Left ventricular dilatation and neurohumoral activation as arrhythmogenic factors in myocardial infarction
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Acute intervention with captopril during thrombolysis in patients with first anterior myocardial infarction

Results from the Captopril And Thrombolysis Study (CATS)

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Abstract

Background. Left ventricular dysfunction and prognosis after myocardial infarction can be improved by angiotensin-converting enzyme inhibition started after the ischemic phase. Experimental evidence suggests that intervention during thrombolysis may lead to even further benefit.

Methods. In a randomized, double-blind placebo controlled trial, 298 patients with a first anterior myocardial infarction, eligible for thrombolytic therapy were treated with 6.25 mg captopril or placebo, started immediately upon streptokinase infusion and titrated to 25 mg TID. Effects of captopril by an intention to treat analysis on left ventricular volumes, ventricular arrhythmias, neurohumoral activation and enzymatic infarct size were measured.

Results. During dose titration, mean blood pressure and heart rate were not different in both groups. However, first dose hypotension was reported in 18 patients on placebo and 31 patients on captopril (p < 0.05). At discharge 80% of patients were on study medication. Left ventricular volumes were significantly increased in both groups at three months. Left ventricular volumes in the captopril group tended to be lower, but differences were not statistically significant. Incidence of accelerated idioventricular rhythm and nonsustained ventricular tachycardia in captopril patients was lower (p < 0.05), paralleled by transiently lower norepinephrine levels (p < 0.05) upon thrombolysis. Enzymatic infarct size showed to be smaller in captopril patients, especially in larger infarcts (p < 0.05). A 34% (95% confidence interval; 0-56%) lower incidence of heart failure during three months of follow up was reported in the captopril group.

Conclusion. Captopril is well tolerated, although first dose hypotension was more common in patients on captopril. In agreement with experimental studies captopril reduces repetitive ventricular arrhythmias and catecholamine levels in the acute thrombolytic phase of myocardial infarction. Although left ventricular volumes were not significantly smaller in captopril patients, in the chronic phase, these patients showed a reduced incidence of heart failure.

Introduction

Over the last decade the use of thrombolytic therapy has drastically changed the approach to acute myocardial infarction. With intravenous thrombolytic drugs, recanalization is achieved in 68 - 76% of the patients. Early restoration of flow to the jeopardized myocardium greatly contributes to maintenance of function and improvement of survival irrespective of the type of thrombolytic agent used. Although not proven to be of clinical importance, experimental observations indicate that early and acute re-establishment of oxygen supply to a previously
ischemic area, may result in a paradoxical increase of myocardial injury known as ‘reperfusion injury’. There is experimental evidence that the use of the angiotensin-converting enzyme (ACE) inhibitor captopril before or during the time of reperfusion after ischemia, can prevent or limit the occurrence of reperfusion arrhythmias and myocardial injury both in vitro and in vivo. Use of ACE inhibitors in patients with a reduced left ventricular ejection fraction following the acute phase of myocardial infarction can improve ventricular function by reducing diastolic and systolic ventricular expansion. Recently, it was demonstrated that long term use of captopril in patients with asymptomatic left ventricular dysfunction after myocardial infarction could reduce mortality, the incidence of heart failure and the rate of reinfarction. When captopril was given within 24 hours after the onset of symptoms a favorable effect on left ventricular remodeling was demonstrated. However, treatment with intravenous enalapril within 24 hours after the onset of symptoms of myocardial infarction did not reveal an effect on six months survival. A modest but significant effect on mortality of captopril and lisinopril respectively was observed when treatment is started within the first 24 hours after myocardial infarction. The reduction of mortality became even more apparent in patients with clinical evidence of transient or ongoing heart failure when oral ramipril was administered between the second and ninth day after myocardial infarction.

On the basis of the aforementioned experimental evidence, we hypothesized that immediate concomitant administration of captopril would enhance the effects of thrombolysis in the acute phase of myocardial infarction and that its continued use would result in preservation of left ventricular function in the chronic phase. To test this hypothesis we designed the Captopril And Thrombolysis Study (CATS). The primary objectives included attenuation of left ventricular volume expansion, a reduction of ventricular arrhythmias and a decrease in norepinephrine release following thrombolysis. An important aim was the assessment of hemodynamic safety and tolerance of oral captopril administered immediately following thrombolytic therapy with streptokinase in patients with a first anterior myocardial infarction.

