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Scientific Update™

Effects of Valsartan on Morbidity and Mortality in Patients with Heart Failure not receiving ACE Inhibitors

Originally presented by: Aldo P. Maggioni, MD, Florence, Italy.

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Reported and discussed by:
Juan Carlos Monge, M.D.

The use of angiotensin-converting enzyme (ACE) inhibitors has become the cornerstone of heart failure treatment following the results of multiple, large, randomized, clinical trials. Unfortunately, many patients cannot benefit from these drugs due to intolerance of the side effects and are, therefore, denied the life-saving benefits of antagonizing the renin-angiotensin system in this condition. A specific and highly selective approach to the antagonism of angiotensin II is to block the AT-1 receptor with the more recently introduced angiotensin receptor blockers. The role of these drugs in heart failure remains, at present, incompletely characterized and large randomized clinical trials are ongoing in special heart failure populations (ie, ACE inhibitor-intolerant heart failure patients or patients with preserved left ventricular systolic function and predominantly diastolic heart failure). The Valsartan Heart Failure Trial (Val-HeFT) examined the effects of adding an ARB to conventional heart failure therapy which, in most cases, included ACE inhibitors. This *Cardiology Scientific Update* discusses in detail the recent report of a new subgroup analysis of the 7.3% of patients enrolled in Val-HeFT who were not taking an ACE inhibitor at baseline. The use of valsartan in these patients resulted in significant improvements in mortality and morbidity, as well as in surrogate endpoints such as left ventricular remodeling, neurohormonal activation, and quality of life.

Introduction

The results of multiple, large, randomized, clinical trials show that ACE inhibitors significantly reduce the mortality and morbidity associated with heart failure.[1-9] Consequently, ACE inhibitors have become the cornerstone of treatment for this increasingly common cardiovascular condition. In practice, however, up to 20% of heart failure patients cannot be prescribed ACE inhibitors, principally because of side effects such as cough. More recently, a new drug category was introduced that achieves a highly specific blockade of the renin-angiotensin system by antagonizing the angiotensin II type-1 receptors (AT-1). These angiotensin receptor blockers (ARBs) exhibit placebo-like tolerability, but their role in the management of heart failure has not been as intensely investigated as that of ACE inhibitors. In addition, their role, to a significant extent, remains to be clarified since there have been no large placebo-controlled trials with these agents. The second Evaluation of Losartan In The Elderly trial (ELITE II) compared the effects of the ARB losartan with captopril in 3,152 patients, age ≥ 60 years, with New York Heart Association (NYHA) class II-IV and left ventricular ejection fraction (LVEF) ≤ 40%. This study did not establish greater efficacy for the ARB or its equivalency to the ACE inhibitor.[10]

The Val-HeFT Trial

The Valsartan Heart Failure Trial (Val-HeFT) was designed to evaluate whether the addition of the ARB, valsartan, improves the outcomes of heart failure patients receiving a standard

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

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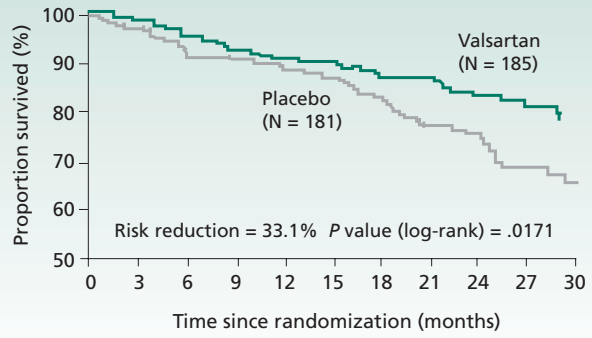
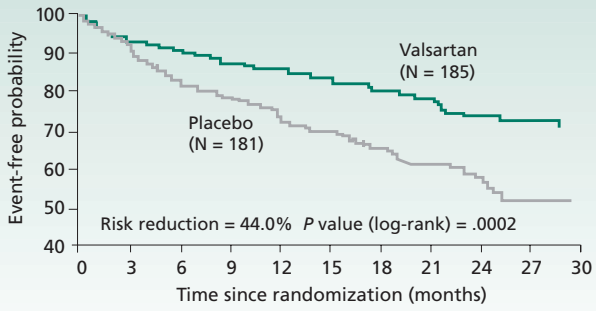
Figure 1: Reduction in mortality with valsartan (No ACEI subgroup)[12]



