Commentary

Angiotensin receptor blockers in heart failure after the ELITE II trial

Ronnie Willenheimer

University Hospital Malmö, Malmö, Sweden

Received: 31 July 2000
Revisions requested: 14 August 2000
Revisions received: 21 August 2000
Accepted: 21 August 2000
Published: 12 September 2000

Curr Control Trials Cardiovasc Med 2000, **1**:in press

(Print ISSN 1468-6708; Online 1468-6694)

Abstract

Specific blockers of the angiotensin type 1 receptor, angiotensin receptor blockers (ARBs), have been introduced as an alternative to angiotensin-converting enzyme inhibitors (ACEi) for the treatment of heart failure. In comparison with ACEi, ARBs are better tolerated and have similar effects on haemodynamics, neurohormones and exercise capacity. Early studies have suggested that ARBs might have a superior effect on mortality. However, the first outcome trial, ELITE II (Losartan Heart Failure Survival Study), did not show any significant difference between losartan and captopril in terms of mortality or morbidity. This commentary outlines the role of ARBs in the treatment of heart failure.

Keywords: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, efficacy, heart failure, tolerability

Introduction

Angiotensin-converting-enzyme inhibitors (ACEi) improve survival and decrease morbidity in patients with heart failure (HF) [1], asymptomatic left ventricular systolic dysfunction [2], myocardial infarction [3] and high cardiovascular risk [4]. However, there is a substantial under-use of ACEi [5], due at least partly to the side effect profile and concerns among many physicians of side effects [6]. Recently specific blockers of the angiotensin type 1 receptor (AT_1 receptor), angiotensin receptor blockers (ARBs), have been introduced as an alternative to ACEi. Specific receptor blockade is potentially advantageous compared with the non-specific interaction of ACEi and expectations are high that ARBs will prove to be a useful therapeutic option in HF.

Tolerance and efficacy of ARBs

ARBs are well tolerated, even by HF patients who cannot tolerate an ACEi [7], and the side effects are at the placebo level. The haemodynamic and neurohormonal effects in HF patients are similar to those of ACEi [8–14], and short-term studies have indicated that ARBs are at least as efficacious as ACEi in terms of exercise capacity and symptoms [10,11]. In a study of 844 HF patients a dose-dependent increase in exercise capacity was demonstrated for candesartan [15].

The ELITE trial

The first ELITE trial was conducted primarily to investigate the safety and tolerability of the ARB losartan compared with the ACEi captopril [16]. The study included 722 patients aged 65 years or more, with chronic symptomatic HF and left ventricular systolic dysfunction. Patients were randomized to losartan 50 mg once daily or captopril 50 mg three times daily, and followed up for 48 weeks. The primary endpoint, a persistent increase in creatinine concentration of at least 26.5 μmol/l, was met by 10.5% of the patients in both groups. Mortality and hospitalization

ARB = angiotensin receptor blocker; ACEi = angiotensin-converting enzyme inhibitor(s)/inhibition; AT_1 receptor = angiotensin type 1 receptor; CI = confidence interval; HF = heart failure.

Table 1

Ongoing mortality trials with ARBs in heart failure

Study	Drugs	Type of patients	*n*	Power primary endpoint reduction (%)	Endpoints	Expected to be concluded
Val-HeFT	Valsartan vs placebo (open ACEi)	Symptomatic HF, LVEF ≤40%	5009	20	Total mortality Morbidity	2000 906 deaths
CHARM	Candesartan vs placebo	Symptomatic HF + LVEF≤40, on ACEi LVEF≤40, ACEi intolerant LVEF>40, no ACEi	 2550 2000 2970	16–20	CV mortality/ HF hospitalization (total mortality in the combined arms)	2002

LVEF, left ventricular ejection fraction; CV, cardiovascular; MI, myocardial infarction.

were secondary endpoints, and there was an unexpected 46% lower ($P < 0.05$) mortality from all causes as well as significantly fewer hospitalizations in the losartan group. Losartan was also tolerated significantly better.

The ELITE II trial

As a consequence of the ELITE results, the ELITE II trial was initiated to examine whether losartan would be superior to captopril in terms of survival and morbidity in patients with HF [17]. A total of 3152 patients with symptomatic HF and a left ventricular ejection fraction of 40% or less were randomized to either losartan 50 mg once daily ($n=1578$) or captopril 50 mg three times daily ($n=1574$). Patients were essentially naive for ACEi and were stratified for beta-blocker use at baseline. The mean age was 71.5 years; 70% were men. About half of the patients were in New York Heart Association class II, ie mildly symptomatic, and 45% were in class III, ie moderately symptomatic. Approximately 80% had ischaemic cause for the HF. The trial was completed when 530 deaths had occurred, after 555 days of mean follow-up.