Methods

Organization. CATS was a double-blind, randomized, placebo-controlled study in patients with a first anterior wall myocardial infarction treated with thrombolytic therapy with intravenous streptokinase. A total of 298 patients were enrolled in 12 hospitals in the Netherlands and assigned to either placebo or captopril. The coordination center was the St Antonius Hospital, Nieuwegein,
The Netherlands. The study was controlled and supervised by two study-directors with support of a steering committee including the principal investigators from all participating hospitals and representatives from the sponsor. All measurements of the primary objectives and enzymatic infarct size were performed in central core laboratories and data were reviewed and stored in the database in the coordination center. Data on safety including serious adverse clinical events were reviewed by the study directors and filed in the database of the sponsor. An independent Data Quality Committee reviewed the data on clinical endpoints. The progress and conduct of the study with emphasis on the safety of patients, was supervised by an international Policy Advisory Board. At regular intervals the Board was provided by the sponsor with blinded data on serious adverse clinical events represented per treatment group. If there would be a strong indication that adverse clinical events would occur more frequently in one of the treatment groups, the Board had access to the randomization code and could decide to terminate the study prematurely. Data analysis in the coordination center and by the sponsor at the end of the study was supervised by a member of the Policy Advisory Board (J.G.P.T.). The study was approved by the Institutional Review Board of all participating hospitals.

Objectives of the study. Primary objectives were the assessment of the effect of captopril relative to placebo:

- on the preservation of left ventricular volume as measured by serial 2D-echocardiography at three months after myocardial infarction;
- on the incidence of episodes of nonsustained ventricular tachycardia (VT) and accelerated idioventricular rhythm (AIVR) assessed by serial ambulatory ECG monitoring during the first 12 hours after admission;
- on neurohumoral activation as determined by serial assay of norepinephrine levels and plasma renin activity in the acute phase.

Secondary objectives were the assessment of the effect of captopril, relative to placebo:

- on infarct size, calculated from α-hydroxybutyrate dehydrogenase (α-HBDH) determinations;
- on radionuclide left ventricular ejection fraction, obtained at rest three months after myocardial infarction;
- on clinical event rate during follow up, including mortality, reinfarction, development of heart failure, unstable angina, need for percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass grafting (CABG).
Eligibility of patients. Patients were considered eligible for enrollment, if a first anterior wall myocardial infarction within 6 hours after the onset of symptoms was present, and if they were treated with thrombolytic therapy (1.5 million international units intravenous streptokinase administered in 30 minutes). Informed consent was obtained by witnessed oral consent, later confirmed by written consent following the acute phase of myocardial infarction. Diagnosis was based on the presence of characteristic symptoms of acute anterior myocardial infarction, with at least 1 mm ST-segment elevation in lead I and aVL and/or 2 mm ST elevation in two precordial leads of the 12-lead electrocardiogram compatible with infarction of the anterior wall and adjacent areas, including septal and lateral portions of the left ventricle. Patients were excluded if there was known intolerance to ACE inhibitors, renal insufficiency, systolic blood pressure over 200 mmHg or below 100 mmHg and diastolic blood pressure over 120 mmHg or below 55 mmHg. Additional exclusion criteria were severe valvular heart disease, arrhythmias requiring anti-arrhythmic therapy, serious systemic or metabolic disease except diabetes mellitus, AV conduction disturbances, (PR interval $\geq$ 0.24 s), left bundle branch block, a history of transient ischemic attacks and a cerebrovascular accident within six weeks.

