Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II

Bertram Pitt, Philip A Poole-Wilson, Robert Segal, Felipe A Martinez, Kenneth Dickstein, A John Camm, Marvin A Konstam, Günter Riegger, George H Klinger, James Neaton, Divakar Sharma, Balasamy Thiyagarajan, on behalf of the ELITE II investigators*

Summary

Background The ELITE study showed an association between the angiotensin II antagonist losartan and an unexpected survival benefit in elderly heart-failure patients, compared with captopril, an angiotensin-converting-enzyme (ACE) inhibitor. We did the ELITE II Losartan Heart Failure Survival Study to confirm whether losartan is superior to captopril in improving survival and is better tolerated.

Methods We undertook a double-blind, randomised, controlled trial of 3152 patients aged 60 years or older with New York Heart Association class II–IV heart failure and ejection fraction of 40% or less. Patients, stratified for β-blocker use, were randomly assigned losartan (n=1578) titrated to 50 mg once daily or captopril (n=1574) titrated to 50 mg three times daily. The primary and secondary endpoints were all-cause mortality, and sudden death or resuscitated arrest. We assessed safety and tolerability. Analysis was by intention to treat.

Findings Median follow-up was 555 days. There were no significant differences in all-cause mortality (11.7 vs 10.4%; average annual mortality rate), or sudden death or resuscitated arrest (9.0 vs 7.3%) between the two treatment groups (hazard ratios 1.13 [95% CI 0.95–1.35], p=0.16 and 1.25 [95% CI 0.98–1.60], p=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse effects (9.7 vs 14.7%, p=0.001), including cough (0.3 vs 2.7%).

Interpretation Losartan was not superior to captopril in improving survival in elderly heart-failure patients, but was significantly better tolerated. We believe that ACE inhibitors should be the initial treatment for heart failure, although angiotensin II receptor antagonists may be useful to block the renin angiotensin aldosterone system when ACE inhibitors are not tolerated.

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See Commentary page 1568

Introduction

Angiotensin-converting-enzyme (ACE) inhibitors, generally given with diuretics and digoxin, are the standard treatment for patients with heart failure and systolic left-ventricular dysfunction.1–3 Despite the established benefits of ACE-inhibitor treatment, physicians do not prescribe these agents to all their patients because of concerns related to adverse effects.4–6 The benefit of ACE inhibition has been attributed largely to blockade of the production of angiotensin II, but also to bradykinin accumulation.7 Bradykinin accumulation, however, has been implicated as a contributor to the adverse effects associated with ACE-inhibitor treatment and has also been suggested to result in prejunctional norepinephrine release.8,9 Since angiotensin II antagonists, such as losartan, directly block angiotensin II at the AT₁ receptor with no accumulation of bradykinin, these drugs should provide similar benefits to ACE inhibitors in blocking the harmful effects of angiotensin II with fewer side-effects.6,7,10–12 By direct blockade of AT₁-receptor activation, angiotensin II antagonists block angiotensin II irrespective of its generation by ACE-dependent or non-ACE-dependent pathways, and allow unopposed stimulation of AT₁ receptors, which theoretically would prevent ventricular remodelling associated with progression of heart failure.6,12,13

In the 48-week ELITE study in 722 ACE-inhibitor-naïve elderly patients with symptomatic heart failure, we saw an unexpected 46% lowering of mortality (a secondary endpoint) with losartan compared with the ACE inhibitor captopril (losartan 17 [4.8%] vs captopril 32 [8.7%] deaths; risk reduction 46% [95% CI 5–69]; p=0.035).14 In addition, losartan reduced the rate of all-cause hospital admissions, and, as anticipated, was generally better tolerated than captopril with significantly fewer discontinuations because of adverse effects, despite a similar rate of persistent rise in serum creatinine concentrations (primary endpoint of study).

The rate of hospital admissions for heart failure and improvements in functional status (measured by changes

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in New York Heart Association [NYHA] functional class and quality of life) were similar.

