

# Improving Outcomes in Congestive Heart Failure: Val-HeFT

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## Key Words

Quality of life · Mortality · Val-HeFT · AT<sub>1</sub> receptor blocker

## Abstract

The aims of the treatment of heart failure are to improve the quality of life and slow the progression of cardiac disease. Improvement of quality of life is best assessed by questionnaire; progression of the disease is assessed by measuring mortality and morbidity. The agenda for the future is to establish intermediate markers for progression of cardiac disease that can be substituted for morbidity and mortality, and thus improve the efficiency and shorten the follow-up of clinical trials. At present, polypharmacy is required to achieve optimal improvements in quality and duration of life. Furthermore, some drugs may favorably affect one end point and adversely affect the other; for example, beta-blockers may exert adverse short-term effects on quality of life but may slow progression of the disease. Certain inotropic drugs may reduce symptoms but shorten life expectancy. Angiotensin-converting enzyme (ACE) inhibitors have exerted favorable effects on both quality of life and mortality, but the magnitude of these benefits has been disappointingly small. Persistent angiotensin-induced vasoconstriction and endocrine effects, despite ACE inhibition, is one

possible explanation. The Valsartan in Heart Failure Trial (Val-HeFT) has been designed to test the efficacy and safety of the AT<sub>1</sub> receptor blocker (ARB) valsartan in combination with ACE inhibitors and all other prescribed therapies in patients with heart failure. The study is powered to detect a mortality benefit and should therefore establish the role of ARBs in this patient group. When this trial and other ongoing studies are completed, we will be more able to define the role of ARBs in the treatment of heart failure.

Heart failure is an increasingly prevalent condition representing an advanced stage of all forms of heart disease affecting the ventricular myocardium. The frequency of heart failure is directly related to age both in men and women, and its prevalence is increasing, not only because of the aging of the population but also because of the reduction in mortality from acute cardiac events including acute myocardial infarction [1]. Indeed, all patients who have sustained damage to their myocardium from ischemia, infarcts, viral infections, toxins, or genetic disorders are at risk of subsequent development of heart failure because of progression of structural and functional abnormalities of the heart. Since the manifestations of heart failure are diverse, targets for therapy may be widely

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divergent. Fluid retention is a frequently occurring component of the syndrome and thus relief of congestion or edema is often a target for therapy. Hemodynamic derangement characterized by a decreased cardiac output and elevated cardiac filling pressure is a feature of the disease and a possible therapeutic target. Activation of neurohormonal mechanisms occurs frequently in the syndrome of heart failure [2], and its activation appears to relate both to the severity of the disease and its prognosis [3]. Some have advocated this neurohormonal activation as a target for therapy. Left ventricular structural enlargement in the syndrome appears to be progressive and thus remodeling has also become a potential target for therapy [4]. Ventricular arrhythmias occur frequently and may be associated with sudden death accounting for more than one-third of the deaths in this syndrome [5]. Consequently, ventricular tachyarrhythmias have also served as a target for therapy.

These physiological markers for severity of heart failure do not address the clinical syndrome affecting the patient. Quality of life is impaired in heart failure, with much of the impairment considered to be related to a reduction in exercise capacity. Thus, a variety of exercise tests has been used to quantify the disability and serve as a guide to clinical improvement [6]. None of these tests, however, provide an accurate guide to symptoms and have therefore not been as useful as hoped in quantifying the disease and its response to treatment. Questionnaires to assess quality of life have become popular recently because they address the overall disturbances that relate to the disability [7]. These have been used to quantitate both the severity of the disease and its therapeutic response.

The most measurable and unwanted outcome in heart failure is premature mortality. Shortened life expectancy is the most feared adverse event in heart failure and its mechanism of occurrence does not appear to be uniform. About one-third of patients with heart failure die suddenly and without premonitory symptoms suggesting a worsening of their syndrome [8]. These events are usually assumed to be related to ventricular tachyarrhythmia, but it is clear that bradyarrhythmias and electromechanical dissociation as well as other events may account for a considerable number of these sudden deaths [9]. About one-third of patients with heart failure die of what is interpreted as progressive heart failure with progressive worsening of symptoms often resulting in increased drug therapy and frequent hospitalizations [5]. Another one-third of patients with heart failure die from events that are difficult to interpret. Most of these relate to the cardiovascular

system, but they may involve concurrent illnesses, stroke, or other vascular events. The long-term aim of therapy for heart failure is to delay death by reducing the risk of one or more of these events. In addition, health care costs are an important consideration when dealing with this prevalent disease process. Heart failure admissions represent the most frequent cause of hospitalization in the Medicare population in the United States, the cost of which often represents the single largest expenditure of health care payers [10]. Thus, a reduction in the frequency of hospitalization is another aim, both to improve the quality of life for the patient and to reduce health care costs. Therefore, most trials carried out today with long-term therapeutic approaches to heart failure address mortality and hospitalization as primary end points for therapy.