Treatment protocol. Immediately after admission to the coronary care unit, 1,500,000 international units of streptokinase was administered in 30 minutes, by continuous intravenous infusion. Nitrates were withheld during this phase and were only allowed when specifically indicated, such as for elevated systolic blood pressure or severe angina pectoris. Double-blind medication was initiated immediately upon completion of the streptokinase infusion, provided the systolic blood pressure was stable and above or equal to 100 mmHg. If systolic blood pressure was below 100 mmHg, the initiation of double-blind medication could be postponed for a maximum of 1 hour following start of the streptokinase infusion. Initially, an oral dose of 6.25 mg was given, repeated after 4 and 8 hours and at 16 and 24 hours doses of 12.5 mg and 25 mg respectively were administered. Dose titration was continued provided the systolic blood pressure, measured immediately prior to the next scheduled dose of study medication was above or equal to 95 mmHg. If the systolic blood pressure was below 95 mmHg, the study medication was withheld until the next dosing time. The target maintenance dose of the double-blind study medication was 25 mg TID, administered from day 2 until three months after myocardial infarction. During the three months of double-blind therapy, concomitant therapy with calcium antagonists, beta-blockers or nitrates was instituted only for specific indications, e.g. angina and hypertension. However the protocol did not prohibit the use of beta-blockers for secondary prevention. Also the use of aspirin was at the dis-
cretion of the local investigator. The recommended dose of aspirin was 80 mg to minimize a possible interaction with captopril. Blood pressure and heart rate were monitored during the initial phase with an automatic cuff blood pressure measurement device (Dynamap, Criticon, Germany) with digital print-out every three minutes during the first hour.

Echocardiography. For echocardiographic measurement of left ventricular end-diastolic and end-systolic volumes, apical four- and two-chamber views were obtained and recordings made with respiration held at end-expiration or partial inspiration. Patient angulations, transducer position and respiratory phase were recorded. End-diastolic and end-systolic frames were outlined from both apical views using the Dataview Microsonics cardiac analysis system (Nova Microsonics). Left ventricular volumes were calculated by the biplane (modified) Simpson’s rule method using both views. The mean of two measurements on consecutive cycles was taken for each examination. Left ventricular end-diastolic volume index and left ventricular end-systolic volume index, were derived from body surface area, which was estimated at each time-point. Initial echocardiographic determination of left ventricular volume was done when possible, within 12-24 hours after admission and at least 4 hours after the last dose of double blind study medication. All subsequent echocardiographic determinations obtained at day 3, prior to discharge and at three months were made not earlier than 8 hours post-dose of double blind study medication. To assure that return to the same echocardiographic view, a method of locating the transducer in reference to bony landmarks was applied. Lateral rotation and elevation of the upper body were noted and maintained at subsequent studies.

Long-term ambulatory ECG. The presence of ventricular arrhythmias was assessed by two-channel 24-hour ambulatory ECG, (Reynolds Medical Tracker recorder) at baseline for at least 12 hours, predischarge and after three months of double blind study medication. Analysis was performed using the Reynolds Medical Pathfinder 3. The number and duration of episodes of AIVR, pairs of ventricular premature beats and VT were determined by real time counting. Premature ventricular beats were disregarded in the analysis. AIVR was defined as a repetition of three or more monomorphic ventricular beats with a rate of less than 100 beats per minute. Pairs of ventricular premature beats were defined as a repetition of two ventricular beats with a maximum interval of 0.6 s. VT was defined as a repetition of three or more ventricular beats with a rate exceeding 100 beats per minute.

Neurohormones. Neuroendocrine determinations, including samples for determination of norepinephrine and plasma renin activity, were collected at the start of the study medication at 1 and 12 hours post-dose and twice daily thereafter from day 2 to 5. Epinephrine and norepinephrine were measured using a
sensitive HPLC assay with electrochemical detection. Plasma renin activity was measured by means of a radio-immuno assay (Dupont, Ria NEN kit No NEA-022, 026).

Enzymatic infarct size and radionuclide ejection fraction. Infarct size was estimated from the cumulative release of α-HBDH activity per liter of plasma within the first 72 hours, calculated from serial plasma α-HBDH determinations from blood samples taken twice daily during the first five days, as described by van der Laarse et al. Left ventricular ejection fraction was determined at rest by radionuclide scanning after three months of double-blind therapy. All determinations were made not earlier than 8 hours post-dose of study medication.

Clinical events. Clinical events including development or worsening of congestive heart failure, serious rhythm disturbances, angina, reinfarction, need for PTCA or CABG, cardiac morbidity and mortality were noted in the patient record forms and transcribed on adverse event forms in case of serious events.