The survival benefit with losartan in the ELITE study seemed to be attributable primarily to a reduction in sudden cardiac death (losartan 5 [1·4%] vs captopril 14 [3·8%], relative risk reduction 64% [3·86]). In patients with heart failure, ACE inhibitors do not always lower probabilities of late death, as shown by the ELITE QT dispersion study, but this explanation for the observed reduction in sudden death with losartan in ELITE remains uncertain. The apparent superior effects seen with losartan on morbidity and mortality were based on a small number of events that were not the primary endpoint. Therefore, we designed a large, randomised, double-blind trial—the Losartan Heart Failure Survival Study ELITE II—to compare the effects of losartan with those of captopril on mortality and morbidity, safety, and tolerability.

**Patients and methods**

**Study population**

We enrolled patients, from June, 1997, to May, 1998, aged 60 years or older (we required that 85% be aged >65 years) with NYHA class II–IV heart failure and left-ventricular ejection fraction of 40% or less, measured by echocardiography or radionuclear ventriculography. Most patients were to be ACE-inhibitor and angiotensin-II-antagonist naïve. Some patients were eligible, however, if such treatment had been recently started and the exposure period was 7 days or less within the 3 months before randomisation, since there would probably be no impact on long-term clinical outcomes. Exclusion criteria were: intolerance of ACE inhibitors or angiotensin-II-receptor antagonists; systolic blood pressure less than 90 mm Hg; diastolic pressure more than 95 mm Hg; angina, coronary artery intervention or revascularisation, and haemodynamically important stenotic valvular heart disease; active myocarditis or pericarditis; automatic implanted cardioverter defibrillators; coronary angioplasty within 1 week of enrolment; coronary artery bypass graft surgery, acute myocardial infarction, or unstable angina pectoris within 2 weeks of enrolment; cerebrovascular accident or transient ischaemic attack within 6 weeks of enrolment; documented or suspected significant renal artery stenosis; haematuria; and serum creatinine concentrations higher than 220 μmol/L.

**Study design**

We did the study in 289 centres in 46 countries. The study design has been reported previously. Ethics review committees at all sites approved the protocol, and all participants provided written informed consent. The study was done under the direction of a steering committee. An independent data and safety monitoring committee continually reviewed study-drug use of these drugs with changes in clinical practice. We limited the proportion of randomised patients receiving β-blockers to 25% in the protocol, but this limit was not reached. All other treatments were allowed, apart from open-label ACE inhibitors or angiotensin II antagonists, while patients were taking the study drugs.

After a run-in period of 1–28 days of single-blind placebo (matched to losartan or captopril tablets) to enable adequate stabilisation and assessment of patients and to ensure adherence to study treatment, we randomly assigned patients losartan 12·5 mg once daily, titrated to 25 mg, and up to 50 mg three times daily (plus placebo), or captopril 12·5 mg three times daily titrated to 25 mg, and up to 50 mg three times daily (plus placebo, figure 1). Titration to the maximum tolerated dose, generally at weekly intervals, was recommended.

Clinical assessments were done during titration and every 4 months thereafter. Laboratory assessments were done at 1 month and then every 4 months while patients remained on study drugs. Patients who discontinued treatment were followed up every 4 months by clinical assessment and mortality and morbidity data were collected until the end of the study.

The primary endpoint was all-cause mortality. The secondary endpoint was the composite of sudden cardiac death or resuscitated cardiac arrest. Other prespecified outcome variables were: hospital admission (all-cause and cause-specific cardiovascular admissions such as heart failure, myocardial infarction, coronary artery disease defined as angina, unstable angina, coronary artery intervention or revascularisation, and stroke or transient ischaemic attack) and the composite variables (assessed by time to first event) of all-cause mortality or all-cause hospital admissions (which we thought to be the outcome of greatest interest), and all-cause mortality or hospital

