Clinical question.

In patients with suspected ACS/MI in prehospital and emergency department settings (P), does the use of ACE inhibitors or Angiotensin Receptor Blockers (I), compared with standard management (ie. no prehospital and emergency department use of ACE inhibitors) (C), improve outcome (eg. infarct size, survival to discharge, 30/60 d mortality) (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/Therapy

State if this is a proposed new topic or revision of existing worksheet:

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

Key words:
Angiotensin converting enzyme inhibitor
Acute coronary syndrome
Myocardial infarction
Acute myocardial infarction
Emergency Department
Pre-hospital

Databases Searched

angiotensin receptor blocker[MeSH Terms]) AND (myocardial infarction[MeSH Terms]) AND ("pre-hospital"[Text Word]), angiotensin receptor blocker [MeSH Terms]) AND (myocardial infarction[MeSH Terms]) AND ("emergency"[Text Word]), angiotensin receptor blocker [MeSH Terms]) AND (myocardial infarction[MeSH Terms]) AND ("early"[Text Word]), Limits, human studies, clinical trials, metaanalysis, randomized controlled trials.

Cocharane Database: keywords myocardial infarction and angiotensin receptor blocker
AHA Endnote Master library

References were reviewed and each article was reviewed for new citations. Primary studies were presented instead of subgroup analyses when available.

State inclusion and exclusion criteria

Inclusion: All patients treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker at the time of presentation) in the emergency department, prehospital setting, or within 1 hours of reperfusion therapy if location is undefined.

The following articles were excluded based on treatment over 24 hrs, randomization treatment initiated over 1 hours after presentation to the hospital , review article

Number of articles/sources meeting criteria for further review:

A total of 37 of the 311 trials met criteria for review meeting search criteria including angiotensin convertering inhibitor term. Two studies were not able to be reviewed and the abstracts are listed.

A total of 2 of the 35 trials met criteria for review meeting search criteria including angiotensin receptor blockade term. Two studies were not able to be reviewed and the abstracts are listed.
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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### Level of evidence

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
- **Italics** = Animal studies
### Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Good</th>
<th>deKam 2000, 2047 (E)</th>
<th>Kingma 1994, 898 (B)</th>
<th>Voors 2005, 119(B)</th>
<th>Swedberg 1992, 678 (B)</th>
<th>CCS-1 1995, 686 (B)</th>
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<td>Kurz 2001, 1351 (E)</td>
<td>Spinar 2000 197 (E)</td>
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<td>Spinar 1999 (E)</td>
<td>Yoshimoto 2000, E27 (E)</td>
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<td>Poor</td>
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<td>Di Pasquale 1999,606</td>
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**Level of evidence**

A = Return of spontaneous circulation  
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C = Survival to hospital discharge  
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*Italics = Animal studies*

### Evidence Opposing Clinical Question

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A = Return of spontaneous circulation  
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REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Discussion: It has been well established that Angiotensin-converting enzyme inhibitors (ACEI) reduce mortality after an acute myocardial infarction. Data regarding Angiotensin Receptor Blockers (ARB), although not as robust also shows similar results. The mechanisms behind this reduction in mortality have largely been attributed to mediation of the activation of the renin-angiotensin aldosterone system and attenuation of the remodeling process after a myocardial infarction.

The benefit of ACEI and ARB in myocardial infarction has been established by numerous large clinical trials. The Survival of Myocardial Infarction Long-Term Evaluation study enrolled patients within 24 hours of symptom onset of an acute myocardial infarction to receive zofenopril or placebo. There was a significant absolute 4% reduction in mortality at 1 year in patients receiving Zofenopril. (Ambrosioni, 1995, 80) The Chinese Cardiac Study (CCS-1) enrolled 13,654 patients up to 36 hours after the onset of a suspected myocardial infarction. Although there was a non-significant 0.5% reduction in mortality in this trial. (CCS-1 investigators, 1995, 686) A large meta-analysis of 100,000 patients reported that there was a 0.48% cumulative reduction in mortality at 30 days in those patients receiving an ACE-I. (ACE I Myocardial Infarction Collaborative Group, 1998, 2202). Similar results in terms of reduction in cardiovascular events have been noted in patients treated with angiotensin receptor blockers. The Valsartan in Acute Myocardial Infarction trial enrolled 14,703 patients within 12 h and 10 days after the onset of acute MI with signs of heart failure or reduced ejection fraction. There was no difference in one year mortality of recurrent myocardial infarction between those on valsartan or captopril (OR 0.97 (0.89–1.05)). (Peiffer 2003, 1893) These studies have led to the recommendation for the use of ACE-I or ARBs in the treatment of patients with a myocardial infarction.

