Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial

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Summary

Background ACE inhibitors attenuate the detrimental effects of angiotensin II, and improve survival and reduce morbidity in patients with acute myocardial infarction and evidence of heart failure or left-ventricular dysfunction. Selective antagonism of the angiotensin type 1 receptor represents an alternative approach to inhibition of the renin-angiotensin system. We did a multicentre, randomised trial to test the hypothesis that the angiotensin II antagonist losartan would be superior or non-inferior to the ACE inhibitor captopril in decreasing all-cause mortality in high-risk patients after acute myocardial infarction.

Methods 5477 patients 50 years of age or older (mean age 67·4 years [SD 9·8]), with confirmed acute myocardial infarction and heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction, were recruited from 329 centres in seven European countries. Patients were randomly assigned and titrated to a target dose of losartan (50 mg once daily) or captopril (50 mg three times daily) as tolerated. The primary endpoint was all-cause mortality. Analysis was by intention to treat.

Findings There were 946 deaths during a mean follow-up of 2·7 (0·9–9) years: 499 (18%) in the losartan group and 447 (16%) in the captopril group (relative risk 1·13 [95% CI 0·99–1·28], p=0·07). The results for the secondary and tertiary endpoints were as follows: sudden cardiac death or resuscitated cardiac arrest 239 (9%) versus 203 (7%), 1·19 (0·98–1·43), p=0·07; and fatal or non-fatal reinfarction 384 (14%) versus 379 (14%), 1·03 (0·89–1·18), p=0·72. The all-cause hospital admission rates were 1806 (66%) versus 1774 (65%), 1·03 (0·97–1·10), p=0·37. Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (458 [17%] vs 624 [23%], 0·70 [0·62–0·79], p=0·0001).

Interpretation Since we saw a non-significant difference in total mortality in favour of captopril, ACE inhibitors should remain first-choice treatment in patients after complicated acute myocardial infarction. Losartan cannot be generally recommended in this population. However, it was better tolerated than captopril, and was associated with significantly fewer discontinuations. Although the role of losartan in patients intolerant of ACE inhibition is not clearly defined, it can be considered in such patients.


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Introduction

Patients with acute myocardial infarction and substantial myocardial injury frequently show clinical evidence of heart failure or left-ventricular dysfunction. Such patients have a high risk of morbidity and mortality. Angiotensin-converting-enzyme (ACE) inhibitors reduce morbidity and improve survival in chronic heart failure and after acute myocardial infarction, especially in selected, high-risk patients.1 Treatment attenuates infarct expansion,2 reduces reinfarction rate,3 reduces the incidence of subsequent heart failure,4 and is regarded as the treatment of choice in such patients.5 Blockade of the production of angiotensin II is incomplete during ACE inhibition:6 some conversion of angiotensin I continues, especially after low-dose and long-term treatment,7 and myocardial production of angiotensin II persists.8 As well as being caused by incomplete ACE inhibition, this continued generation of angiotensin II also results from non-ACE-dependent pathways.9 Angiotensin II production can be almost completely maintained in the myocardium despite effective suppression of circulating angiotensin II by ACE inhibition.10 An increased concentration of plasma angiotensin II despite ACE inhibitor treatment is associated with increased mortality.9 Antagonism of the effects of angiotensin II at the receptor level would therefore seem sensible, as would assessment of whether a selective angiotensin II antagonist could provide equal or better protection than an ACE inhibitor.

OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) was an investigator-initiated, multinational, double-blind, randomised, parallel-group study designed to compare the effects of the receptor antagonist losartan with those of the ACE inhibitor captopril on mortality and morbidity in patients with acute myocardial infarction and evidence of heart failure or left-ventricular dysfunction. Losartan is a highly specific, non-peptide antagonist of the type-1 angiotensin II receptor.11 Captopril was chosen as the ACE inhibitor because it has an established dose and efficacy in patients after complicated acute myocardial infarction compared with placebo.12