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Losartan (n=1578)</th>
<th>Captopril (n=1574)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>71·4 (6·7)</td>
<td>71·5 (6·9)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>1102 (70%)/475 (30%)</td>
<td>1083 (69%)/481 (31%)</td>
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<tr>
<td>Ethnic origin</td>
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<tr>
<td>White</td>
<td>12B8 (82%)</td>
<td>1296 (82%)</td>
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<tr>
<td>Black</td>
<td>38 (2%)</td>
<td>29 (2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>74 (5%)</td>
<td>83 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>177 (13%)</td>
<td>168 (11%)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
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<tr>
<td>History of ischaemia</td>
<td>1247 (79%)</td>
<td>1243 (79%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>817 (52%)</td>
<td>819 (52%)</td>
</tr>
<tr>
<td>III</td>
<td>687 (43%)</td>
<td>683 (43%)</td>
</tr>
<tr>
<td>IV</td>
<td>74 (5%)</td>
<td>72 (5%)</td>
</tr>
<tr>
<td>Drug treatment</td>
<td></td>
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</tr>
<tr>
<td>Previous ACE inhibitor</td>
<td>365 (23%)</td>
<td>378 (24%)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>359 (23%)</td>
<td>328 (21%)</td>
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<td>Diuretic</td>
<td>1220 (77%)</td>
<td>1238 (79%)</td>
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<td>Cardiac glycoside</td>
<td>783 (50%)</td>
<td>793 (50%)</td>
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<td>Aspirin or salicylates</td>
<td>934 (59%)</td>
<td>929 (59%)</td>
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<tr>
<td>Calcium channel blockers</td>
<td>361 (23%)</td>
<td>361 (23%)</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>347 (22%)</td>
<td>331 (21%)</td>
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<tr>
<td>Mean (SD) measurements</td>
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<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>31 (7-0)</td>
<td>31 (6-9)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 (11·8)</td>
<td>75 (11·9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 (15·5)</td>
<td>73 (15·4)</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134 (18·9)</td>
<td>134 (18·6)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78 (9·5)</td>
<td>78 (9·9)</td>
</tr>
</tbody>
</table>

*ARTICLES*
All patients were analysed according to treatment because of progressive heart failure, fatal myocardial infarction, and multiple occurrences of myocardial infarction or multiple admissions for heart failure, cardiovascular reasons, or any reason. We classified deaths as sudden cardiac death or death because of progressive heart failure, fatal myocardial infarction, stroke, other cardiac causes, other vascular disease, and non-cardiovascular causes.

Statistical analysis
The study was an event-driven superiority trial designed with 90% power to detect a relative 25% difference in total mortality between treatments. With the assumption of an annual mortality rate of 9-4% in the captopril group, based on data from ELITE, we planned to enrol at least 3000 patients and to continue follow-up until 510 deaths had been recorded. We included study endpoints occurring until July 18, 1999, in the analyses (this date was established in advance by the steering committee when at least 510 deaths would have been expected to occur). Based on the 46% relative-risk reduction (95% CI 5-69) in the ELITE study, the study was originally powered to detect a 30% relative reduction in mortality (midpoint of the CI) in the losartan group compared with captopril. At the recommendation of the steering committee, before any unmasked review of data by the drug safety monitoring committee, we amended the protocol to detect a more conservative 25% treatment effect, which was thought to be a clinically relevant difference.

We did primary analysis of all efficacy variables by intention to treat. All patients were analysed according to treatment group, irrespective of whether they continued on treatment. Patients lost to follow-up were censored at the time of last contact.

We analysed the primary endpoint of death from any cause by time to event. The hazard rate, CI, and test for differences between treatments were based on Cox's regression model (terms included in the model: treatment group, geographical region, and stratification level based on β-blocker use at randomisation). Similar methods were used for all time-to-event outcome variables. For combined outcome variables, the time to the first event was used. We included geographical region in the model to account for any potential differences in mortality.

Several interim analyses of the primary endpoint (all-cause mortality) were done by the independent drug safety monitoring committee during the trial. An O'Brien-Fleming type stopping boundary was used as a guideline for any recommendation to stop the study early because of an overwhelming effect on mortality.21 The committee did not consider futility of observing a significant treatment effect as a reason to stop the study. To maintain the overall significance level at 5%, the critical p value for the primary endpoint at the final analysis was adjusted to 0·043 (two-sided) and 95·7% CI are reported. Other outcome variables were assessed at a significance level of 5%, according to the protocol.