The presence of congestive heart failure was based on clinical judgment of the principal investigators. Patients with congestive heart failure were subdivided in those without medication, those in whom digoxin and/or diuretics were started, those in whom open treatment with an ACE inhibitor was started, those in whom hospitalization was prolonged or who had to be rehospitalized. All patients on diuretics and/or digoxin, and those in whom open treatment with an ACE inhibitor was started were considered to have congestive heart failure.

Sample size consideration. Based on the anticipated variances in left ventricular volumes as measured by 2D-echocardiography, sample size was estimated at 280 patients. It was assumed that technically adequate echocardiographic measurements of left ventricular volume would be available in 70-75% of randomized patients. In addition, left ventricular volume measurements beyond the initial 24-hour recording, would not be present in approximately 8-10% of the patients, due to early mortality. Therefore, it was estimated that from about 65% of the projected 280 randomized patients (180 patients) left ventricular volumes would be available for evaluation. The effective sample size (N=180) was anticipated to be sufficient to detect a mean difference in left ventricular end-diastolic volume index between the treatment groups of 8 ml/m² at three months with a power exceeding 0.8. The standard deviation for left ventricular end-diastolic volume index was assumed to be 18 ml/m². A mean difference of 5 ml/m² in left ventricular end-systolic volume index at three months would be detectable with similar power and a standard deviation of 12 ml/m².
Statistics. If not otherwise indicated, continuous variables were compared using Student’s t-test and categorical variables using Chi-square test. Results were considered statistically significant if the p-values were less than or equal to 0.05, using the two-sided level of significance. Data on left ventricular volumes and enzymatic infarct size are represented by mean values with 95% confidence intervals. Left ventricular volume change and neurohumoral data over time were evaluated by analysis of variance for repeated measurements. The incidence of clinical endpoints is represented by relative risk estimates with corresponding 95% confidence intervals. According to intention-to-treat principle all outcome analyses were based on the treatment group to which the patients had been randomly assigned.

Table 7.1. Baseline characteristics and medication in the two treatment groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (N=149)</th>
<th>Captopril (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 9</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>Male (%)</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Clinical history (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ischemic heart disease</td>
<td>8.0</td>
<td>9.4</td>
</tr>
<tr>
<td>hypertension</td>
<td>16.1</td>
<td>27.5</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>9.4</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Figure 7.1. Mean (± SEM) systolic and diastolic blood pressure after repeated doses of captopril compared to placebo.
Results

During the enrollment period of the CATS study, 298 patients were included, with 149 patients allocated to each treatment group. The time from onset of symptoms to the time of streptokinase infusion was 166 ± 70 minutes in the placebo group and 163 ± 76 minutes in the captopril group. The time of the first dose of study medication from onset of symptoms was 213 ± 76 minutes and 212 ± 86 minutes respectively. A complete clinical follow-up over the three-month period was obtained in 282 patients (94.6%). Fifteen patients (5.0%) died and one patient was lost during follow up. Twenty-four hours after randomization, the target dose of 25 mg TID was reached in 95% of patients. At discharge, 80% of patients were still on study medication. At the end of the three-month follow-up period, 79% of patients were still on study medication (placebo 81% and captopril 77%). After the dose titration phase, the mean dose administered at 24 hours was 24.3 mg (placebo 24.2 mg and captopril 24.5 mg). Compliance of patients with study medication based on pill count was 79.9%. The clinical characteristics of the two groups were comparable at baseline (Table 7.1), although smoking and hypertension tended to be more frequent in the captopril group.

