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Scientific Update™

Does Combined Angiotensin Receptor Blockade and ACE Inhibition Improve Clinical Outcomes in Patients with Heart Failure? Results of the Valsartan Heart Failure Trial (Val-HeFT)

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Interruption of the renin-angiotensin-aldosterone system (RAAS) is the most important therapeutic approach in patients with heart failure, and angiotensin-converting enzyme (ACE) inhibition is the cornerstone of therapy for these patients. However, growing evidence supports an important role of non-ACE pathways in the generation of angiotensin II (Ang II), resulting in the persistence of Ang II production despite ACE inhibition. The angiotensin receptor blockers (ARBs) may produce a more complete blockade of Ang II generation; therefore, an attractive treatment strategy in heart failure is to combine an ACE inhibitor with an ARB. This treatment strategy has been examined recently in the Valsartan Heart Failure Trial (Val-HeFT). The results of Val-HeFT and its clinical implications will be reviewed in this issue of *Cardiology Scientific Update*.

Despite significant advances in diagnosis and therapy, the mortality of patients with heart failure remains extremely high.[1] ACE inhibitors have been shown to prolong survival in patients at almost any stage of symptomatic heart failure[2-4] and these agents have therefore become the standard of therapy. Indeed, subsequent pharmacologic therapy shown to improve clinical outcomes of patients with heart failure, including the ß-blockers, have all been tested on background therapy with ACE inhibitors.[5-8]

The ACE inhibitors were initially thought to act primarily by blocking the formation of angiotensin II (Ang II). However, there is now a deluge of evidence supporting a functional role of non-ACE mediated pathways of Ang II generation.[9] Furthermore, data from experimental models of heart failure have attributed the anti-remodeling effect of ACE inhibition in part to increased bradykinin as a result of decreased breakdown.[10] On the other hand, increased bradykinin has also been purported as a mechanism for the common side effects of ACE inhibitors such as cough.

Angiotensin receptor blockers (ARBs) selectively block the type 1 angiotensin (AT_1) receptor which should block all the known detrimental effects of Ang II that are mediated via the AT_1 receptors. However, the recent ELITE-II trial demonstrated that the ARB losartan is no better than the ACE inhibitor captopril in reducing mortality and sudden death in patients with severe heart failure.[11] It is known that patients with heart failure who

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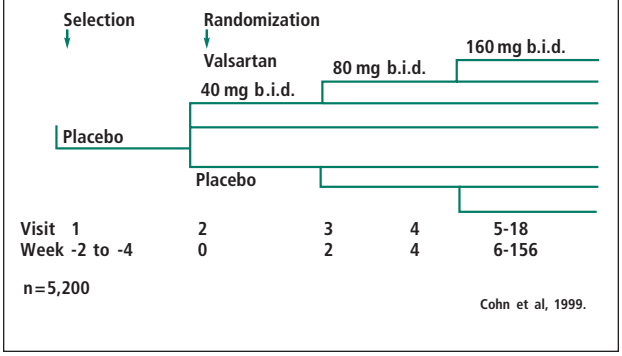
deteriorate while on ACE inhibitors have higher plasma Ang II levels than stable patients,[12] indicating that Ang II production may persist in a great many patients despite ACE inhibition. Based on these considerations, a theoretically appealing therapeutic approach is to combine an ACE inhibitor with an ARB.

In a pilot study, the ARB valsartan has been shown to exert beneficial hemodynamic and neurohormonal effects in patients with heart failure already taking ACE inhibitors.[13] Another study, the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD), demonstrated that a combination of the ARB candesartan with the ACE inhibitor enalapril exerted more pronounced effects on lowering arterial blood pressure and preventing ventricular remodeling than monotherapy with either agent.[14] Importantly, the combination was well tolerated. However, although this study was not designed to examine clinical outcomes, patients treated with candesartan alone or combined with the ACE inhibitor appeared to have worse clinical outcomes than those treated with enalapril. Accordingly, the Valsartan Heart Failure Trial (Val-HeFT) was designed to test the hypothesis that the ARB valsartan, by exerting a more complete and selective interruption of the RAAS, results in further improvement in clinical outcomes in patients with heart failure who are treated with ACE inhibitors.

Methodology

The primary objectives of Val-HeFT were to investigate the effects of valsartan compared with placebo on mortality and morbidity symptoms and quality of life in patients with chronic heart failure treated with conventional therapy. Details of the study design and protocol have been reported.[15] Patients aged 18 years or older with a history of heart failure for at least 3 months were considered for entry. Recruited patients had to have left ventricular ejection fraction (LVEF) <40% accompanied by LV chamber enlargement (as defined by a measured end-diastolic internal diameter >2.9 cm/m^2 by echocardiography). In addition, patients had to have New York Heart Association (NYHA) class II to IV symptoms and be clinically stable on a stable pharmacologic regimen for 2 weeks.