Results
Of the 3152 patients enrolled, 1578 were assigned losartan and 1574 captopril (figure 1). Median follow-up was 1·5 years for each group. We saw all patients at a final visit within 6 weeks of the end of the study or established vital status. Only two patients were lost to follow-up. The baseline characteristics were similar in the two groups (table 1). 85% of patients were aged 65 years and older, mean left-ventricular ejection fraction was 31%, 69% were men, and 70% had a history of ischaemic heart disease. Severity of heart failure was evenly distributed between mild and moderate to severe.

In the losartan group there were 280 (17-7%) deaths compared with 250 (15-9%) in the captopril group (hazard ratio 1·13 [95-7% CI 0·95–1·35], p=0·16; figure 2, table 2). The estimated average annual mortality rate was 11·7% in the losartan group and 10·4% in the captopril group. Mortality did not generally differ significantly between participating regions, across predefined baseline demographic subgroups, or by concomitant therapy at randomisation (figure 3).

The rate of sudden death or resuscitated cardiac arrest did not differ significantly between the losartan and captopril groups (table 2).
captopril groups (9.0 vs 7.3%, 1.25 [0.98–1.60], p=0.08; figure 2, table 2).

The total number of hospital admissions did not differ significantly overall (table 2), nor did hospital admissions for heart failure. No significant difference was seen for the time to first event in the combined endpoint all-cause mortality or all-cause hospital admission (1.07 [0.97–1.19], p=0.18; figure 2, table 2).

Significantly fewer patients taking losartan (excluding patients who died) discontinued treatment because of adverse effects (p<0.001), including effects attributed to the study drug (p<0.001), or because of cough (p<0.001, figure 4). The frequency of discontinuations in the two treatment groups did not differ for worsening of heart failure (figure 4); similar frequencies of worsening heart failure (25%) were reported for each group during the course of the study. There were no significant differences in heart rate or lowering of blood pressure between the two treatment groups in the last measurements taken on treatment.

**Discussion**

Losartan treatment did not prove superior to captopril in improving survival in elderly patients with chronic symptomatic heart failure and systolic left-ventricular dysfunction, as was suggested by the findings of the ELITE study. Mortality and sudden cardiac death or resuscitated cardiac arrest did not differ significantly between groups. ELITE II did, however, confirm the superior tolerability of losartan seen in ELITE, with a significantly lower rate of discontinuation of treatment because of adverse effects.

The baseline characteristics of ELITE II and ELITE have several differences. Mean age was lower in ELITE II (71.4 vs 73.5 years), frequency of ischaemic heart disease was higher (79 vs 68%), some patients had a history of ACE-inhibitor use (23 vs 0%), use of β-adrenergic-receptor blocking agents was higher at randomisation (22 vs 16%), and more patients had NYHA class III–IV heart disease (48 vs 35%). These differences do not easily account for the contrast in findings on survival between the two studies. More likely, the superiority of losartan to captopril in reducing mortality, mainly due to decreasing sudden cardiac death, seen in ELITE should be taken as a chance finding. The observations from ELITE were based on a small number of deaths. ELITE II had four times as many patients and ten times more events.

The results on total mortality in ELITE II were generally consistent across subsets, based on predefined baseline characteristics (figure 3). The on-treatment analysis gave similar results to that by intention to treat. The subsets of patients did not generally differ significantly in effect of losartan and captopril apart from those who were taking β-blockers at randomisation (22% of the population). This difference was not seen if use was based on concomitant treatment with β-blockers during the study. Patients on losartan and captopril also
taking β-blockers did better than most patients not on such treatment at randomisation, which is consistent with data from studies supporting a benefit of β-blockers in such a population.23,24 The interaction between treatment effect and baseline β-blocker use should be interpreted with caution given the small number of patients receiving these drugs and potential bias related to the reasons for administering these agents.

