JANUARY 2002 volume VII, issue 1

CARDIOLOGY Rounds™

AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Angiotensin receptor blockade in the treatment of heart failure: New data from the Valsartan Heart Failure Trial (Val-HeFT)

GORDON MOE, MD

Inhibition of the renin-angiotensin-aldosterone system remains the most important strategy in the treatment of heart failure. The angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists are the most commonly used agents in this treatment strategy. However, results from experimental and clinical studies have provided evidence of an important role for 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) potentially produce a more complete blockade of Ang II generation, and these agents have been considered as alternatives to ACE inhibitors in the treatment of heart failure. A theoretically appealing treatment strategy is to combine an ACE inhibitor with an ARB. This treatment strategy was examined in the recently published Valsartan Heart Failure Trial (Val-HeFT). This issue of *Cardiology Rounds* reviews the results of the Val-HeFT study, the clinical implications, and includes new data presented at the recent Scientific Sessions of the American Heart Association.

Congestive heart failure (CHF) is major public health problem in the industrialized world.[1] In Canada, over 350,000 individuals are afflicted with the disorder and the one-year mortality after diagnosis ranges between 25% and 40%.[2] The hallmark of CHF is a progressive clinical course in afflicted patients, manifested frequently by repeated hospital admissions that impose a large burden on the healthcare delivery system.[3] Accordingly, the principal goal for any treatment of CHF in these patients should be directed not only at improving symptoms, but also improving survival and reducing hospital admissions.

Inhibition of the renin-angiotensin-aldosterone system is the most established treatment strategy in patients with CHF. Within this strategy, the angiotensin-converting enzyme (ACE) inhibitors and the aldosterone receptor antagonists have been shown to prolong survival and reduce hospitalizations in patients with a wide spectrum of CHF symptoms accompanied by systolic left ventricular (LV) dysfunction.[4-6] The ACE inhibitors have become the standard of therapy in these patients and subsequent pharmacological therapies shown to improve clinical outcomes of patients with CHF, including the ß-blockers and spironolactone, have all been examined in patients who have had background therapy with ACE inhibitors.[4,7-10]

ACE inhibitors were initially thought to act primarily by blocking the formation of angiotensin II (Ang II). However, there is now a great deal of evidence supporting a functional role of non-ACE mediated pathways of Ang II generation.[11] Patients with CHF who deteriorate while on ACE inhibitors have higher plasma Ang II levels than stable patients,[12] indicating that Ang II production may persist in many patients despite ACE inhibition. Therefore, ARBs that selectively block the type-1 angiotensin (AT_1) receptor should block all the known detrimental effects of Ang II that are mediated via the AT_1 receptors.

Two therapeutic strategies have been considered for ARBs,[13-15] the first as an *alternative* to ACE inhibitors, and the second in *combination* with ACE inhibitors. The rationale behind the two approaches is quite different. Proponents of the first strategy purport that bradykinin is a mediator of some of the undesirable effects of ACE inhibitors, such as cough and angioedema.[13] On the other hand, data from experimental models of CHF have attributed the cardiac anti-remodeling effect of ACE inhibition largely to increased bradykinin as a result of decreased breakdown.[16] The second strategy there-

St. Michael's Hospital
30 Bond St.,
Room 9-004, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5330

The opinions expressed are only those of the Divisional members. This publication is made possible through unrestricted grants.

fore views increased bradykinin, with its vasodilator, antithrombotic and growth inhibiting actions, as a desirable property of ACE inhibitors.[16-19] Based on these considerations, the combined use of ACE inhibitors and ARBs is theoretically more appealing. 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.[20] The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study demonstrated that the combination of an ARB, candesartan, with an ACE inhibitor, enalapril, exerts more pronounced effects on lowering arterial blood pressure and preventing ventricular remodeling than monotherapy with either agent.[14] Importantly, the combination was well tolerated. These studies, however, were not designed to examine clinical outcomes.