Figure 1: Study protocol for the Val-HeFT trial.



The study protocol is summarized in Figure 1. A single-blind 2- to 4-week placebo run-in period preceded randomization. All patients were expected to be on optimal recommended doses of ACE inhibitors unless they were intolerant to these agents. Beta-blockers were permitted and a stratified randomization was used to ensure balanced distribution. Patients were randomized to receive valsartan or matching placebo beginning with 40 mg twice daily, doubled every 2 weeks with a target dose of 160 mg twice daily. There were *two* pre-specified primary outcomes: time to death *and* time to the first morbid event (including death, sudden death events with resuscitation, hospitalizations for heart failure, and requirement of at least a 4-hour duration of IV inotropic or vasodilating agents for worsening heart failure). Secondary outcomes included changes from baseline in NYHA functional class, signs and symptoms of heart failure, LVEF, LV diastolic internal diameter, quality-of-life scores, and neurohormonal parameters (plasma norepinephrine, brain natriuretic peptide, endothelin-1, renin activity, and aldosterone). To achieve an overall significance level of .05 or greater, an adjustment for two primary endpoints was made with each primary end point tested at a two-sided significance of .02532 based on the Dunn-Sidak inequality. Sample size calculation was based solely on time to death, one of the two primary endpoints. Death rate in the placebo group was assumed to be 12% per year. In order to detect a 20% reduction in mortality (ie, a mortality rate of 9.6% per year with a 90% power and a two-sided significance at the .02532

Table 1: Primary endpoint analysis				
	Valsartan n=2511	Placebo n=2499	Risk ratio (95% C.I.)	P-value
All-cause mortality	494 (19.7%)	484 (19.4%)	1.02 (0.9, 1.15)	0.8
All-cause mortality + morbidity	723 (28.8%)	801 (32.1%)	0.87 (0.79, 0.96)	0.009

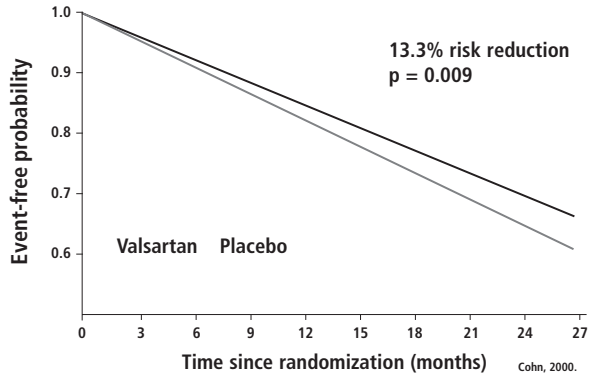
Table 2: Secondary endpoint analysis				
	Valsartan n=2511	Placebo n=2499	Risk ratio (95% C.I.)	P-value
Heart failure hospitalization	349 (13.9%)	463 (18.5%)	0.73 (0.63, 0.83)	0.00001

level), 906 deaths was thought to be required. The goal was to enroll 5000 patients.

Results

Five thousand and ten patients were recruited from 300 centers in 16 countries. The two study groups were comparable in baseline demographics. The mean age was 62 years. The ratio of men to women was about 4:1 and 90% were white. Ischemic etiology constituted 57% of the patients with the majority with NYHA class II (62%) and class III (36%) symptoms. Mean LVEF was 27% and LV end diastolic diameter was 3.7 cm/m^2. Eighty five percent of patients were on treatment with diuretics, 67% on digitalis, 35% on ß-blockers, and 93% on ACE inhibitors at doses recommended by current guidelines. The average dose of the study medication achieved was 254 mg per day.

Figure 2: Combined all-cause mortality and mobidity in Val-HeFT



Results of the two primary endpoints are shown in Table 1. All-cause mortality was similar for the two treatment groups. The valsartan treatment group had a significant 13% reduction in combined all-cause mortality and morbidity (Figure 2). The reduction of this combined primary endpoint was accounted for mostly by a reduction in heart failure hospitalization. As demonstrated in Table 2, heart failure hospitalization was reduced by 28% in the valsartan group and this reduction was highly significant.

The subgroup analysis of the combined mortality and morbidity end point is shown in Figure 3. Except for the use of ACE inhibitors, all subgroups were *pre-specified*. As shown in Figure 3, the point estimates trended favorably for valsartan for most of the pre-specified subgroups, indicating a treatment benefit from valsartan on the combined endpoint regardless of age, gender, LVEF, or heart

Figure 3: Combined morbidity/mortality in subgroups.