Based on the findings of ELITE II, the importance of several mechanisms that had been suggested to favour the use of angiotensin II antagonists over ACE inhibitors should be reassessed: first, blockade by angiotensin II antagonists of the effects of angiotensin II at the AT1 receptor generated by ACE-dependent and non-ACE-dependent pathways;17 second, the stimulation of AT2 receptors by increased angiotensin II concentrations and associated effects on ventricular remodelling;25 third, the breakdown of bradykinin by ACE inhibitors and its accumulation, leading to norepinephrine release from presynaptic sympathetic neurons18 and, conversely, the benefit of ACE inhibitors on morbidity and mortality, 31 such as patients who have had myocardial infarction,25 or to other populations in which losartan is being studied, clinical outcomes based on any particular mechanism, results also show the difficulty of attempting to predict especially a comparative trial such as ELITE II. Our caution is needed in interpretation of the role of any differences in clinical outcomes in our study population. It is important enough for the two treatment strategies to conclude from ELITE II data whether any of these advantages of ACE-inhibitor-induced bradykinin treatment effect and baseline information on the efficacy of losartan compared with placebo for exercise duration has not been shown.36 We thank Deborah Bradstreet, Leila Ikeda, Blythe Koslowski, and Marcie Velvis for assisting in directing the study. This study was funded by Merck Research Laboratories.

The results from ELITE II should not be extrapolated to other populations in which losartan is being studied, such as patients who have had myocardial infarction,31 or to other angiotensin II antagonists, some of which are currently being assessed in patients with chronic heart failure.26,27 No current continuing large-scale heart-failure trial directly compares an angiotensin II antagonist with an ACE inhibitor or any other angiotensin II antagonists, and, therefore, interpretation across studies may be difficult.28 ELITE II was designed as a superiority trial. The trial was not designed to address equivalence between the two treatments, and, since it was not appropriate to include heart failure or angioconstriction, our findings provide no direct information on the efficacy of losartan compared with placebo on a background of diuretics and digoxin in heart failure.

In view of these results and extensive data from previous placebo-controlled trials such as CONSENSUS20 and SOLVD30 showing a significant benefit of ACE inhibitors on morbidity and mortality,31 we believe that clinicians should prescribe an ACE inhibitor for the initial treatment of patients with heart failure and systolic left-ventricular dysfunction. Losartan has been studied extensively in patients with heart failure. In controlled clinical trials involving about 5000 patients, of whom 2800 received losartan, acute and sustained haemodynamic benefits with chronic dosing have been seen,23,24 as well as effects similar to enalapril on exercise duration.11,12 A significant benefit compared with placebo for exercise duration has not been shown.14 Our ELITE II findings, together with previous experience in heart failure and the known pharmacology of losartan, make it probable that losartan resembles an ACE inhibitor in heart failure. It still remains to be established, however, whether angiotensin II antagonists are a fully effective substitute for ACE inhibitors in heart failure.29 Based on extensive randomised, placebo-controlled, observations, ACE inhibitors should remain the treatment of choice in heart failure. In patients in whom ACE inhibitors are not tolerated, an angiotensin II antagonist might be a useful alternative agent to block the renin-angiotensin-aldosterone system.36

ELITE II committees

Steering Committee—B Pitt (co-chairperson), P Poole-Wilson (co-chairperson), A J Camm, K Dickstein, M Konstam, F Martinez, J Neaton, G Riegger.

Data and Safety Monitoring Committee—C Furberg (chairperson), D DeMets, D Julian, H Just, J Wei.

Clinical Endpoint Classification Committee—L Frame (chairperson), J Burke, H Levine, E Loh, R Peters, M Rich.


Details of participating investigators and study centres are available on The Lancet web site at www.thelancet.com

Contributors

Bertram Pitt, Philip Poole-Wilson, and Robert Segal designed the study and were the primary investigators; other Steering Committee members (Marvin Konstam, Felipe Martinez, John Camm, Günter Riegger, James Neaton, George Klinger, Divakar Sharma, and Balasamy Thyagarajan) contributed to the study design, conduct of the study, and writing of the paper. Statistical analyses were done by Divakar Sharma, Balasamy Thyagarajan, and James Neaton. The study was directed by Robert Segal with the assistance of George Klinger.

Acknowledgments

We thank Deborah Bradstreet, Leila Ikeda, Blythe Koslowski, and Marcie Velvis for assisting in directing the study. This study was funded by Merck Research Laboratories.

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