Hazard ratio (Cox model): 0.6694

Figure 2: Reduction in combined morbidity endpoint with valsartan (No ACEI subgroup)[12]



Hazard ratio (Cox model): 0.560
First morbid event, including death or hospitalization

therapy that in most cases includes an ACE inhibitor. Val-HeFT enrolled 5,010 patients who were randomized to receive valsartan 160 mg or placebo twice daily. The two co-primary endpoints were all-cause mortality and the composite of mortality and morbidity, defined as the incidence of hospitalization for heart failure, resuscitated sudden death, or administration of intravenous inotropic or vasodilator therapy for at least 4 hours. Hospitalizations accounted for 94% of the nonfatal endpoints in the study. Mortality was similar in the 2 groups, but the combined mortality and morbidity endpoint was 13.2% lower with valsartan (relative risk, 0.87; 97.5% confidence interval, 0.77-0.97; $P = 0.009$) primarily because of a reduction in the number of patients hospitalized for CHF (13.8% vs 18.2%). Several secondary endpoints were also improved by valsartan, such as ejection fraction, signs and symptoms of CHF, and quality of life.[11]

An analysis of subgroups according to background therapy also yielded interesting findings. In the subgroup of patients receiving both an ACE inhibitor and a beta-blocker at baseline, valsartan had an adverse effect on mortality ($P = 0.009$) and was associated with a trend toward an increase in the mortality and morbidity composite ($P = 0.10$). This raises important questions and concerns about the advisability of triple therapy with beta-blockers, ACE inhibitors, and an ARB in patients with moderate to severe heart failure.

New subgroup analysis: patients not on ACE inhibitors

Perhaps more interestingly, in view of the great number of patients who cannot take ACE inhibitors, is that an analysis of the subgroup of patients who were not receiving ACE inhibitors showed that the use of the ARB (valsartan) significantly reduced mortality and morbidity. This *Cardiology Scientific Update* reviews the latest data to emerge from Val-HeFT on the subgroup of patients not taking ACE inhibitors as background therapy.

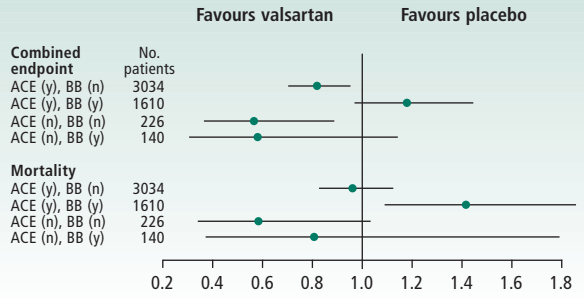
The primary endpoints of the substudy of patients not receiving ACE inhibitors were all-cause mortality, combined mortality/morbidity (all-cause death, sudden death with resuscitation, heart failure hospitalization, or administration of intravenous inotropic or vasodilator drugs for ≥ 4h without hospitalization). The secondary endpoints were: measurements of the levels of the neurohormones, norepinephrine (NE) and brain natriuretic peptide (BNP), determination of the left ventricular internal diameter in diastole (LVIDd) and LVEF, as well as assessment of quality of life. Of the 5010 patients enrolled in Val-HeFT, 366 (7.3%) were not receiving ACE inhibitors at baseline and 185 were randomized to valsartan, while 181 were randomized to placebo.