The optimal timing of initiation of these agents however remains less clear. The ISS-4 trial enrolled patients with a median of 8 hours after the onset of symptoms of their myocardial infarction to receive 1 month of captopril or placebo. They excluded patients in cardiogenic shock or hypotension. After 35 days there was a 0.5% reduction in death compared to placebo (reduction of 5 deaths/1,000), but was associated with significant hypotension requiring cessation of therapy in 52 per1,000 patients. (ISIS-4, Lancet 669). Di Pasquale et al. randomized patients to receive 6.25mg captopril prior to urokinase or captopril 3 days after thrombolytic treatment. A significant reduction in mortality at 30 months was reported only those patients with an anterior myocardial infarction. (DiPasquale, 1994, 43) In the Captopril and Thrombolysis study (CATS) patients with an anterior myocardial infarction were randomized to receive captopril 6.25 mg immediately after streptokinase therapy. There was no difference in mortality at 12 months but a reduction in heart failure. However there was an increase risk of hypotension after the first dose in those receiving captopril. (RR 1.3, 95%Cl 1.02-1.77) (Van Gilst 1996, 114, Kingma 1994, 898) A meta-analysis of 3 trials randomizing patients with largely anterior myocardial infarction to very early ACEI compared to delayed ACEI or placebo reported no difference in left ventricular diastolic or systolic dilation at 3 months. (DeKam 2000, 2047) Voors et al performed a meta-analysis the same 3 trials and reported no difference in mortality rates in those patients receiving very early ACEI compared to early ACEI or placebo. However they noted a significant decrease in 3 month diagnosis of heart failure. Most concerning from this meta-analysis was the significant increase in reinfarction in those receiving very early ACEI (RR 2.0, 95% CI 1.1-3.8). The investigators suggest that this finding may be due reduced flow as a result of early blood pressure reduction. (Voors 2005, 119)

The use of ACEI or ARB in the prehospital or emergency department setting has not been evaluated. Extrapolation from trial that evaluate the use of ACE at the time of fibrinolytic therapy provide the best approximation of administration of these agents in the prehospital or emergency department setting. French et al. randomized 493 subjects to receive 6.35 mg of captopril or placebo 2 hrs after commencing streptokinase. There was no difference in mortality, but a reduction in the incidence of heart failure at 1 year. As noted in meta-analyses of early treatment by Voors and DeKam acute therapy has not been shown to be associated with
a reduction in mortality. This in part has been attributed to early hypotension in the groups receiving ACEI. (Voors 2005, 119, DeKam 2000, 2047)

Acknowledgements:

Citation List


Treatment initiated within 1 hour of fibrinolytic therapy. After 35 days patients with captopril had a -0.5% reduction in death when compared to placebo. There was an increase in hypotension in the group that received captopril, but this did not result in increased death. There was also an increase in heart block (6 per 1000 patients treated) and cardiogenic shock (5 per 1000 patients treated).


Treatment initiation from time of presentation was not well defined clear. Significant increase in hypotension. There was no difference in mortality at 4 weeks.


Eligible patients were enrolled in a coronary care unit within 24 hours of symptom onset. No difference was noted in adverse events of reinfarction, supraventricular tachycardia, or angina. Magnitude of effect at 6 months(6 lives saved per 1000) is less than 6 weeks (8 lives saved per 1000).

(1998). "Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group." Circulation 97(22): 2202-12. Level 5, support, good

This study included 3 trials enrolling patients within 24 hours and 1 trial enrolling up to 36 hours. All the involved studies enrolled patients outside the predefined very early time period. The impact of mortality in all the trial was significant with a -0.48% reduction in mortality. The benefits were not significantly influenced by the delay from onset of symptoms to randomization (within 24 to 36 hours).


This study enrolled patients admitted to an intensive care unit. This was a pilot study that led to the larger SMILE trial published in N Engl J Med. There was no difference in mortality.

level 5, good support

*This study enrolled patients admitted to an intensive care unit with a median time from symptom onset to hospital presentation of 9 hours and a median time to randomization from symptom onset of 15 hours. There was no difference in death, but a reduction in the rate of moderate to severe heart failure in those with zofenopril (2.2%) compared with placebo (4.1%). There was also a significant increase in the rate of hypotension with zofenopril (17.1%) compared with placebo (8.9%).*


Level 5, good, support

*This study enrolled patients admitted to an intensive care unit with a median time from symptom onset to hospital presentation of 9 hours and a median time to randomization from symptom onset of 15 hours. This is the long term follow-up from the original study and there continued to be no difference in death, but a reduction in heart failure progression.*


Level 5, fair, support

*This is a subgroup analysis of patients from the SMILE trial, but represents the only study that evaluated patients non-ST elevation ACS. These patients had a mean time to treatment of 3 hours from symptom onset. The reduction in heart failure accounted for the benefit noted in this study. However there was significant unadjusted reduction in death at 1 year (-7.9%, p=0.025). There were less concomitant therapies used in the zofenopril group.*


Level 5, support, fair

*Eligible patients were randomized in an intensive care unit 9 hours after symptom onset. The initial dose was given within 3 hours of fibrinolytic therapy. There was no difference in the single outcome of death between groups. The composite outcome was significant and this was driven by a reduction in class III-IV heart failure with fosinopril. There was a significant increase in hypotension (17.4% placebo and 29.3% fosinopril).*


Level 5, fair, support

*This study enrolled patients <75 years within 72 hours of symptom onset. The time from presentation to randomization is not recorded nor is the protocol for the timing of study drug initiation. Patients were randomized to receiving captopril or placebo and then stratified by age within the
randomization groups. This study reports that the benefit in mortality is largely limited to those elderly patients over the possible 54 month follow-up period.