Patients and methods

Patients

Patients of either sex with documented acute myocardial infarction and who were at least 50 years of age were eligible for screening. A description of the recruitment details, the total cohort at baseline, a comparison between countries, and the results of the screening process have been published.12 Baseline acute myocardial infarction was defined as fulfilling at least two of the following criteria: a history of typical chest pain for longer than 20 min, ST elevation on electrocardiograph, or an increase in cardiac markers to above the decision level. We included patients with an acute myocardial infarction and signs or symptoms of heart failure during the acute
phase as suggested by one or more of the following: treatment with diuretic or intravenous vasodilator therapy for heart failure, pulmonary rales, third heart sound, persistent sinus tachycardia (≥100 bpm) or radiographic evidence of pulmonary congestion. Patients with an acute myocardial infarction and an ejection fraction of less than 35% or a left-ventricular end-diastolic dimension of greater than 65 mm (optional) and/or a new Q-wave anterior-wall acute myocardial infarction, or any reinfarction with previous pathological Q-waves in the anterior wall were also eligible. Patients were enrolled within 10 days of onset of symptoms.

Important exclusion criteria were: supine systolic arterial blood pressure of less than 100 mm Hg at the time of randomisation, current receipt of an ACE inhibitor or angiotensin II antagonist, unstable angina, haemodynamically significant stenotic valvular heart disease, haemodynamically significant dysrhythmia, and planned coronary revascularisation. The most commonly logged reasons for exclusion of otherwise eligible patients were: previous use of an ACE inhibitor or angiotensin II antagonist (43%), unwillingness or inability to give consent (15%), and participation in another research trial (10%).

The first patient was enrolled on Feb 25, 1998, and during the next 18 months, 5477 patients were enrolled at 329 sites. The trial was stopped on Feb 10, 2002, on the basis of projected accrual of the target of 937 deaths.

Hypotheses
A detailed description of the design and organisation of the trial has been published. The primary hypothesis was that treatment with losartan would be superior or non-inferior to captopril at decreasing the risk of all-cause mortality in high-risk patients after acute myocardial infarction. The secondary hypothesis was that the patients treated with losartan would have a lower incidence of the combination of sudden cardiac death or resuscitated cardiac arrest than those on captopril; and the tertiary hypothesis was that such patients would have a lower incidence of fatal or non-fatal reinfarction. Other prespecified objectives were to compare the effects of losartan with those of captopril on the following in patients with acute myocardial infarction: cardiovascular death, death from progressive heart failure, all-cause mortality and fatal or non-fatal reinfarction, fatal or non-fatal stroke, heart failure requiring hospital admission, any hospital admission, coronary revascularisation procedures, and New York Heart Association (NYHA) functional class. The causes of hospital admission were determined by the investigator and were not independently adjudicated. Safety and tolerability were assessed by the incidence of discontinuations due to adverse events and adverse events selected before the start of the trial.

The clinical endpoints adjudicated by the endpoint committee are listed in the panel. Other clinical measures included biochemical tests done at a core laboratory, and health-related quality-of-life assessment.

Study design and organisation
Patients were randomly assigned treatment with losartan (12.5 mg daily) or captopril (12.5 mg three times daily) and titrated to a target dose of losartan (50 mg daily) or captopril (50 mg three times daily), as tolerated. The initial dose of captopril was 6.25 mg. Allocation numbers were associated with treatment groups by use of a...
computer-generated allocation schedule; we classed patients as assigned to a group when they had received an allocation number. Block randomisation was used at each centre. Because the study drugs were different in appearance, all patients received two sets of tablets, one active and one placebo, to ensure adequate masking.

The trial protocol was approved by the local ethics committees and done in accordance with the Declaration of Helsinki. The study was carried out under the scientific monitoring board. An independent data and safety monitoring board monitored the interim results. A masked endpoint classification committee classified causes of death and adjudicated selected major morbidity events. Fatal events were reported separately and directly to the data and safety monitoring board.

**Statistical analysis**

The study was designed to continue until at least 937 patients reached the primary endpoint of all-cause mortality, which would allow detection of a relative difference between treatment groups of at least 20% with 95% power. The target sample size of 5004 patients was based on projection of a 17% annual primary endpoint event rate in the captopril group and a 13.6% event rate in the losartan group; the actual event rate was lower than projected, necessitating an extended duration of follow-up.