The Val-HeFT study

The Valsartan Heart Failure Trial (Val-HeFT) was designed to test the hypothesis that the ARB, valsartan, by exerting a more complete inhibition of the renin-angiotensin-aldosterone system, results in further improvement of clinical outcomes in patients with CHF who are treated with ACE inhibitors. The study design and the principal results of the Val-HeFT trial were reviewed in a previous issue of *Cardiology Scientific Update,* and the study has been recently published.[21]

In brief, 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 CHF treated with ACE inhibitors. Patients aged 18 years or older with a history of CHF for at least 3 months and LV ejection fraction (LVEF) <40%, accompanied by chamber enlargement as defined by a measured end-diastolic internal diameter >2.9 cm/m^2 by echocardiography, were eligible for entry. 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. 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 of the 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 first morbid event which included death, sudden death events with resuscitation, hospitalizations for CHF, and requirement of intravenous inotropic or vasodilating agents for worsening CHF of at least a 4-hour duration. Secondary outcomes included changes from baseline in NYHA functional class, signs and symptoms of CHF, 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 0.05 or greater, an adjustment for two primary endpoints was made with each primary endpoint 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 0.02532 levels, 906 deaths were thought to be required.

Table 1: Primary endpoint analysis[21]

	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

Results

Patients (5010) were recruited from 300 centres in 16 countries. The two study groups were comparable in baseline demographics. Ischemic etiology constituted 57% of the patients, and the majority had 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 per cent 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.

Primary and secondary endpoints

Data on the 2 primary endpoints are shown in Table 1. All-cause mortality was similar for the 2 treatment groups. However, the valsartan-treated group had a significant 13% reduction in combined all-cause mortality and morbidity. The reduction of this combined primary endpoint was accounted for primarily by a 28% reduction in CHF hospitalizations (Table 2). The rate of hospitalizations for any cause was also reduced, from 3106 in the placebo group to 2856 in the valsartan group (P=0.14),[21] while the number of cardiovascular hospitalizations was similar between the placebo (1976 events) and the valsartan group (1672 events).[22] Valsartan produced a significant improvement in every pre-specified parameter of signs and symptoms. Valsartan also significantly improved quality of life as measured by the Minnesota Living With Heart Failure Score, 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 valsartan and the placebo group (9.9% vs 7.2%). The frequency of renal impairment was

Table 2: Secondary endpoint analysis: heart failure hospitalizations[22]

	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

similar (1.0% vs 0.2%), and changes in serum blood urea nitrogen, creatinine, and potassium levels were 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.

Subgroup analysis

Analysis of the combined mortality and morbidity endpoint based on *pre-specified* subgroups, revealed that the point estimates for this combined endpoint favoured valsartan in most of the subgroups, including age, gender, diabetes, median LVEF or CHF etiologies. The subgroup analyses on the use of ACE inhibitors and ß-blockers have generated considerable discussion since they were first presented at the American Heart Association meeting in November 2000. In general, the 7% of patients who were not on ACE inhibitors at the time of randomization experienced benefits derived from valsartan that were significantly greater than in the 93% of patients on ACE inhibitors. Within the group of patients not on ACE inhibitors, the valsartan (n=185) and placebo-treated (n=181) groups were similar in baseline characteristics, including concurrent therapy with diuretics, digoxin and ß-blockers. On the other hand, an opposite trend was observed with the use of ß-blockers. A treatment benefit was observed in the 65% of patients not on ß-blockers, whereas the point estimate favoured placebo in the 35% of patients treated with ß-blockers. This unfavorable trend for valsartan in patients taking ß-blockers, however, was not significant since the 95% confidence intervals crossed unity and, at the time the analysis was first presented, it appeared to be confined to patients who were on ACE inhibitors.

New data on subgroup analysis and neurohormonal parameters

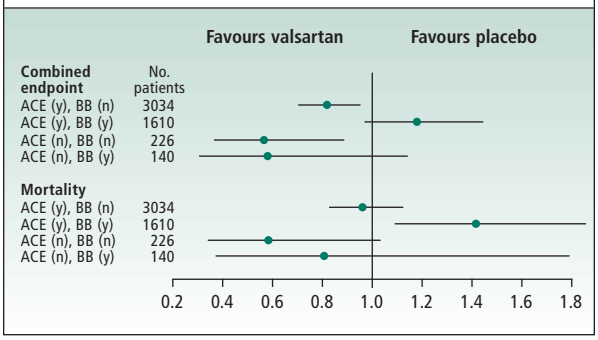
Subgroup analysis of endpoints

New information regarding the interaction of ACE inhibitors and ß-blockers on the effect of valsartan on mortality and morbidity has become available and the data were presented at the recent American Heart Association Scientific Sessions.[22] In the subgroup analysis, the patients were grouped according to use of ACE inhibitors and ß-blockers into 4 subgroups:

- Patients who were not on ACE inhibitors or ß-blockers [ACE(n) BB(n)], n=115 for placebo, n=112 for valsartan
- Patients who were not on ACE inhibitors but were on ß-blockers [ACE(n) BB(y)], n=66 for placebo, n=73 for valsartan
- Patients who were on ACE inhibitors, but not on ß-blockers [ACE(y) BB(n)], n=1503 for placebo, n=1535 for valsartan
- Patients who were on both ACE inhibitors and ß-blockers [ACE(y) BB(y)], n=815 for placebo, n=791 for valsartan.

