Valsartan is as safe and effective as enalapril for people with heart failure

Abstracted from: Willenheimer R, Helmers C, Pantev E et al. Safety and efficacy of valsartan versus enalapril in heart failure patients. *Int J Cardiol* 2002; 85: 261–270.

BACKGROUND ACE inhibitors are underused when treating heart failure, partly due to adverse effects. Angiotensin-receptor blockers may replace ACE inhibitors in heart failure, if similarly effective, because they are better tolerated.

OBJECTIVE To compare the safety and efficacy of valsartan and enalapril for people with heart failure stabilised on an ACE inhibitor.

SETTING Multiple centres; location and timeframe not specified.

METHOD Randomised trial.

PARTICIPANTS One hundred and forty-one adults with stable moderate or mild heart failure and left ventricular ejection fraction of 0.45 or less. Mean age 68 years (range 46 to 90); 26% women. All had been treated with an ACE inhibitor for at least 3 months and were able to perform a 6-minute walking test. Exclusion criteria were myocardial infarction or coronary intervention within 3 months; heart failure due to pulmonary disease; significant primary valvular disease; infective cardiomyopathy; unstable coronary disease; severe arrhythmia; recent stroke; significant laboratory abnormalities; other reason for limited exercise capacity angiotensin-receptor blocker treatment within 3 months, and persistent systolic blood pressure less than 90 mmHg.

INTERVENTION One hundred and sixty milligrams of valsartan once daily or 10 mg enalapril twice daily for 12 weeks.

MAIN OUTCOMES Exercise capacity (using distance walked during 6-minute test); left ventricular size and function.

MAIN RESULTS There was no significant difference between groups in changes in the 6-minute walk test, patients' well-being, left ventricular size and function or adverse effects. Left ventricular size ($p < 0.001$) and function ($p = 0.05$) improved slightly from baseline in the valsartan group.

AUTHORS' CONCLUSIONS Valsartan is as safe and effective as enalapril for people with mild-to-moderate heart failure previously stabilised on an ACE inhibitor.

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Commentary I

Renin–angiotensin system inhibition is widely used in heart failure. Inhibitors of the angiotensin converting enzyme (ACE-I) have been investigated in a number of randomised trials with more than 12 000 participants.[1] ACE inhibitors have become the cornerstone of present-day treatment of chronic heart failure.[2] ACE inhibitors work by blocking conversion of angiotensin I to angiotensin II and thereby preventing AT_1 receptor stimulation. AT_1 receptor blockers directly block the AT_1 receptor and are therefore more pharmacologically efficient than ACE inhibitors.[3,4]

Willenheimer and colleagues' findings support previous studies comparing ACE inhibitors and AT_1 receptor antagonists. ELITE, the first comparative trial, found nearly twice as many deaths in the captoptril group as with losartan. The primary end-point, influence on renal function, remained unchanged, however.[5] This left open the question of whether AT_1 receptor blockers could replace ACE inhibitors in heart failure, a question examined in ELITE II.

The ELITE II trial was the first to compare mortality with ACE inhibitors and AT_1 blockers in chronic heart failure. ELITE II did not confirm the findings of the ELITE study, but was terminated after 530 deaths. The mean observation period was 555 days. Mortality was 15.9% for captopril and 17.7% for losartan ($p = 0.16$). Thus, losartan did not improve survival over captopril, although early termination meant that the study may have lacked power to detect a clinically important difference in mortality.[6]

The RESOLVD study was terminated prematurely due to higher mortality in people receiving candesartan plus enalapril compared to enalapril or candesartan alone.[7] In this study, enalapril was more efficacious than candesartan alone, but differences in mortality and number of hospital stays did not reach statistical significance.

The ValHeFT study assessed the long-term effect of the angiotensin II receptor blocker, valsartan, when added to standard heart failure therapy (including ACE-I). There was no difference in all-cause mortality. The combined end-point of mortality plus morbidity was 13.2% lower with valsartan, mainly due to reductions in the number of hospital stays due to heart failure.[8]

This study by Willenheimer and colleagues found that 12 weeks of valsartan and enalapril had a similar effect on exercise capacity, symptoms of heart failure, quality of life and left ventricular function and size. Exercise end-points are related to quality of life rather than mortality. Thus, the study reinforces what we already know: that ACE-I and angiotensin II receptor blockers are comparable and well tolerated. Further studies comparing ACE-I with angiotensin II receptor blockers using surrogate end-points are unlikely to unearth anything new. Angiotensin II receptor blockers are no more effective that ACE-I inhibitors for chronic heart failure. As Reimer and Califf say, this is 'good news for [an] experimental concept but bad news for clinically effective therapy'[9].

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Commentary 2

The incidence and prevalence of chronic heart failure is increasing. The complexities of heart failure progression are not completely understood. One-year mortality for severe heart failure is about 36%.[1] Angiotensin-converting enzyme (ACE) inhibitors have become a standard treatment because large, long-term trials found marginally improved morbidity and mortality rates.[2] Angiotensin II receptor blockers (ARBs) like valsartan are among several classes of drugs being studied for people with chronic heart failure.[3] Valsartan was recently approved by the United States Food and Drug Administration for use in heart failure patients unable to tolerate ACE inhibitors.

The Val-HeFT trial compared 160 mg valsartan twice daily and placebo added to conventional therapy in 5010 people with chronic heart failure over a mean duration of 23 months.[4] Valsartan reduced the combined end-points of mortality and morbidity and improved clinical signs and symptoms. A post-hoc analysis in 1610 people receiving the triple combination of valsartan added to an ACE inhibitor and a β-blocker found an increased mortality rate compared to placebo ($p = 0.009$). This result will require further investigation to determine its clinical implications.

This article by Willenheimer and colleagues examined whether people with mild-to-moderate stable heart failure could safely be switched directly from an ACE inhibitor to once daily valsartan (160 mg) for 12 weeks. There were no significant differences in exercise tolerance, New York Heart Association Class, dyspnea index, quality of life score or left ventricular chamber size from echocardiography. The study has no dramatic news for clinicians, but adds to our confidence that we can safely switch from an ACE inhibitor directly to valsartan in people with mind-to-moderate stable heart failure. This supports findings with other ARBs.[5–7]

In this study, the dose of valsartan was 160 mg once daily, just half the dose found to be most beneficial in an earlier dose-finding trial. This raises questions about the target dosage for this drug. There are also questions about the long-term safety and effectiveness of ARBs. Although current guidelines suggest that standard heart failure therapy should include an ACE inhibitor,[2] it appears that ARBs may be appropriate for people intolerant of ACE inhibitors.

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