The baseline characteristics of the patients assigned to both groups were similar with two exceptions: there was a higher proportion of women (33.1% vs 24.3%) and of patients with NYHA III-IV (53% vs 41.1%) in the group randomized to placebo compared to valsartan. However, LVEF and LVIDd were not different between the groups. A total of 38.3% of the patients were receiving beta-blockers and they were fairly well-balanced between the two groups.[12]

Results

Treatment with valsartan of patients not receiving ACE inhibitors resulted in a reduction in mortality of 33.1% ($P = .0171$) and of the combined morbidity endpoint of 44% ($P = .0002$; Figures 1 and 2). The curves for the latter endpoint began to separate at 3 months and continued to diverge at the end of the study. There was a 24% reduction in the total number of hospitalizations, but this did not reach statistical significance. In contrast, the reduction of 56.4% in hospitalizations for heart failure did reach statistical significance ($P = .010$). Of great interest is the finding that the beneficial effects of valsartan were seen whether or not the patients were receiving beta-blockers. Indeed, patients not receiving beta-blockers had significant reductions in mortality (51%) and in the combined endpoint of mortality and morbidity (48%). In patients on beta-blocker therapy, allocation to valsartan led to a significant (49%) reduc-

Figure 3: Relative risk of morbidity and mortality by ACE inhibitor/ß-blocker subgroups



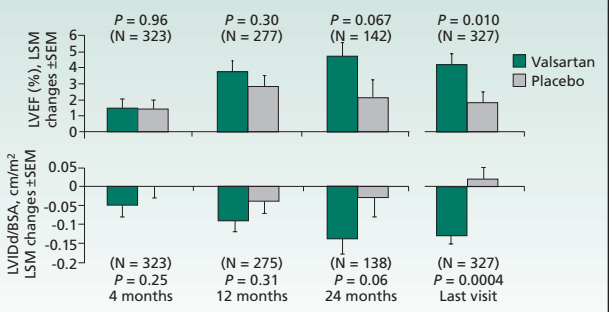
tion in morbidity and mortality, and a trend towards a reduction in mortality by 20%. Of note, the patients who received beta-blockers and valsartan did not exhibit an increased mortality compared to those receiving only valsartan. Indeed, the patients on this double therapy appeared to have lower mortality than the patients who received only valsartan (Figure 3).

These findings suggest that therapy with two agents to suppress neurohormonal activation — such as an ARB and a beta-blocker — may be more beneficial than treatment with a single agent in patients not receiving an ACE inhibitor. This would stand in contrast with the results of the main study suggesting that there are potentially negative consequences of using triple anti-neurohormonal therapy with an ACE inhibitor, a beta-blocker, and an ARB.

Longitudinal follow-up of LVEF and LVIDd was carried out by echocardiography at 4, 12, and 24 months, and at the time of the last visit. A significant increase in ejection fraction and a significant decrease in LVIDd were observed at the time of the last visit in the group assigned to valsartan. Therefore, treatment with this ARB resulted in beneficial cardiac remodeling in patients not receiving an ACE inhibitor and provides a good structural correlation with the positive impact of valsartan on clinical outcomes (Figure 4). In terms of blood pressure effects, a significant reduction of 8 mm Hg was seen in patients assigned to valsartan compared to placebo that was maintained during the study period. However, despite this reduction in blood pressure, the heart rate did not increase and, in fact, there was a trend towards its reduction.

The neurohormonal studies also yielded results of great interest in this patient population. BNP, arguably one of the best, if not the best, neurohormonal marker of adverse prognosis in heart failure, had a favourable impact from treatment with valsartan. At 4 months, there was a marked, highly significant decrease in the levels of BNP and this was maintained until the end of the study ($P = 0.0004$). In contrast, for patients assigned to placebo, the BNP levels increased steadily throughout the study period. A similar trend, although not statistically significant, was seen in the levels of norepinephrine, considered an inferior prognostic marker (Figure 5).