Data for the two primary endpoints of mortality and combined morbidity and mortality were grouped according to the use of ACE inhibitors and ß-blockers, and are shown in Figure 1.[21] The global test for the interaction between treatment and subgroup for the four subgroups was significant for mortality (P=0.009), as well as for the combined endpoint of mortality and morbidity (P=0.001). Valsartan significantly reduced the risk of the combined endpoint of all-cause mortality and morbidity in the ACE(y) BB(n) (P=0.002), ACE(n) BB(n) (P=0.003), and ACE(n) BB(y) (P=0.037) subgroups, and also reduced total mortality in the 226 patients who were not on ACE inhibitors or ß-blockers (P=0.012). Among all patients who were not on ACE inhibitors (n=366), with or without ß-blockers, combined all-cause mortality and morbidity was markedly reduced (relative risk, 0.56, 95% CI, 0.39 to 0.81, P=0.0002). A trend for the reduction of all-cause mortality was also observed (relative risk, 0.67, 95% CI, 0.42 to 1.06). On the other hand, the point estimate for all-cause mortality favoured placebo in the 1610 patients who were on both ACE inhibitors and ß-blockers.

Figure 1: Relative risk of morbidity and mortality by ACE inhibitor/ß-blocker subgroups[21]



The new data on the subgroup analysis of the secondary endpoint of morbidity (death, sudden death events with resuscitation, hospitalizations for CHF, and requirement of at least a 4-hour duration of intravenous inotropic or vasodilating agents for worsening CHF) are shown in Figure 2. As indicated earlier, the effect on morbidity was driven mostly by changes in hospitalizations for CHF. As shown in Figure 2, morbidity was reduced significantly by valsartan in all subgroups, except for patients who were on both ACE inhibitors and ß-blockers.

Neurohormone data

The neurohormone data of Val-HeFT constitute the largest neurohormone study ever conducted in patients with CHF and the results were presented for the first time at the recent American Heart Association Scientific Sessions.[23,24] Plasma brain natriuretic peptide (BNP) levels, a strong prog-

Figure 2: Morbidity by ACE inhibitor/ß-blocker subgroups

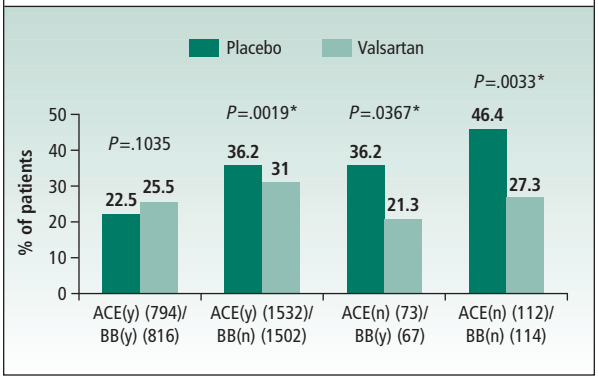
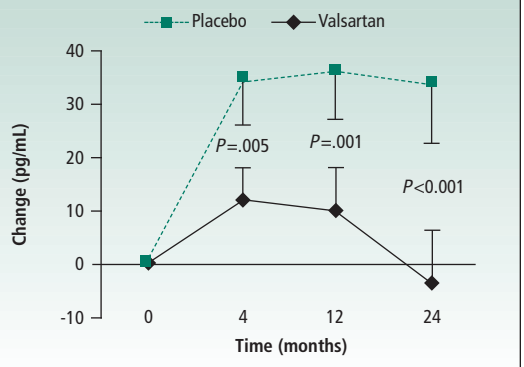


Figure 3: Plasma norepinephrine data



nostic indicator in patients with CHF,[25,26] were monitored sequentially at baseline, 4-, 12-, and 24-months post-randomization. Baseline plasma BNP levels were similar in the placebo- (178±5 pg/mL, n=2160) and valsartan-treated groups (183±5 pg/mL, n=2145). Baseline BNP again predicted clinical outcomes. The survival curves of freedom from the composite endpoint separate widely among patients within the four quartiles of BNP levels (41; 41-97; 98-238; >238 pg/mL). Patients in the highest quartile experienced the highest event rate. The effect of valsartan on plasma BNP levels is shown in Table 3 and grouped according to ACE inhibitor and ß-blockade therapy. In the placebo group, plasma BNP levels did not change over time. By contrast, in the valsartan group, plasma BNP levels declined over time, regardless of therapy, but the lowering effect of valsartan was most pronounced in patients not on ACE inhibitors. These data indicate that treatment with valsartan reduces plasma BNP level, an effect that is consistent with its favourable effect on clinical outcomes.