Safety: blood pressure and heart rate during titration phase

Heart rate remained unchanged from baseline in both groups during the titration phase. Mean systolic and diastolic blood pressure decreased significantly after the first dose in both groups. Mean systolic blood pressure decreased by 8.7 ± 2.3 mmHg in the placebo group and 13.3 ± 2.2 mmHg in the captopril group (both p < 0.05, Figure 7.1). No significant blood pressure changes were recorded after the second and third doses. There were no distinguishable differences in mean blood pressure between the two groups during dose titration. Acute hypotension after the first dose, defined as a drop in systolic blood pressure below 90 mmHg, measured by automatic cuff blood pressure equipment, was reported in 18 patients in the placebo group and in 31 patients in the captopril group (relative risk (RR) 1.3, 95% confidence interval (CI) 1.02 - 1.77). The total incidence of hypotension during the titration phase was 22 (14.8%) in the placebo and 33 (22.3%) in the captopril group (RR 1.3, 95% CI 0.96 - 1.66). The reported incidence of hypotension during the three-month follow-up was 18.1% in the placebo and 26.8% in the captopril group (RR 1.5, 95% CI 0.96-2.28).

Echocardiographic measurements
Biplane projections for appropriate measurement of left ventricular volumes were available in 66% of echocardiograms. Both left ventricular end-systolic and end-diastolic volume indexes at first measurement (i.e., within 24 hours after randomization) were at the upper range of normal (Figure 7.2). The placebo group showed a sustained increase in left ventricular end-diastolic volume of 6.2 ml/m$^2$ (95% CI 1.7 - 10.8) over the three-month period. In the captopril group there was an early but transient decrease in both left ventricular end-diastolic volume index and left ventricular end-systolic volume index. Overall, left ventricular end-diastolic volume for the captopril group increased by 5.4 ml/m$^2$ (95% CI 0.6 - 10.2) over the three-month period while both the left ventricular end-diastolic and end-systolic volume indexes for the captopril group tended to be lower than for the placebo group at all time intervals.
Figure 7.2. Left ventricular end-systolic index (LVESVI, panel A) and end-diastolic volume index (LVEDVI, panel B) of patients allocated to captopril or placebo during the first three months.
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This difference was most pronounced at day 3 for the left ventricular end-diastolic volume index, with a difference of 3.5 ml/m$^2$ (95% CI 0.0 - 7.0). For left ventricular end-systolic volume index, this difference was most pronounced prior to discharge, being 3.3 ml/m$^2$ (95% CI 1.1 - 5.5). The overall difference (repeated measurements analysis) between the captopril and placebo group was not statistically significant.

Ventricular arrhythmias

Of all Holter tape recordings 67% were adequate for analysis. The incidence of ventricular arrhythmias, in particular of AIVR and nonsustained VT, was highest at admission. All arrhythmias diminished prior to discharge but tended to become more frequent at three months. In the captopril group the number of patients with pairs of ventricular premature beats, AIVR and nonsustained VT were lower at all time intervals than in patients allocated to placebo (Table 7.2). During the acute thrombolytic phase nonsustained VT and AIVR in the captopril group were significantly less (by 22% and 25%, respectively, both p < 0.05) than in the placebo group (Table 7.2).

Neurohumoral activation

Plasma samples for neurohumoral measurements were available in 92% of the patients. Norepinephrine levels and plasma renin activity were both increased at randomization (Table 7.3). In contrast to the placebo group, norepinephrine in the captopril group was significantly lower 1 hour after the first dose

<table>
<thead>
<tr>
<th>AIVR</th>
<th>PAIRS</th>
<th>nsVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolysis 44.5 33.8* 59.9 52.1 40.9 31.7*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge 2.4 1.6 16.8 15.8 4.0 1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three months 4.1 3.4 22.1 18.5 3.3 2.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AIVR indicates accelerated idioventricular rhythm; C, captopril; PAIRS, pairs of ventricular premature beats; nsVT, nonsustained ventricular tachycardia; PL, placebo. Based on data from all patients with Holter monitoring, including those with failed registrations. Values compared to placebo * p < 0.05 (Fisher’s Exact test).
compared to baseline. However, after 12 hours no significant differences in norepinephrine levels between the two groups could be detected. During the first five days plasma renin activity showed an increase in the captopril group and remained within normal range in the placebo group (p < 0.05, Table 7.3). In the captopril group ACE activity was significantly lower compared to baseline from the first hour after start of the study.