The trial was analysed by intention to treat; clinical endpoints were captured for all randomised patients until death or end of study. All deaths were adjudicated as to cause and were included in the analysis of the primary endpoint; only adjudicated endpoints were used in the analyses of refinements and strokes. Safety analyses included all randomised patients from the time of randomisation throughout the trial, or permanent discontinuation of study medication, whichever came first.

A Cox’s regression model assessed the difference between treatment groups with respect to clinical events, with country of randomisation as covariates. Treatment effects were measured by relative risks and their 95% CIs on the basis of Cox’s regression models. The risk reduction for losartan versus captopril is calculated as $100\% \times (1 - \text{relative risk})$. Event rates over time are presented as Kaplan-Meier curves: the numbers below the curve represent the number of event-free patients remaining in follow-up at the corresponding time-point. After completion of the trial, the primary efficacy data were made available to and confirmed by the steering committee statistician. Differences between groups in the frequency of adverse experiences were analysed with Fisher’s exact test.

The non-inferiority hypothesis was addressed by comparison of the upper one-sided 95% boundary for the relative risk for losartan versus captopril to the prespecified constant of 1.10. This boundary was chosen on the basis of the findings of previous studies that consistently showed the benefit of ACE inhibitors relative to placebo in similar patients to be about 20%, with a lower confidence boundary of greater than 10%. The results of SAVE,14 AIRE,15 and TRACE,16 and the anterior acute myocardial infarction subsets of SMILE,17 GISSI III,18 CONSENSUS II,19 and ISIS IV20 were combined in deciding a confidence boundary. For example, if the observed hazard ratio were 0.95 (corresponding to an estimated 5% risk reduction) with an upper confidence bound of 1.05 (corresponding to a 5% risk increase), then losartan would be declared non-inferior to captopril.

The independent data safety monitoring board used two-sided, symmetric O’Brien-Fleming stopping boundaries as a guideline for any recommendation for early termination due to superiority of one treatment over the other—ie, the same evidence was required to stop the trial prematurely for harm as for benefit. To adjust for sequential
monitoring, the final analysis of the superiority hypothesis for the primary efficacy variable was tested at a two-sided 4.3% significance level. All other tests were done at two-sided 5% significance levels.

Role of the funding source
The sponsor provided data management assistance and two non-voting members of the steering committee. The scientific conduct of the study and manuscript preparation were independent of the sponsor.

Results
5477 patients were randomised and all were included in the final analyses (figure 1). 946 deaths (all-cause mortality) were reported during the 14 866 patient-years of follow-up. Only one patient was lost to follow-up. Table 1 provides a comparison of baseline characteristics for the entire cohort and according to treatment group. The groups were closely matched and no important differences in the specified demographics were detected. Table 2 provides a comparison of major inclusion criteria according to treatment group. 5271 patients (96%) were randomised more than 24 h after the index acute myocardial infarction (median 3 days).

Losartan was administered once daily and captopril three times daily. Figure 2 shows the distribution of dose levels between treatment groups over time, including patients off-drug. At the end of the trial, the number of patients still on study medication and on the target dose had risen to 1895 (83%) for losartan and 1699 (78%) for captopril at 1 month had reached the target dose of study therapy. The relative risk was above the prespecified boundary of 1.25 for the non-inferiority criterion. A supportive analysis (1.0 in the intention-to-treat analysis, p=0.07). The upper one-sided 95% confidence boundary (1.25) for the relative risk of death from any cause was above the prespecified boundary of 1.10 in the intention-to-treat analysis, showing that losartan did not satisfy the non-inferiority criterion. A supportive on-treatment analysis censored patients 28 days after permanent discontinuation of study therapy. The relative risk determined from this on-treatment analysis (1.13 [0.97–1.31], p=0.07) was nearly identical to that of the intention-to-treat analysis.

Figure 2: Dose of study drug
Losartan was administered once daily and captopril three times daily.