Current recommended therapy for heart failure includes: converting enzyme inhibitors, diuretics when fluid retention is present, digoxin when the left ventricle is dilated, and beta-blockers in stable patients to slow disease progression. This optimally recommended therapy for heart failure has shown a reduction of morbidity and mortality in the syndrome as compared with therapy not including an angiotensin-converting enzyme (ACE) inhibitor or a beta-blocker [11–13], and is now standard recommendation in guidelines worldwide for the management of the syndrome [14]. Nonetheless, morbidity and mortality in heart failure remain unacceptably high. In Studies Of Left Ventricular Dysfunction (SOLVD) and Vasodilator-Heart Failure Trial (V-HeFT), the mortality rate at 4 years remains approximately 40% despite optimal therapy with enalapril [11, 15], and morbidity in terms of impaired quality of life, reduced exercise tolerance and need for hospitalization remains high. The addition of beta-blockers to ACE inhibitors in the management of this syndrome results in a further reduction in morbidity and mortality [12, 13].

The introduction of ACE inhibitors to manage heart failure is based on the presumed adverse effects of angiotensin on the cardiovascular system and the presumed efficacy of converting enzyme inhibitors in reducing the circulating and tissue levels of angiotensin. Angiotensin is a potent vasoconstrictor and stimulator of vascular smooth muscle growth, a stimulator of aldosterone secretion, a facilitator of post-synaptic norepinephrine release, and a stimulator of myocyte and collagen growth in the myocardium. All of these physiological and structural effects of angiotensin may contribute to the progression of the syndrome by way of impedance to left ventricular ejection, cardiac remodeling and hormonal stimulation.

Plasma renin activity varies widely in patients with heart failure [16] but is often at extraordinarily high levels. This activation of the renin-angiotensin system provides further justification for the clinical use of converting enzyme inhibitors.

Recent evidence has suggested that converting enzyme inhibitors are not uniformly effective in suppressing circulating angiotensin II levels. Even with high levels of ACE inhibition, alternative pathways of angiotensin II production through the kinase system may exist, particularly in tissues such as those of the heart [17–19]. Furthermore, ACE inhibition stimulates the production of renin activity. This may facilitate the formation of additional angiotensin I, possibly leading to formation of angiotensin II, even in the presence of converting enzyme inhibition because of the competitive nature of that blockade [20, 21]. In addition, patients with heart failure are often treated with doses of ACE inhibitor that do not provide 24-hour blockade of the enzyme. Even clinically recommended doses of ACE inhibitor do not exert their effect throughout a 24-hour period [22, 23], and the doses of ACE inhibitor used are usually far lower than those recommended [24]. In view of this pharmacologic and clinical experience, it seemed prudent to consider the possibility that angiotensin receptor blockade would produce a further clinical benefit in patients already treated with conventional doses of ACE inhibitor.

A pilot study was therefore undertaken in a number of Veterans Affairs Medical Centers to assess the effect of adding valsartan to conventional converting enzyme inhibitor therapy in patients with heart failure [25]. Eighty-three patients treated with recommended doses of ACE inhibitor were randomly assigned to therapy with placebo, valsartan 80 mg twice daily, or valsartan 160 mg twice daily. The acute response to the first dose and the chronic response to 4 weeks of such therapy were assessed by hemodynamic monitoring of right heart pressures and by measurement of plasma hormone levels. This pilot study demonstrated a dose-response effect of valsartan in such patients, both during the first dose of the drug and at the end of 4 weeks of continuous therapy. In particular, the 160-mg dose produced a greater reduction in both pulmonary capillary wedge pressure and blood pressure than was observed with placebo. Furthermore, plasma aldosterone levels were significantly further suppressed by valsartan and there was a trend for a dose-response reduction in plasma norepinephrine. These observations confirmed that angiotensin II was maintaining a hemodynamic and hormonal effect even in patients receiving ACE inhibitors, and provided the rationale for undertak-

ing a large-scale trial to demonstrate the outcomes effect of valsartan in such a patient group.

The Valsartan in Heart Failure Trial (Val-HeFT) was initiated in April 1997 to evaluate the effects of valsartan therapy on mortality and morbidity in heart failure. Patients have been randomly assigned to valsartan 160 mg daily or placebo in addition to conventional therapy for heart failure, including beta-blockers if the physician has chosen to use them. All patients entering into the trial exhibited a dilated left ventricle and an ejection fraction lower than 40%, as well as symptoms of heart failure from class II to IV in severity. Documentation of a dilated left ventricle by echocardiography was also required. The primary end point will be supplemented by other measures of physiological efficacy, including sequential measurement of plasma hormone levels and quality of life assessment. Several substudies will address more specific outcome variables including exercise tolerance, ventricular arrhythmias, heart rate variability, and left ventricular remodeling. Val-HeFT is being carried out in the United States, Europe, South Africa, and Australia with the aim of entering 5,000 patients in order to power the trial to identify a 20% reduction in mortality. A total of 906 deaths are required to achieve that power and the study will be continued until that number has been achieved. Recruitment was completed in April 1999.