Enzymatic infarct size and radionuclide ejection fraction

Table 7.3. Plasma renin activity, norepinephrine levels and ACE activity during the first five days after acute myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 hour</th>
<th>12 hours</th>
<th>5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (U/lh)</td>
<td>P</td>
<td>2.86 ± 0.25</td>
<td>1.87 ± 0.46</td>
<td>1.78 ± 0.56</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>3.01 ± 0.37</td>
<td>3.29 ± 0.14</td>
<td>2.04 ± 0.25</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>P</td>
<td>1173 ± 73</td>
<td>1080 ± 78</td>
<td>813 ± 51</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1081 ± 60</td>
<td>914 ± 46</td>
<td>812 ± 53</td>
</tr>
<tr>
<td>ACE activity (nmol/ml/min)</td>
<td>P</td>
<td>20.7 ± 1.5</td>
<td>20.1 ± 1.4</td>
<td>20.3 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>19.4 ± 1.2</td>
<td>17.3 ± 1.2</td>
<td>14.4 ± 1.3^§</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin converting enzyme; C, captopril; P, placebo; PRA, plasma renin activity.
Values are represented as mean ± SEM. Differences compared to baseline values: * p < 0.05, ^ p < 0.001, # p < 0.0001.

Table 7.4. Peak plasma enzyme activities of CK and α-HBDH and calculated cumulative release of α-HBDH in the two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Captopril</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CK (U/l)</td>
<td>1907 ± 1635</td>
<td>1618 ± 1360</td>
<td>289 (-61 - 639)</td>
</tr>
<tr>
<td>peak α-HBDH (U/l)</td>
<td>876 ± 720</td>
<td>699 ± 454</td>
<td>177 (36 - 318)^*</td>
</tr>
<tr>
<td>α-HBDH Q72 (U/l)</td>
<td>1390 ± 1109</td>
<td>1166 ± 886</td>
<td>224 (-22 - 470)</td>
</tr>
<tr>
<td>small infarcts 1)</td>
<td>587 ± 314</td>
<td>491 ± 278</td>
<td>96 (-7 - 199)</td>
</tr>
<tr>
<td>large infarcts 2)</td>
<td>2193 ± 1035</td>
<td>1873 ± 738</td>
<td>320 (6 - 634)^*</td>
</tr>
</tbody>
</table>

1) mean values of the lower two quartiles (50%) of infarcts; 2) mean values of the upper two quartiles (50%) of infarcts; α-HBDH indicates α-hydroxybutyrate dehydrogenase; Q72 cumulative α-HBDH release in the first 72 hours; CI, confidence interval; CK, creatine phosphokinase. Values are represented as means ± SD. * p < 0.05.
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Serum creatine kinase and α-HBDH activity could be determined in 86.9% of patients. Peak creatine kinase, peak α-HBDH and cumulative α-HBDH release over 72 hours (α-HBDH Q72) were lower in the captopril patients than in the placebo group (Table 7.4). This reduction in cardiac enzyme release indicates an attenuation of myocardial injury, i.e., infarct size. However, this was not reflected in a difference in nuclear left ventricular ejection fraction, measured at three months which amounted to 43.9 ± 1.4% in the placebo group and 44.7 ± 1.6% in the captopril group.

Clinical events

Incidence of clinical events are summarized in Table 7.5. Mortality rate was low with no significant difference between the two treatment groups. However, there was a 34% (95% CI 0 - 56) lower reported incidence of heart failure in the captopril group compared to the placebo group. The incidence of coronary re-vascularization procedures was equal in both groups. Reinfarction occurred in 14 patients, seven of which within 72 hours, with four cases PTCA related.

<table>
<thead>
<tr>
<th>Table 7.5. Clinical endpoints. Figures represent numbers of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>hospitalization</td>
</tr>
<tr>
<td>open label ACE inhibitor start diuretics/digitalis</td>
</tr>
<tr>
<td>PTCA</td>
</tr>
<tr>
<td>CABG</td>
</tr>
<tr>
<td>Reinfarction</td>
</tr>
<tr>
<td>overall</td>
</tr>
<tr>
<td>&lt; 72 hours</td>
</tr>
<tr>
<td>&gt; 72 hours</td>
</tr>
</tbody>
</table>

* One placebo patient had PTCA and CABG and is counted once under each procedure.
* Three capt o-
pril patients had PTCA and CABG and are counted once each under both procedures. * re-lecting p=0.05 (placebo vs captopril).
Discussion