Table 3: Crude rates and relative risks for prespecified endpoints

Table 3 presents the results for the prespecified endpoints. The average follow-up was 2.7 years (0.9) from randomisation until death or study end. Figure 4 displays a Kaplan-Meier plot for the primary endpoint of all-cause mortality. There was no significant difference between the losartan and captopril groups (499 deaths [18%] vs 447 deaths [16%], relative risk 1.13 [95% CI 0.99–1.28], p=0.07). The upper one-sided 95% confidence boundary (1.25) for the relative risk of death from any cause was above the prespecified boundary of 1.10 in the intention-to-treat analysis, showing that losartan did not satisfy the non-inferiority criterion. A supportive on-treatment analysis censored patients 28 days after permanent discontinuation of study therapy. The relative risk determined from this on-treatment analysis (1.13 [0.97–1.31], p=0.07) was nearly identical to that of the intention-to-treat analysis.
There were significant but inconsistent differences among countries with respect to overall mortality and to the treatment effects with losartan and captopril. These findings require further investigation. Table 4 presents the causes of death. Figure 5 shows relative risks and 95% CIs for the primary endpoint according to selected demographics and background treatments. Subgroup analysis stratified by β-blocker use before randomisation revealed no significant between-group differences with respect to survival (without β-blockers: losartan 144 [25·1%] vs captopril 135 [22·6%], relative risk 1·11 [95% CI 0·88–1·41], p=0·38; with β-blockers: losartan 355 [16·4%] vs captopril 312 [14·6%], 1·14 [0·98–1·32], p=0·098). The test for interaction with β-blocker treatment was not significant (p=0·88). Similarly, we did not detect any significant interaction between treatment and β-blocker use at 1 month.

Figure 6 provides Kaplan-Meier plots for other major endpoints in the trial. The results for the secondary and tertiary endpoints were as follows. Sudden death or resuscitated cardiac arrest: losartan 239 (9%) versus captopril 203 (7%), relative risk 1·19 (95% CI 0·99–1·43), p=0·07; fatal/non-fatal reinfarction: losartan 384 (14%) versus captopril 379 (14%), 1·03 (0·89–1·18), p=0·72. The relative risks for these secondary and tertiary endpoints were consistent with those of the primary endpoint (table 3). There were no significant differences in the treatment effect for any of the other unspecified endpoints apart from cardiovascular death. There were fewer cardiovascular deaths in the captopril group: losartan 420 (15%) versus captopril 363 (13%), 1·17 (1·01–1·34), p=0·032. Among the 5301 survivors of the initial hospital admission, the mean number of days spent in hospital after the admission for the index acute myocardial infarction was 13·6 (23·9) days for losartan and 13·1 (21·6) days for captopril.

NYHA functional class was assessed at each follow-up visit. Modest improvement was seen in both groups over time, but the distribution between treatment groups was essentially identical throughout the trial and no significant differences were detected.

Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication for any reason (458 [17%] vs 624 [23%], 0·70 [0·62–0·79], p<0·0001). Overall, in 202 losartan patients (7%) and 387 captopril patients (14%), discontinuation was judged to be due to adverse experience (0·50 [0·42–0·59], p<0·0001). Table 5 contains the rates of and
reasons for discontinuation and the occurrence of prespecified adverse experiences. Figure 7 shows discontinuation rates due to adverse events, suspected drug-related adverse events, and serious adverse events.

Initiation and titration of treatment were well tolerated. Two episodes of hypotension (both on captopril) were classified as serious adverse events by the investigator, but they did not require discontinuation of study medication. Blood pressure was measured for 6 h after the first dose and routinely during follow-up. Captopril (6.25 mg) was associated with significantly lower pressures than losartan (12.5 mg) for the first 2 h. The mean systolic/diastolic values at 1 h were 119/69 mm Hg for losartan versus 114/66 mm Hg for captopril (p<0.0001). Otherwise, recorded blood pressures were similar. Table 6 provides the results for selected laboratory values at baseline and study end. A significant between-group difference was detected for serum uric acid and serum potassium.

Discussion

The OPTIMAAL trial compared the treatment effect of losartan 50 mg once daily with captopril 50 mg three times daily on mortality and morbidity in patients with evidence of heart failure or left-ventricular dysfunction after acute myocardial infarction. This trial did not show superiority or non-inferiority of losartan relative to captopril. A non-significant difference in total mortality was seen in favour of captopril. The incidence of reinfarction, revascularisation, and all-cause hospital admission were essentially identical between the two groups. Losartan was significantly better tolerated, with fewer discontinuations due to adverse experience.