There were no statistically significant differences between the two treatment regimens with regard to the main efficacy parameters. There were 280 and 250 deaths in the losartan and captopril groups, respectively [hazard ratio losartan:captopril 1.13, 95% confidence interval (CI) 0.95–1.35, $P=0.16$]. There were 142 and 115 sudden deaths or resuscitated cardiac arrests in the losartan and captopril groups, respectively (hazard ratio 1.24, 95% CI 0.97–1.59, $P=0.08$). The corresponding figures for the composite of mortality and hospitalization from all causes were 752 and 707 events, respectively (hazard ratio 1.07, 95% CI 0.96–1.18, $P=0.21$). Losartan was better tolerated than captopril in that significantly fewer patients discontinued prematurely owing to adverse events, excluding deaths, in the losartan group (9.7% compared with 14.7%, $P=0.001$).

Ongoing trials with ARBs in heart failure

More information about the effects of ARBs on mortality and morbidity in HF is expected soon. Table 1 depicts the two mortality trials currently examining the effects of ARBs in HF [18,19]. It should be noted that neither trial compares an ARB with an ACEi directly. Instead, both investigate the effects of an ARB compared with placebo on top of standard HF therapy, including an ACEi. In addition, the CHARM (candesartan in heart failure – assessment of reduction in mortality and morbidity) trial compares candesartan with placebo in patients intolerant of ACEi and in patients with a left ventricular ejection fraction of more than 40% who are not on an ACEi [19].

What is the role of ARBs in the treatment of heart failure?

Are ARBs better than, equal to or worse than ACEi?

The ELITE II trial is the only mortality trial comparing an ARB and an ACEi that has been conducted up to now. Consequently, there is no documentation that ARBs are better than ACEi. ELITE II did not have the aim of demonstrating non-inferiority for losartan compared with captopril, and we do not know whether ARBs and ACEi are equally efficacious. There is no evidence that ACEi are better than ARBs, but given their superior documentation in HF the general opinion is that ACEi remain first-line therapy and that ARBs (i.e. losartan) might be considered in patients who cannot tolerate an ACEi.

Although ARBs are directly compared with an ACEi in ongoing mortality trials in high-risk myocardial infarction patients [20], there is a need to perform a second mortality trial comparing an ARB and an ACEi directly in HF patients. When designing such a trial there are some important points to consider. Firstly, we do not know the optimum dose of an ARB in terms of a survival effect in HF, and it has been suggested that the losartan dose used in the ELITE II trial might have been too low to show superiority compared with captopril. The doses of ARBs used in other ongoing trials in HF are equivalent to four times that losartan dose [18,19]. Secondly, the timing might be important. Theoretically ARBs might be superior to ACEi especially when ACEi escape is present, in other words when plasma levels of angiotensin II after some duration of ACE inhibition return to pretreatment levels [21,22]. This phenomenon seems to be present in around

half of ACEi-treated HF patients, and these have a significantly worse prognosis than those who have no escape [23]. In the ELITE II trial, patients were essentially naive for ACEi at baseline and could not have had any escape. Although some might have developed escape during the course of the trial, they would not have been exposed to the drawbacks of the escape for a long time, because the trial duration was only 1.5 years. If patients treated with an ACEi for 2 years, for example, were to be randomized to an ARB or an ACEi, there is theoretically a better chance to show superiority for the ARB.

Are ARBs better than placebo?

A definite answer in terms of mortality and morbidity is not yet available. The 95% CI of the ELITE II trial suggests that losartan is at worst 35% less efficacious than captopril in terms of mortality. This places losartan at approximately the placebo level. A meta-analysis of observed mortality data from losartan studies in HF, excluding the ELITE II trial, included 1894 patients [24]. The odds of dying in the losartan groups were 0.51 (95% CI 0.31–0.81) times those of the controls. Because the control patients mainly received an ACEi and only a minority received placebo, this analysis is an underestimation of the efficacy of losartan compared with placebo. However, this meta-analysis does not give a true answer to the question. The CHARM trial is designed to provide such an answer (Table 1) [19].

Is combined therapy better than an ACEi alone?