Plasma norepinephrine levels were also measured and 3921 patients had both baseline and at least one post-basal measurement. As with BNP, baseline norepinephrine levels were comparable between the placebo group (472±368 pg/mL, mean ±SD) and the valsartan group (456±270 pg/mL). Baseline levels also predicted all-cause mortality, although the separation of survival curves of the four quartiles (<274; 274-394; 395-572; >572 pg/mL) was not as striking as in BNP. Changes of plasma norepinephrine levels over time are depicted in Figure 3. In the placebo group, plasma norepinephrine levels increased steadily over time. In the valsartan group, the increase demonstrated in the placebo group was markedly attenuated. This effect was independent of concomitant ACE inhibitor or ß-blocker therapy. The norepinephrine data therefore confirm the favourable neurohormonal effects of valsartan therapy.

Discussion

The following are the principal findings of Val-HeFT. In patients with moderately severe CHF, valsartan significantly reduced combined all-cause mortality and morbidity by 13.3%. This benefit was accounted for almost exclusively by a 27.5% reduction of CHF hospitalizations. Valsartan, however, had no effect on all-cause mortality. Valsartan also significantly improved signs and symptoms of CHF, quality of life, LVEF, and the drug is well tolerated in spite of high doses. New subgroup analysis suggests that the benefits of valsartan on combined mortality and morbidity were most pronounced in patients not on ACE inhibitors and ß-blockers, and this beneficial effect was more modest in patients on ACE inhibitor with no ß-blockers. On the other hand, there exists a possibility of an adverse effect of valsartan on mortality and morbidity in patients who were on both ACE inhibitor and ß-blockade therapy. Finally, valsartan exerts favourable neurohormonal effects by reducing plasma BNP level and attenuating the increase in plasma norepinephrine.

Table 3: Plasma brain natriuretic peptide data[24]

Valsartan: Mean of absolute changes from baseline (pg/mL)				
	ACE(y) BB (y)	ACE(y) BB(n)	ACE(n) BB (y)	ACE(n) BB(n)
4 months	-34**	-34**	-57**	-76**
12 months	-22**	-26**	-55**	-57**
24 months	-23**	-17**	-56**	-26**
Placebo				
	ACE(y) BB(y)	ACE(y) BB(n)	ACE(n) BB (y)	ACE(n) BB(n)
4 months	-3**	1**	71**	-13**
12 months	-8**	16**	224**	2**
24 months	19**	18**	131**	7**

y= yes; n= no.

* p<0.01, ** p<0.001, valsartan vs placebo

Previous animal and clinical data have provided the rationale for examining the effects of combined ACE inhibitors and ARBs on clinical outcomes in patients with CHF. In a pig model of pacing-induced CHF, valsartan in combination with ACE inhibition resulted in more pronounced improvement in cardiac performance, myocardial blood flow, and alleviation of neurohormonal activation.[27,28] Patients with CHF who deteriorated while taking ACE inhibitors were found to have higher plasma Ang II level than stable patients.[12] A recent study has further demonstrated that 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.[29] These observations strongly suggest that Ang II production may persist despite ACE inhibition in many patients with CHF and provides a rationale for combined ACE inhibitor and ARB therapy. 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.[18] Therefore, both experimental and clinical data on the combined use of ACE inhibitor and ARBs are consistent with the current results of Val-HeFT.

The new data on subgroup analysis and neurohormonal parameters of Val-HeFT have helped to provide further mechanistic insights on the results of the study. Although only a small number of patients in Val-HeFT (366 or 7%) were not on ACE inhibitors, presumably due to intolerance, the magnitude of the benefit of valsartan on combined mortality and morbidity and all-cause mortality in these patients was nevertheless quite substantial, regardless of whether these patients were on ß-blockers or not. This is, therefore, the first demonstration that an ARB is superior to placebo in improving clinical outcome in patients with CHF.