The findings with losartan must be interpreted in light of the fact that an efficacious, active control at an adequate dose (captopril 150 mg) was the comparator. There was no placebo group. The non-inferiority hypothesis was designed such that a finding of non-inferiority would imply that there is great confidence that losartan is superior to placebo. The question of losartan’s effect relative to placebo should therefore be reconsidered. The results fail to show conclusively that losartan is better than placebo (as it would have if the non-inferiority criteria had been met), but they did not show that losartan is no better than placebo.

We did a prospective meta-analysis of placebo-controlled trials of ACE inhibitors in patients with acute myocardial infarction to define the non-inferiority margin. Data from trials that enrolled patients who had heart failure or left-ventricular dysfunction, and data on patients with anterior acute myocardial infarction were pooled.1,14 The former suggested a reduction in total mortality of about 26%, whereas the latter suggested a reduction of about 14%. Despite the fact that 81% of the OPTIMAAL population had heart failure in the acute phase, we conservatively estimated the effect of captopril relative to placebo in OPTIMAAL to be 19.5%, or a relative risk of 0.805. To estimate the effect of losartan relative to placebo, this relative risk is multiplied by the OPTIMAAL relative risk to obtain 0.805×1.126=0.906—ie, we estimate that losartan reduced total mortality relative to placebo by 9.4%. However, the CI around this estimate cannot rule out lack of effect relative to placebo.

Clinical studies with losartan have shown excellent tolerability, with a side-effect profile similar to that of placebo.21 In two invasive studies in patients with heart failure or left-ventricular dysfunction, data on patients with anterior acute myocardial infarction were included.
symptomatic heart failure, losartan produced modest but beneficial haemodynamic effects acutely\(^{22}\) and after chronic treatment.\(^{23}\) A trial to assess the short-term efficacy of losartan versus captopril on renal function in elderly patients (\(n=722\)) with symptomatic heart failure.\(^{26}\) Unexpectedly, losartan was associated with improved survival, which seemed to be almost entirely related to a reduction in the incidence of sudden death in the losartan group. This finding led to the incorporation of sudden death as a secondary hypothesis in the OPTIMAAL trial protocol. The ELITE II trial (Losartan Heart Failure Failure Study) included a symptomatic population (\(n=3152\)) randomly assigned losartan or captopril.\(^{27}\) No significant differences between treatments with respect to mortality (relative risk 1·13), sudden death or resuscitated cardiac arrest, or hospital admission were shown, although the overall results favoured captopril. The results of OPTIMAAL, taken in the context of ELITE II, reinforce the conclusion that captopril treatment, if tolerated, should remain the preferred treatment for patients with heart failure.

Treatment with ACE inhibitors after acute myocardial infarction has improved morbidity and mortality in patients who have had an acute myocardial infarction with evidence of left-ventricular systolic dysfunction with and without clinical heart failure.\(^{19,31}\) Treatment has been shown to reduce the incidence of the development of heart failure,\(^{1,4}\) attenuate infarct expansion,\(^{4}\) and reduce infarction rate.\(^{1}\) Trials with short-term ACE inhibitor treatment in unselected patients with acute myocardial infarction showed a significant, but relatively small, outcome benefit compared with that seen in selected high-risk patients on long-term treatment.\(^{1,4,19,30}\) The extensive documentation for ACE inhibitors precludes placebo treatment in clinical trials involving high-risk patients after acute myocardial infarction.\(^{1}\)

The between-treatment mortality curves seem to separate early during the period with the highest mortality rate and remain parallel thereafter. To explore this observation, a cutoff of 210 days was chosen, since this value identified the point at which the curves were furthest apart. During the first 210 days, the relative risk between groups was 1·24 (1·04–1·50), and after that time the relative risk was 1·02 (0·86–1·22). These data suggest that the trial assessed a population in two phases of the disease process, and this view is supported by the fact that non-cardiovascular death as a proportion of total death increased from 6% in the first 210 days to 28% thereafter. The observation that the greatest treatment effect coincides with the increased early risk of death supports the initiation of therapy shortly after infarction in high-risk patients.