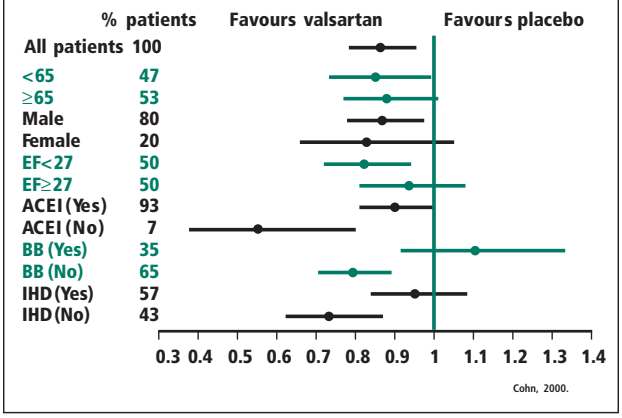
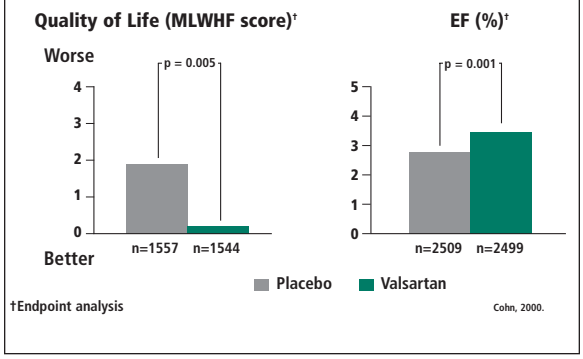


Table 3: NYHA Class and signs/symptoms†					
Sign/Symptom	Treatment	Percent of patients (%)		p-value	Benefit favouring
		Improve	Worse		
NYHA Class	Valsartan	22.9	10.0	<0.001	Valsartan
	Placebo	20.5	12.8		
Effort dyspnea	Valsartan	34.0	18.7	<0.001	Valsartan
	Placebo	31.4	21.1		
Fatigue	Valsartan	31.5	21.5	<0.01	Valsartan
	Placebo	29.2	25.1		
Edema	Valsartan	11.7	10.1	<0.05	Valsartan
	Placebo	9.6	12.2		
Rales	Valsartan	7.0	6.1	<0.01	Valsartan
	Placebo	6.4	8.2		
† At Endpoint					

failure etiologies. However, for the 7% of patients who were not taking ACE inhibitors, the benefit derived from valsartan was greater than for patients who were taking ACE inhibitors. On the other hand, the opposite trend was observed with the use of ß-blockers. A treatment benefit was observed in the 65% of patients not treated with ß-blockers, whereas the point estimate actually favoured placebo in the 35% of patients treated with ß-blockers. Further analysis in both the ACEI and ß-blocker subgroups indicated that the possible negative trend was confined to patients taking all three drugs, and not to those taking either an ACEI or a ß-blocker in combination with valsartan.

Figure 4: Secondary variables: Change from baseline



In an attempt to further study the beneficial effects of valsartan in patients who were not on ACE inhibitors, further analysis was carried out in this subgroup. First, in this small group of patients (n=366), the second primary endpoint of combined all-cause mortality and morbidity was reduced by 44.5% (p=0.0002). Second, the valsartan (n=185) and placebo treated (n=181) groups were very similar in baseline characteristics, including the concurrent therapy with diuretics, digoxin and ß-blockers.

Data on the secondary endpoints of signs and symptoms of heart failure are shown in Table 3. Valsartan produced a significant improvement in every pre-specified parameter of signs and symptoms. Data on quality of life, as measured by the Minnesota Living With Heart Failure Score (MLWHF), and data on EF are depicted in Figure 4 as change from baseline. A higher MLWHF signifies worse quality of life. As seen in Figure 4, valsartan significantly improved quality of life as well as LVEF compared to placebo. Valsartan was well tolerated by patients on ACE inhibitor therapy. The frequency of study drug discontinuation due to adverse reactions was similar for the valsartan and placebo groups (9.9 vs 7.2%). The frequency of renal impairment was similar (1.0 vs 0.2%) with changes in serum blood urea nitrogen, creatinine, and potassium levels also similar (+2.1 vs

1.2 mg/dL, +0.18 vs +0.1 mg/dL, and +0.1 vs -0.07 meq/L, respectively).