In the ELITE-II study,[15] another ARB, losartan, was found to be no better than the ACE inhibitor, captopril, in terms of all-cause mortality and sudden death. Because the trial was not powered to test for equivalence or non-inferiority, an inferior effect of losartan on clinical outcome compared to captopril could not be excluded. Some investigators have also expressed concern with the dose and dosing frequency of losartan employed in ELITE-II. However, while the results of the ELITE-II study cannot support definitively the replacement of ACE inhibitors with ARBs, the results of the aforementioned subgroup analysis of Val-HeFT have provided reassurance to those who prescribe ARBs to patients who cannot tolerate ACE inhibitors, a strategy that is commonly employed. This strategy is being formally tested in the ACE inhibitor-intolerant arm of the ongoing Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study.[30]

The potential adverse interaction between valsartan, ACE inhibitor, and ß-blockade therapy raises concerns regarding the safety of the combined use of three neurohormone inhibitors. To address this issue, several potential mechanisms need to be considered. First, it should be realized that subgroup analyses of the type carried out in Val-HeFT, could, at times, be misleading and should therefore be interpreted with some trepidation.[31] The potential adverse interactions between ARBs, ACE inhibitors, and ß-blockers may therefore, be due to chance alone. To interpret results generated from such analyses, one would need to consider external, as well as internal, consistency of the data. In terms of internal consistency, it is useful to note that directionally similar interactions for the 3 classes of agents were noted in both morbidity, as well as mortality (Figures 1 and 2). On the other hand, there was no significant interaction in terms of changes in plasma norepinephrine level.[23] There is equally conflicting evidence when it comes to external consistency. Some investigators have cited a directionally similar interaction with ß-blockers in ELITE-II.[14] However, the fact that an even smaller number of patients (22%) was on ß-blockers and that there was no background therapy of ACE inhibitors in ELITE-II, render such a comparison of little value. Furthermore, so far no concerns have been raised in the large on-going valsartan in acute myocardial infarction trial (VALIANT), where patients are randomized to captopril, valsartan, and their combination, and more than 70% are on ß-blockade therapy.[32] Further information regarding external consistency may also be available on completion of the systolic dysfunction arm of the CHARM study where over 50% of patients are on ß-blockers.[30]

A second consideration regarding the potential adverse interactions of the 3 classes of agents is biologic plausibility. The only biologically plausible explanation appears to be a hypothesis that extensive neurohormonal blockade in patients with CHF is detrimental. Excessive inhibition of the sympathetic nervous system, reflected by the marked lowering of plasma norepinephrine levels, has been purported as a mechanism for the detrimental effect of moxonidine in the MOXCON trial.[33] However, the aforementioned norepinephrine data in the Val-HeFT study does not seem to support such a hypothesis, at least in so far as blockade of the sympathetic nervous system is concerned. This issue, however, may be clarified further when the data on plasma endothelin-1, renin, and aldosterone in Val-HeFT become available.

Clinical Implications

- Data of the Val-HeFT study and the totality of currently available evidence support the use of an ARB, such as valsartan, as an alternative to ACE inhibitors in patients with CHF who are intolerant of the latter. At the time of this publication of *Cardiology Rounds*, the United States Food and Drug Administration has issued an approval letter for valsartan in the treatment of CHF for patients who are not on ACE inhibitors.
- Based on the results of Val-HeFT, the combined use of valsartan and an ACE inhibitor to reduce CHF-related morbidity can be considered in patients who cannot take ß-blockers. Likewise, valsartan may be added to ß-blockers in patients who cannot take ACE inhibitors.
- These above recommendations are based in part on subgroup of analyses of Val-HeFT, they are to be confirmed and may be subjected to modification by further data from the ongoing VALIANT and CHARM studies.
- ARBs are not general alternatives to ACE inhibitors and ß-blockers, which should remain as first line therapies in patients who can tolerate them.

References

1. Cowie MR, Mosterd A, Wood DA, et al. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-225.
2. *Cardiovascular health & services in Ontario: An ICES atlas*. Toronto: ICES; 1999:111-122.
3. O'Connell JB, Bristow MR. Economic impact of heart failure in the United States: time for a different approach. *J Heart Lung Transplant* 1994;13:S107-S112.
4. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-717.

5. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-1435.
6. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
7. CIBIS-II Investigators and Committee. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9-13.
8. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-2007.
9. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;334:1349-1355.
10. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-1658.
11. Balcells E, Meng QC, Johnson WH Jr, Oparil S, Dell'Italia LJ. Angiotensin II formation from ACE and chymase in human and animal hearts: methods and species considerations. *Am J Physiol* 1997;273:H1769-H1774.
12. Rousseau MF, Konstam MA, Benedict CR, et al. Progression of left ventricular dysfunction secondary to coronary artery disease, sustained neurohormonal activation and effects of ibopamine therapy during long-term therapy with angiotensin-converting enzyme inhibitor. *Am J Cardiol* 1994;73:488-493.
13. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-752.
14. Pitt B, Poole-Wilson PA, Segal R, et al. Effects of losartan versus captopril on mortality in patients with symptomatic heart failure: rationale, design, and baseline characteristics of patients in the Losartan Heart Failure Survival Study—ELITE II. *J Card Fail* 1999;5:146-154.
15. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582-1587.
16. McDonald KM, Mock J, D'Aloia A, et al. Bradykinin antagonism inhibits the antigrowth effect of converting enzyme inhibition in the dog myocardium after discrete transmural myocardial necrosis. *Circulation* 1995;91:2043-2048.
17. Cohn JN, Tognoni G, Glazer RD, Spormann D, Hester A. Rationale and design of the Valsartan Heart Failure Trial: a large multinational trial to assess the effects of valsartan, an angiotensin- receptor blocker, on morbidity and mortality in chronic congestive heart failure. *J Card Fail* 1999;5:155-160.
18. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation* 1999;100:1056-1064.
19. Tsuyuki RT, Yusuf S, Rouleau JL, et al. Combination neurohormonal blockade with ACE inhibitors, angiotensin II antagonists and beta-blockers in patients with congestive heart failure: design of the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study. *Can J Cardiol* 1997;13:1166-1174.
20. Baruch L, Anand I, Cohen IS, Ziesche S, Judd D, Cohn JN. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme in patients with heart failure. Vasodilator Heart Failure Trial (V-HeFT) Study Group. *Circulation* 1999;99:2658-2664.
21. Cohn JN, Tognoni G, For the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-1675.
22. Cohn JN, Anand IS, Carson P, et al. Effect of valsartan on hospitalization rate in Valsartan-Heart Failure Trial (Val-HeFT) (abstract). *Circulation* 2001;104:II-594.
23. Anand IS, Latini R, Masson S, et al. Attenuation of the increase in plasma norepinephrine by valsartan in the Val-HeFT trial (abstract). *Circulation* 2001;104:II-595.
24. Latini R, Anand IS, Masson S, et al. Sustained decrease in plasma brain natriuretic peptide by valsartan in the Val-HeFT Trial: effect of concomitant ACE inhibitors and beta-blockers at entry (abstract). *Circulation* 2001;104:II-594.
25. Stanek B, Frey B, Hulsmann M, et al. Prognostic evaluation of neurohumoral plasma levels before and during beta-blocker therapy in advanced left ventricular dysfunction. *J Am Coll Cardiol* 2001;38:436-442.
26. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997;96:509-516.
27. Krombach RS, Clair MJ, Hendrick JW, et al. Angiotensin converting enzyme inhibition, AT1 receptor inhibition, and combination therapy with pacing induced heart failure: effects on left ventricular performance and regional blood flow patterns. *Cardiovasc Res* 1998;38:631-645.
28. Spinale FG, de Gasparo M, Whitebread S, et al. Modulation of the renin-angiotensin pathway through enzyme inhibition and specific receptor blockade in pacing-induced heart failure: I. Effects on left ventricular performance and neurohormonal systems. *Circulation* 1997;96:2385-2396.
29. Jorde UP, Ennezat PV, Lisker J, et al. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. *Circulation* 2000;101:844-846.
30. Swedberg K, Pfeffer M, Granger C, et al. Candesartan in heart failure – assessment of reduction in mortality and morbidity (CHARM): rationale and design. Charm-Programme Investigators. *J Card Fail* 1999;5:276-282.
31. Horton R. From star signs to trial guidelines. *Lancet* 2000;355:1033-1034.
32. Pfeffer MA, McMurray J, Leizorovicz A, et al. Valsartan in acute myocardial infarction trial (VALIANT): rationale and design. *Am Heart J* 2000;140:727-750.
33. Jones CG, Cleland JG. Meeting report—the LIDO, HOPE, MOXCON and WASH studies. Heart Outcomes Prevention Evaluation. The Warfarin/Aspirin Study of Heart Failure. *Eur J Heart Fail* 1999;1:425-431.

Upcoming Scientific Meetings

17-20 March, 2002
American College of Cardiology (ACC '02)
Atlanta, Georgia
CONTACT: Phone: 301-897-5400
Fax: 301-897-9745
Website: Acc.org

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.