It has been suggested that the adjunctive use of ACE inhibitors during thrombolytic therapy for myocardial infarction may improve clinical outcome. It has been suggested that the adjunctive use of ACE inhibitors during thrombolytic therapy for myocardial infarction may improve clinical outcome. In the present study captopril was administered to patients with acute myocardial infarction concomitantly with thrombolytic therapy. We demonstrate that at least part of the ACE inhibitor associated advantageous effects, observed in animal models in ischemia reperfusion i.e. a decrease in ventricular arrhythmias and norepinephrine release, are present as well in patients with acute myocardial infarction treated with thrombolytic therapy. However, remodeling indicated by an enlargement of left ventricular end-systolic or end-diastolic volumes was not prevented, although mean left ventricular volumes were smaller at all time intervals in the captopril group than in the placebo group.

Safety and tolerance

First dose hypotension and hypotension during the first 24 hours was more frequent in the captopril group as compared to the placebo group, but in only five patients did this necessitate discontinuation of treatment. Nabel et al. published data from 38 patients with acute myocardial infarction who underwent thrombolytic therapy with rtPA. Captopril was given intravenously in that study 90 minutes after rtPA and no significant changes in blood pressure were observed. However, in the Captopril And Thrombolysis pilot Study, captopril when administered intravenously concomitantly with streptokinase infusion, produced profound, although short lasting drops in systolic blood pressure. Transient hypotension may be observed during streptokinase infusion itself and is possibly related to transiently increased bradykinin levels. Use of intravenous captopril, which acutely inhibits the breakdown of circulating bradykinin, apparently aggravates streptokinase induced hypotension. This unfavorable interaction was avoided in the present study, since captopril was administered orally, immediately upon completion of the streptokinase infusion and resulted in a more gradual ACE inhibition without interfering with the streptokinase. The intravenous use of enalapril in acute myocardial infarction also induced untoward hypotensive effects, as observed in CONSENSUS II, although this was unrelated to thrombolysis, since enalapril was administered approximately 18 hours after admission and mainly in patients without concomitant thrombolytic therapy. One may speculate that the extent of suppression of ACE activity obtained after a relatively high dose of intravenous enalapril in CONSENSUS II may have been inappropriate, whereas in the CATS study only moderate dos-
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Ages of captopril were used initially, resulting in a moderate but significant reduction of plasma ACE activity.

Left ventricular volumes

Several reasons can be postulated for the absence of the anticipated reduction of left ventricular volumes with captopril compared to placebo. First, the consecutive enrollment of patients in the CATS study yielded an overall equal distribution of small, moderate and large infarcts with a limited proportion of patients showing left ventricular expansion. The average extent of dilatation may have been too small for an effect to appear. The patients included in this study were not selected on the basis of left ventricular dysfunction, and as such represent the common population of patients eligible for thrombolysis treatment with a relatively good prognosis. Infarct-related vessel patency may be estimated to be 68 - 76%, which is an important determinant of change in left ventricular volume shortly after myocardial infarction. The second reason for the lack of effect may be the short observation period i.e. the short exposure to the risk associated with left ventricular expansion in this three months study. Interestingly, despite the lack of effect on remodeling, the reported incidence of heart failure during follow up was clearly reduced indicating that other mechanisms than remodeling alone may have affected clinical outcome. A third reason could be the insufficient sensitivity of quantitative echocardiography as a tool to reliably detect small changes in left ventricular volumes.

