) is a reasonable approach to reduce morbidity. Moreover, this study is the first to demonstrate a mortality benefit for ARB therapy when prescribed to ACEI-intolerant patients not on beta blockade. Based on the above data, the recognition and licensing process in both the US and Europe for use of valsartan in heart failure are well underway and it is likely that approval will be obtained in the near future.

Aside from the definitive endpoints of Val-HeFT, this study has also been of significance for the questions that arise from the data. In particular, the issue of triple neurohormonal blockade requires further investigation. This observation underlines the need for heart failure trialists to reconsider the present standard design to trials, wherein investigational therapies are simply added to present guideline therapy. This approach fails to address the issue of individualisation of therapy and leads to progressive polypharmacy and to its attendant problems. Furthermore, the present approach ignores the possibility that certain pharmacological strategies may be more effective in certain individuals, and/or at particular phases of the natural history of systolic dysfunction.

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