The strategy of Val-HeFT to identify the efficacy of valsartan in combination with an ACE inhibitor is supplemented internationally by alternative strategies using different angiotensin receptor blockers. The Evaluation of losartan in the elderly II (Elite II) trial will explore the efficacy of losartan as compared with captopril. Studies with candesartan are being planned to address comparative effects both of ACE inhibitors and candesartan but also the additive effect of these drugs. When these trials have been completed, we should be more able to define the role of AT<sub>1</sub> receptor blockers in the management of heart failure. Preliminary evidence supports the assertion that these drugs and ACE inhibitors do not have a similar mechanism of action, and therefore, differences in outcome may be demonstrable. We await the results.

## References

- 1 Massie BM, Shah NB: Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. *Am Heart J* 1997;133:703-712.
- 2 Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN: Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49:1659-1666.
- 3 Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819-823.
- 4 Cohn JN: Structural basis for heart failure. Ventricular remodeling and its pharmacological inhibition [editorial]. *Circulation* 1995;91:2504-2507.
- 5 Goldman S, Johnson G, Cohn JN, Cintron G, Smith R, Francis G: Mechanism of death in heart failure. The Vasodilator-Heart Failure Trials. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;87:VI24-VI31.
- 6 Ziesche S, Cobb FR, Cohn JN, Johnson G, Tristani F: Hydralazine and isosorbide dinitrate combination improves exercise tolerance in heart failure. Results from V-HeFT I and V-HeFT II. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;87:VI56-VI64.
- 7 Rector TS, Kubo SH, Cohn JN: Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am Heart J* 1993;71:1106-1107.
- 8 Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B: Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;314:1547-1552.
- 9 Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J: Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989;80:1675-1680.
- 10 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.
- 11 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.
- 12 Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH: 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.
- 13 CIBIS-II investigators: The cardiac insufficiency bisoprolol study II (CIBIS II): a randomised trial. *Lancet* 1999;353:9-13.
- 14 Packer M, Cohn JN: Consensus recommendations for the management of chronic heart failure. *Am J Cardiol* 1999;83:2A-38A.
- 15 Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, Bhat G, Goldman S, Fletcher RD, Doherty J, Hughes CV, Carson P, Cintron G, Shabetai R, Haakenson C: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-310.
- 16 Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A, for the V-HeFT VA Cooperative Studies Group: Plasma norepinephrine, plasma renin activity, and congestive heart failure: relations to survival and the effects of therapy in V-HeFT II. *Circulation* 1993;87(suppl VI):VI40-VI48.
- 17 Urata H, Healy B, Stewart RW, Bumpus FM, Husain A: Angiotensin II-forming pathways in normal and failing human hearts. *Circ Res* 1990;66:883-890.
- 18 Okunishi H, Oka Y, Shiota N, Kawamoto T, Song K, Miyazaki M: Marked species-difference in the vascular angiotensin II-forming pathways: humans versus rodents. *Jpn J Pharmacol* 1993;62:207-210.
- 19 Balcells E, Meng QC, Johnson Jr WH, 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.
- 20 Nussberger J, Fleck E, Bahrmann H, Delius W, Schultheiss HP, Brunner HR: Dose-related effects of ACE inhibition in man: quinapril in patients with moderate congestive heart failure. The Study Group on Neurohormonal Regulation in Congestive Heart Failure: Lausanne, Switzerland; Berlin, Dusseldorf, Munich, Germany. *Eur Heart J* 1994;15(suppl D):113-122.
- 21 Schunkert H, Ingelfinger JR, Hirsch AT, Pinto Y, Remme WJ, Jacob H, Dzau VJ: Feedback regulation of angiotensin converting enzyme activity and mRNA levels by angiotensin II. *Circ Res* 1993;72:312-318.
- 22 van den Broek SA, de Graeff PA, van Veldhuisen DJ, van Gilst WH, Hillege H, Wesseling H, Lie KI: Clinical and neurohumoral differences between spirapril and captopril in mild to moderate chronic congestive heart failure. *J Card Fail* 1997;3:165-171.
- 23 Kawamura M, Imanashi M, Matsushima Y, Ito K, Hiramori K: Circulating angiotensin II levels under repeated administration of lisinopril in normal subjects. *Clin Exp Pharmacol Physiol* 1992;19:547-553.
- 24 Packer M: Do angiotensin-converting enzyme inhibitors prolong life in patients with heart failure treated in clinical practice? *J Am Coll Cardiol* 1996;28:1323-1327.
- 25 Baruch L, Anand I, Cohen IS, Ziesche S, Judd D, Cohn JN, for the V-HeFT Study Group: Augmented acute and chronic hemodynamic and hormonal effects of an angiotensin blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. *Circulation* (In press).

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