The results of any trial apply only to the cohort studied. The OPTIMAAL trial excluded patients currently treated with an ACE inhibitor or angiotensin II antagonist before the index acute myocardial infarction.\(^{32}\) Indeed, 33% of the otherwise eligible patients were excluded for this reason and therefore few patients with symptomatic heart failure before the index acute myocardial infarction participated.

Comparison with a placebo control group in this population is not feasible. Captopril was chosen as the ACE inhibitor because its efficacy and dose are well established.\(^{1}\) Captopril is indicated in most countries for the treatment of patients with chronic heart failure and patients who have had acute myocardial infarction, is licensed, and is used widely. Notably, the ongoing VALIANT trial with high dose valsartan in a similar population of patients with complicated acute myocardial infarction is also using captopril 50 mg three times daily as the comparator.\(^{28}\) This trial is also exploring the effects of the potent combination of an ACE inhibitor and an angiotensin II antagonist by the addition of a third group combining captopril and valsartan.

There was no significant interaction between treatment (losartan \(v\) captopril) and \(\beta\)-blocker use with respect to survival, on the basis of \(\beta\)-blocker use before randomisation or at 1 month. However, as expected, patients tolerant of \(\beta\)-blocker therapy had significantly better survival than untreated patients. The data from this trial do not provide information relating to potential interactions among \(\beta\)-blockers, ACE inhibitors, and angiotensin II antagonists in heart failure. A minority of the patients were treated with a \(\beta\)-blocker before hospital admission, and the majority were on a \(\beta\)-blocker at 1 month. We did not test the combination of all three agents, and substantial selection bias occurs in patients after acute myocardial infarction. To draw mechanistic conclusions from these observations would be inappropriate.

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\(^*\)\(p<0·01\) for difference between groups.

Table 6: Laboratory values (baseline and last recorded)
Perhaps most important is the question of the optimum dose of losartan, and this question might even be unresolved still for ACE inhibitors.7 Most studies with losartan in heart failure used 50 mg as the target dose. However, doses of losartan ranging from 5 to 150 mg in patients with heart failure resulted in a step-wise increase in plasma renin activity and angiotensin II concentrations, indicating more potent negative feedback at the highest doses.22

The substantial event rate during the early post-myocardial-infarction phase in the OPTIMAAL trial emphasises the potential importance of rapid titration and adequate dosage. The relatively slow dose titration of losartan might have resulted in a suboptimal effect, especially when compared with an agent administered three times daily. This reduced effect would be consistent with the early separation of the mortality curves. The increase in serum creatinine concentration from baseline to month was larger for captopril than for losartan (7 vs 5 mmol/L; p<0.001). Similarly, the observations that captopril (0.25 mg) lowered first-dose blood pressure significantly more than losartan (12.5 mg) for the first 2 h, and that losartan resulted in fewer adverse experiences of hypotension or syncope following the initial dose23 (13.2 vs 26.3%, p=0.002) suggest a difference in the pharmacodynamic effect of the two agents at the dosages used.

The maximum dose of losartan in this trial was 50 mg once daily. In two recently completed positive trials with losartan, RENAAL in type 2 diabetes with nephropathy24 and LIFE in hypertension with left-ventricular hypertrophy,25 patients were titrated to a target blood pressure up to 100 mmHg and the results support the use of a higher dose in those populations. An ongoing mortality and morbidity trial, HEAL (Heart Failure Endpoint Evaluation with the Angiotensin II Antagonist Losartan), is comparing two doses of losartan, 50 mg and 150 mg in a heart failure population, and should shed additional light on the issue of optimum dosage.

Convincing documentation exists for the use of ACE inhibitors in selected patients after acute myocardial infarction. Since this trial showed neither superiority nor non-inferiority of losartan relative to captopril, ACE inhibition should remain the first choice therapy in patients after complicated acute myocardial infarction. Losartan cannot be generally recommended in this setting. Although the role of losartan in patients intolerant of ACE inhibitors is not clearly defined, it can be considered in such patients.
Conflict of interest statement
Kristen Kristianson and Jonathan Fox are Merck employees and non-voting members of the Steering Committee.

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