Discussion

The following are the principal findings of Val-HeFT. Valsartan significantly reduced combined all-cause mortality and morbidity by 13.3%. This benefit was accounted for almost exclusively by a 27.5% reduction in heart failure hospitalizations. Valsartan, however, had no effect on all-cause mortality. This is not surprising given the likely possibility that the overall population in Val-HeFT had only moderate heart failure as evidenced by the approximately 9% annual placebo mortality rate that was below that expected in both groups (placebo 12%, valsartan 9.6%).

Valsartan also significantly improved signs and symptoms of heart failure, quality of life, and LVEF. Subgroup analysis suggested that the benefit of valsartan on combined mortality and morbidity and heart failure hospitalizations was most pronounced in patients not receiving other neurohormonal inhibitor therapy such as ACE inhibitors and ß-blockers. On the other hand, there existed a possibility of an adverse effect of ARBs in patients who were on ß-blockade therapy.

Previous observations from experimental and clinical studies have provided the rationale for examining combined ACE inhibitor and ARB therapy on clinical outcomes in patients with heart failure. In a pig model of pacing-induced heart failure, the effects of ACE inhibition, alone or in combination with the ARB valsartan, were examined.[16,17] Valsartan, in combination with ACE inhibition, resulted in more pronounced improvement in cardiac performance, myocardial blood flow, and alleviation of neurohormonal activation. In clinical studies, patients with heart failure who deteriorated while taking ACE inhibitors were found to have higher plasma Ang II level when compared to patients who remained in stable condition.[12]

A recent study has further demonstrated that in patients with heart failure, even maximally recommended doses of ACE inhibitors (eg, 150 mg of captopril), do not completely prevent ACE-mediated formation of Ang II as measured by the pressor response to ascending doses of angiotensin I.[18] These observations strongly suggest that Ang II production may persist despite ACE inhibition in many patients with heart failure. Furthermore, it raises the possibility that combined therapy with ACE inhibitors and ARBs may result in better clinical outcomes in these patients. Indeed, the pilot RESOLVD study has demonstrated that the combination of candesartan and enalapril produces a more pronounced effect on blood pressure, LV remodeling, and neurohormonal activation than monotherapy with either agent.[14] These experimental and clinical data are therefore consistent with the results of Val-HeFT.

It is conceivable that introducing a second approach (using ARBs) for inhibiting the same neurohormonal system (RAAS) in patients who have, at most, moderate heart failure and who already have the same neurohormonal system inhibited by reasonably optimal doses of ACE inhibitors, will not likely reduce all-cause mortality any further. In this regard, findings from the subgroup analysis of patients not taking ACE inhibitors provide insightful information. Notwithstanding the limitations of *post hoc* subgroup analysis of a relatively small group of patients, this analysis nevertheless represents the first time an ARB was ever compared with placebo with respect to an impact on clinical outcomes in patients with heart failure. The dramatic benefit of valsartan on heart failure hospitalizations in the group of patients not on neurohormonal inhibitors is therefore within expectation.

Furthermore, the dose utilized in Val-HeFT was sufficiently high; this is in contrast to the ELITE-II study where a relatively low dose of losartan was employed.[11] In the ELITE-II study, losartan was found to be no better than captopril on all-cause mortality and sudden death and because the trial was not powered to test for non-inferiority, an inferior effect of this dose of losartan on clinical outcome compared to captopril could not be excluded.[11] It is also interesting to note that valsartan is the first ARB ever to show a beneficial effect on clinical outcomes in patients with heart failure.

The potential adverse interactions between valsartan, ACE inhibitor, and ß-blockade therapy raise concerns regarding the safety of the combined use of three neurohormone inhibitors. As with the subgroup analysis about the use of ACE inhibitors, the subgroup analysis on the interaction with ß-blockade therapy should also been interpreted with trepidation. To settle this issue, additional data such as the comparability of the baseline demographics of these patients, more detailed analysis of the outcome data, as well as the neurohormone data will be useful and likely forthcoming. Finally, the future completion of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study (especially the systolic dysfunction arm and the ACE inhibitor intolerant arm) will help to further define the role of other ARBs in heart failure.

Summary

Val-HeFT demonstrates that the ARB valsartan is a well-tolerated and effective treatment to reduce heart failure hospitalizations in patients with moderate heart failure already on conventional therapy including ACE inhibitors. The beneficial effect on clinical outcome is accompanied by concurrent and consistent improvements in signs and symptoms of heart failure, quality of life, and LVEF. The use of valsartan may be considered for the above-mentioned patient population and treatment goals. Until further data are available, the routine combined use of ARBs, ACE inhibitors and ß-blockers cannot be recommended. Ongoing clinical trials (ie, VALUE, ABCD-2V, and VALIANT) will continue to expand our knowledge of the role of valsartan in CHF, post-MI, diabetic, and hypertensive patients.

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