Norepinephrine, infarct size and ventricular arrhythmias

An important finding in animal models of ischemia followed by reperfusion, is the effect of ACE inhibition which blunts the norepinephrine release from the myocardium. Although this effect was modest in this group of patients, captopril appears to reduce the acute and transient increase of plasma norepinephrine levels during the first hours following thrombolysis. In animal models, the effect of captopril by blunting the transient release of catecholamines upon reperfusion was also associated with a reduction in myocardial damage. In the present study the transiently lower norepinephrine plasma levels in the captopril group was paralleled by a similar trend towards a reduction of enzymatic infarct size. Peak α-HBDH levels and, more importantly, the calculated cumulative α-HBDH release over 72 hours was reduced in the captopril patients, especially in patients with larger infarcts. The reduction in enzymatic infarct size was not associated with a significant improvement in left ventricular function, as discussed
before. The clinical meaning of a lower incidence of nonsustained VT and AIVR in the captopril group is unclear. However, this finding is in concordance with observations on ventricular arrhythmias and norepinephrine release in animal ischemia-reperfusion models.6 AIVR has been identified as a clinical marker of reperfusion.23 Therefore, reduction of its incidence may reflect attenuation of reperfusion injury possibly mediated by a decrease of norepinephrine levels. Although the observations of transiently reduced norepinephrine levels, reperfusion arrhythmias and a smaller enzymatic infarct size are only modest, all endpoints in this study are in agreement with our experimental observations.6,7

Clinical endpoints

No differences were observed in clinical outcome between the two groups of patients, except for the incidence of congestive heart failure. The extent of this reduction is very comparable to the figures which were reported in SAVE,10 SOLVD,24 CONSENSUS II12 and AIRE.15 However, as mentioned before, this observation cannot be explained by reduction of volumes, i.e. attenuation of left ventricular remodeling. Alternatively, the reduced enzymatic infarct size in large infarcts may have enhanced the beneficial effects of thrombolysis itself. Reinfarction tends to be more frequent in the captopril group. Nevertheless, the mean enzymatic infarct size was smaller in the captopril group, irrespective of the larger number of reinfarctions. In contrast, the SAVE study10 showed a reduction of reinfarction rate, but this occurred during the chronic phase and only became apparent after nine months of follow up.

Limitations of the study

Before any implications for clinical practice can be derived from this study, several limitations should be taken into account. First, the study population is highly selected since only first anterior myocardial infarctions receiving streptokinase were randomized. This represents approximately 10-15% of the total infarct population. This selection may have affected the results on the blood pressure responses, since inferior infarctions are more prone to hypotension. Secondly, the use of echocardiography for quantitative measurements of left ventricular volumes resulted in a loss of one third of the patients for evaluation. Thirdly, it is unknown at present whether captopril may alter the kinetics of myocardial enzymes. Although it has been shown that the use of cumulative α-HBDH as a measure of infarct size is independent of the occurrence of reperfusion, such an effect may have influenced the present results on infarct size on
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this study. Finally, the study was under powered to detect differences in left ventricular end-diastolic volume index less than 4 ml/m$^2$. A study population of at least 700 patients would have been needed to establish whether the presently found differences are due to a true treatment effect.

Implications for clinical practice and future research

The design of the CATS study focused on intervention additional to thrombolysis, as contrasted to most other studies, in which ACE inhibitors were studied for secondary prevention after myocardial infarction. Several effects observed in this study are in favor of early use of captopril in acute myocardial infarction, although one could argue that there appears to be a trend towards more serious adverse clinical events in the captopril group, with respect to the combined incidence of reinfarction and death. However, the numbers in this study are too small to allow for any conclusion. The outcome of the recently presented ISIS-4\textsuperscript{13} and GISSI-3\textsuperscript{14} studies indicate a modest favorable effect on mortality during the first weeks after infarction. Based on the outcome of these studies, there is no need to avoid early use of captopril for safety reasons. However, the results from CONSENSUS II\textsuperscript{12} suggest that the early start of therapy with intravenous enalapril does not actually improve survival. In CONSENSUS II\textsuperscript{12} ACE inhibition was used early, but not as an adjunct to thrombolysis. Furthermore, the drug was administered after a mean delay of 18 hours after admission. It is conceivable that the design of this study with a follow-up of only 180 days may have precluded the observation of a possible beneficial effect on mortality.

In conclusion, the CATS study provides important data on the effects of oral captopril administration of acute anterior myocardial infarction starting during thrombolysis. Despite the outcome of the recently published large scale trials several questions remain to be answered, as to whether earlier use of ACE inhibitors, especially in association with thrombolysis, will improve the long term clinical outcome. Do pharmacological differences between the ACE inhibitors used in these studies play a role? Which dose should be used and finally which type of patients will benefit most from ACE inhibition after myocardial infarction?
References