Figure 4: Valsartan vs. placebo: Echocardiographic changes over time (no ACEI subgroup)[12]

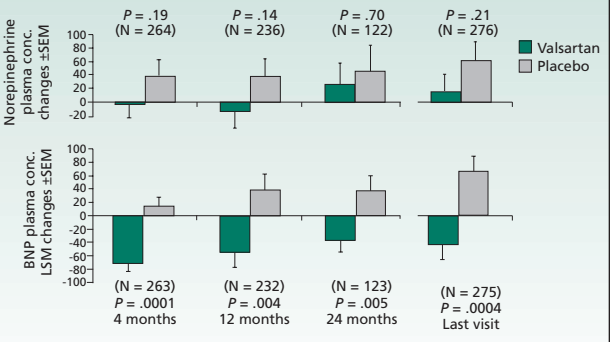


P = refers to comparison valsartan vs. placebo;
N = total number of patients in both treatment groups

The evaluation of quality of life by a well-accepted and standardized method, the Minnesota Living with Heart Failure Questionnaire, was an additional secondary endpoint of the study. A significant improvement in quality of life was observed at one year in patients assigned to valsartan compared to placebo ($P < 0.05$), and a strong trend in this direction was maintained throughout the study (Figure 6).

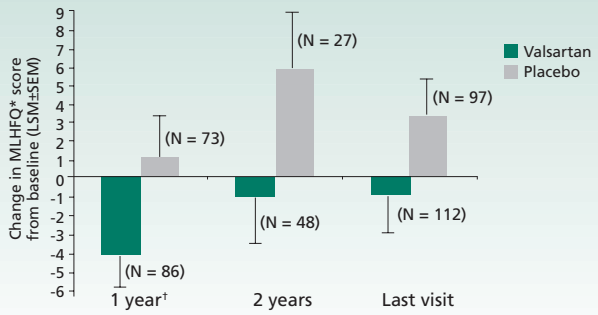
In terms of the safety profile of valsartan on this heart failure population not receiving ACE inhibitors, 21% of the patients permanently discontinued the study medication. There was no statistically significant difference between the two groups and, in fact, there was a trend towards a lower discontinuation in patients taking valsartan (17%) versus those taking placebo (24%, $P = 0.076$). Discontinuation specifically due to adverse events occurred in 11.2% of the total study population, with no

Figure 5: Valsartan vs. placebo: Neurohormonal changes over time (No ACEI subgroup)[12]



BNP = brain natriuretic peptide; *P* = valsartan vs. placebo
N = total # of pts in both treatment groups

Figure 6: Valsartan vs. placebo: Changes in quality of life (No ACEI subgroup)[12]



Least-square mean (LSM change ± standard error of the mean (SEM)
* Minnesota Living With Heart Failure Questionnaire † Statistically significant at $P < .05$

difference between valsartan and placebo. These findings underscore the excellent, placebo-like, tolerability of ARB, even in a population with moderate to severe heart failure.

Summary

To summarize, this analysis of the Val-HeFT patients suggests that valsartan improves morbidity and mortality in heart failure patients with NYHA class II-IV symptoms, not treated with ACE inhibitors, but treated with conventional and recommended heart failure therapy including beta-blockers. The ARB, valsartan, inhibits the renin-angiotensin system effectively and specifically by blocking the AT-1 receptors, and it also has an excellent safety profile in this group of high-risk patients. As well, in a manner that was consistent with its beneficial effects on clinical events, patients randomized to valsartan also exhibited significant improvements in cardiac structural and physiological endpoints, neurohormonal responses, and in standard criteria of quality of life.

In conclusion, this subgroup analysis of the Val-HeFT trial provides the first, placebo-controlled, clinical outcome data demonstrating the beneficial effects of an ARB on mortality and morbidity in heart failure patients not treated with ACE inhibitors. Based on the totality of evidence from the ELITE-II trial and from the current subgroup analysis (notwithstanding the limitations of subgroup analyses), an ARB, such as valsartan, would appear to be a safe and effective therapy in this patient population. These findings potentially are of great clinical interest since, as previously mentioned, up to 20% of all heart failure patients may be unable to benefit from an ACE inhibitor. Large, randomized, clinical trials to address more extensively the question of ARB use in the management of ACE inhibitor-intolerant heart-failure patients are ongoing. In the meantime, it would be reasonable to use valsartan to block the renin-angiotensin system in patients who are intolerant of ACE inhibitors.

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