Combined therapy with an ACEi and an ARB permits both an inhibition of the breakdown of bradykinin and a specific AT_1 receptor blockade, and might lead to more complete inhibition of the renin–angiotensin system [20]. This might provide benefits compared with monotherapy with either agent. However, it is possible that combined therapy is less effective than AT_1 receptor blockade alone. Combined therapy might lead to less formation of angiotensin II, in turn causing less stimulation of the angiotensin type 2 receptors than AT_1 receptor blockade alone would. Because angiotensin II might exert beneficial effects via the type 2 receptor this could be a drawback [20]. Furthermore, and most importantly, combined therapy will most probably cause the same side effects as ACE inhibition alone.

In terms of mortality and morbidity, no results are available to answer this question. Relatively small, short-term studies indicate that combined therapy might be beneficial compared with ACEi alone in terms of neurohormonal activation, exercise capacity, left ventricular ejection fraction and functional class [20]. The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) study included 768 patients with symptomatic HF [25]. Patients were randomized to monotherapy with candesartan, a combination of candesartan and enalapril, or enalapril alone. The aim of the study was to evaluate the effects on exercise capacity, safety and tolerability, neurohormones, ventricular function, quality of life and symptoms. There were no between-group differences in terms of exercise capacity or symptoms, whereas remodelling and neuroendocrine activation were significantly more attenuated with the combined treatment compared with monotherapy with either agent. The safety findings have been discussed. Of patients receiving combined treatment ($n=332$), 8.7% died; in patients given monotherapy with candesartan ($n=327$), 6.1% died; whereas 3.7% of those treated with enalapril in monotherapy ($n=109$) died. Differences between groups were not statistically significant ($P=0.148$). In addition, more hospitalizations were observed in the candesartan groups, but with no significant differences between groups. Because RESOLVD was not designed as a mortality/morbidity study these results should be interpreted cautiously.

A more definite answer to the question will be provided by the Val-HeFT (Valsartan in Heart Failure Trial) [18] and CHARM [19] trials (Table 1).

Are there differences in efficacy between ARBs?

There are some pharmacological differences between the different ARBs [20], and individual studies have demonstrated differences between ARBs in efficacy in lowering blood pressure. However, a large meta-analysis has pointed out that these differences are very small and probably clinically insignificant [26]. Whether there are any differences between ARBs in terms of effects on mortality and morbidity is as yet unknown.

Conclusions

ACEi are at present first-line drugs for the treatment of HF, and ARBs can be considered in patients who cannot tolerate ACEi. Ongoing mortality trials in HF will elucidate the role of combined ARB and ACEi therapy, as well as the efficacy of ARBs compared with placebo. However, it is also important to perform a second mortality trial that directly compares an ARB and an ACEi in HF. When designing such a trial the dosing and timing of therapy should be carefully considered.

References

1. Garg R, Yusuf S: **Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials.** *J Am Med Ass* 1995, **273**:1450–1456.
2. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E: **Long-term ACE-inhibitor therapy in patients with heart failure of left-ventricular dysfunction: a systematic overview of data from individual patients.** *Lancet* 2000, **355**:1575–1581.
3. Latini R, Tognoni G, Maggioni AP, Baigent C, Braunwald E, Chen ZM, Collins R, Flather M, Franzosi MG, Kjekshus J, Kober L, Liu LS, Peto R, Pfeffer M, Pizzetti F, Santoro E, Sleight P, Swedberg K, Tavazzi L, Wang W, Yusuf S: **Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomised patients. Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group.** *J Am Coll Cardiol* 2000, **35**:1801–1807.

4. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G: **Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators.** *N Engl J Med* 2000, **342**: 145–153.
5. Doyle JC, Mottram DR, Stubbs H: **Prescribing of ACE inhibitors for cardiovascular disorders in general practice.** *J Clin Pharm Ther* 1998, **23**:133–136.
6. Houghton AR, Cowley AJ: **Why are angiotensin converting enzyme inhibitors underutilised in the treatment of heart failure by general practitioners?** *Int J Cardiol* 1997, **59**:7–10.
7. Granger CB, Ertl G, Kuch J, Maggioni AP, McMurray J, Rouleau JL, Stevenson LW, Swedberg K, Young J, Yusuf S, Califf RM, Bart BA, Held P, Michelson EL, Sellers MA, Ohlin G, Sparapani R, Pfeffer MA: **Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors.** *Am Heart J* 2000, **139**:609–617.
8. Gottlieb SS, Dickstein K, Fleck E, Kostis J, Levine TB, LeJemtel T, DeKock M: **Hemodynamic and neurohormonal effects of the angiotensin II antagonist losartan in patients with congestive heart failure.** *Circulation* 1993, **88**:1602–1609.
9. Crozier I, Ikram H, Awan N, Cleland J, Stephen N, Dickstein K, Frey M, Young J, Klinger G, Makris L: **Losartan in heart failure. Hemodynamic effects and tolerability.** *Circulation* 1995, **91**:691–697.
10. Dickstein K, Chang P, Willenheimer R, Haunso S, Remes J, Hall C, Kjekshus J: **Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate or severe chronic heart failure.** *J Am Coll Cardiol* 1995, **26**: 438–445.
11. Lang RM, Elkayam U, Yellen LG, Krauss D, McKelvie RS, Vaughan DE, Ney DE, Makris L, Chang PI: **Comparative effects of losartan and enalapril on exercise capacity and clinical status in patients with heart failure. The Losartan Pilot Exercise Study Investigators.** *J Am Coll Cardiol* 1997, **30**:983–991.
12. Mazayev VP, Fomina IG, Kazakov EN, Sulimov VA, Zvereva TV, Lyusov VA, Orlov VA, Olbinskaya LI, Bolshakova TD, Sullivan J, Spormann DO: **Valsartan in heart failure patients previously untreated with an ACE inhibitor.** *Int J Cardiol* 1998, **65**:239–246.
13. Parker AB, Azevedo ER, Baird MG, Smith SJ, Arnold JM, Humen DP, Moe GW, Parker JO, Butt RW, Parker JD: **ARCTIC: assessment of haemodynamic response in patients with congestive heart failure to telmisartan: a multicentre dose-ranging study in Canada.** *Am Heart J* 1999, **138**:843–848.
14. Havranek EP, Thomas I, Smith WB, Ponce GA, Bilsker M, Munger MA, Wolf RA: **Dose-related beneficial long-term hemodynamic and clinical efficacy of irbesartan in heart failure.** *J Am Coll Cardiol* 1999, **33**:1174–1181.
15. Riegger GA, Bouzo H, Petr P, Munz J, Spacek R, Pethig H, von Behren V, George M, Arens H: **Improvement in exercise tolerance and symptoms of congestive heart failure during treatment with candesartan cilexetil. Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH) Investigators.** *Circulation* 1999, **100**;2224–2230.
16. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI: **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.
17. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B: **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.
18. Cohn JN: **Improving outcomes in congestive heart failure: Val-HeFT. Valsartan in Heart Failure Trial.** *Cardiology* 1999, **91(suppl 1)**:19–22.
19. Swedberg K, Pfeffer M, Granger C, Held P, McMurray J, Ohlin G, Olofsson B, Östergren J, Yusuf S: **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.
20. Willenheimer R, Dahlöf B, Rydberg E, Erhardt L: **AT_1-receptor blockers in hypertension and heart failure: clinical experience and future directions.** *Eur Heart J* 1999, **20**:997–1008.
21. Biollaz J, Brunner HR, Gavras I, Waeber B, Gavras H: **Antihypertensive therapy with MK 421: angiotensin II–renin relationships to evaluate efficacy of converting enzyme blockade.** *J Cardiovasc Pharmacol* 1982, **4**:966–972.
22. Rousseau MF, Konstam MA, Benedict CR, Donckier J, Galanti L, Melin J, Kinan D, Ahn S, Ketelslegers JM, Pouleur H: **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.
23. Roig E, Perez-Villa F, Morales M, Jimenez W, Orus J, Heras M, Sanz G: **Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure.** *Eur Heart J* 2000, **21**:53–57.
24. Sharma D, Buyse M, Pitt B, Rucinska EJ, and the Losartan Heart Failure Mortality Meta-analysis Study Group: **Meta-analysis of observed mortality data from all controlled, double-blind, multiple-dose studies of losartan in heart failure.** *Am J Cardiol* 2000, **85**: 187–192.
25. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, Tsuyuki RT, White M, Rouleau J, Latini R, Maggioni A, Young J, Pogue J: **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**:1056–64.
26. Conlin PR, Spence JD, Williams B, Ribeiro AB, Saito I, Benedict C, Bunt AM: **Angiotensin II antagonists for hypertension: are there differences in efficacy?** *Am J Hypertens.* 2000, **13**:418–426.

Author's affiliation: Department of Cardiology, University Hospital Malmö, Malmö, Sweden

Correspondence: Ronnie Willenheimer, MD, PhD, Department of Cardiology, University Hospital Malmö, S-205 02 Malmö, Sweden.
Tel: +46 40 33 10 00; fax: +46 40 33 62 09;
e-mail: ronnie.willenheimer@medforsk.mas.lu.se