This manuscript is only available in Italian and therefore was not graded.


Level of evidence 1, neutral, good

This is a meta-analysis of 3 trials that evaluated the use of angiotensin converting enzyme inhibitors within 6 to 9 hours of symptom onset and received thrombolytic therapy. The primary endpoint was left ventricular dysfunction. There was no benefit in the primary outcome in the 845 patients included in the analysis. The authors did note a benefit in left ventricular function in those who failed reperfusion, however all of these trials included a placebo and it is unclear if administration of therapy at a later time period would have provided benefit.


Level 5, neutral, poor

All patients showed signs of reperfusion and were randomized within 2-4 hours of fibrinolytic therapy. There is no true placebo arm. The study showed no difference in endpoints between captopril alone and captopril plus losartan.


Level 1, neutral, fair

This study treated patients prior to thrombolysis. All patients received captopril and were randomized to early (15 minutes prior to thrombolysis) or late (3 days from admission). Of the 371 eligible patients, 259 were randomized, 51 did not have a final diagnosis of STEMI. A large number of patients were excluded from analysis. There was a significant reduction in the rate of ventricular hyperkinetic arrhythmias in the early treatment group. In patients with an anterior myocardial infarction there was a reduction in mortality in the early treatment group (5.95% verses 17.07%).


Level 5, support, fair

This trial in underpowered to show a clinical difference. However it provides pathophysiologic evidence on why an ACE inhibitor initiated 2-4 hours after fibrinolysis may impact remodeling. No data was presented on adverse events.


Level 5, support, fair
Mean time to entry was approximately 10 hours and all patients were admitted to a coronary care unit. The time from presentation to study drug treatment is not recorded. Baseline echocardiogram was done up to 10 days after infarction. Of the 523 eligible patients, 225 were enrolled and 42 patients were withdrawn and another 43 did not complete electrocardiograms. No significant changes were noted between the 3 groups. This may be due to the small sample size.

Level 5, support, good

Eligible patients were <75 years old and were treated with captopril within 2 hours after streptokinase. The captopril group had an absolute reduction in mortality of 2.8% (p=0.078) at 30 days. Over the median 4 years of follow-up the mortality rate was significantly lower in the captopril group. There was a significant increase in the rate of hypotension in the captopril group with in 24 hours of randomization.

Level 5, support, poor

This study did not contain a true placebo. Patients were randomized in the coronary care unit to receive atenolol or captopril. Time from presentation to study drug administration is not reported. There was no significant change in ejection fraction from baseline to 1 week.

Level 1, neutral, good

Eligible patients were evaluated in a coronary care unit and study drug was initiated immediately following streptokinase infusion. Captopril use was associated with an increase risk of acute hypotension RR 1.3 (95%CI 1.02-1.77). Over the 3 month follow-up period there was no difference in the primary outcome measure. Patients were enrolled in a coronary care unit a mean time of 14 hours from symptom onset. Time from presentation until study drug initiation was not reported. This trial was stopped prematurely.

Level 5, neutral underpowered for clinical outcomes.

Patients were randomized within 24-72 hours after the onset of chest pain. The benefit was limited to the reduction in heart failure.

Level 5, neutral, fair, underpowered.

Although these patients were treated early in their hospitalization these patients are not reflective of emergency department or prehospital patients and treatment was initiated in the cardiac
catheterization laboratory and enalaprilat was given intracoronary. No significant differences were noted in hemodynamic parameters, but the study was underpowered to detect these results.

Level 5, support, poor

*The study was underpowered to determine any true clinical benefit. The patients were randomized into 4 arms while in a coronary care unit with a mean of 22 hours from symptom onset. There was no difference in hypotension between the groups.*

Level 5, support, fair

*This is a small study of patients who underwent coronary angiography and had a study drug given in the catheterization laboratory. There was an increase in ejection fraction at 2 weeks. Confidence intervals are large and the rate of adverse events is not reported.*

Level 5, support, good

*This is a large multicenter trial of patients with an acute myocardial infarction who were randomized within 12 hours to 10 days after a myocardial infarction. Long term follow-up revealed no difference in mortality between the groups treated with either agent.*

Level 5, good, neutral
This scientific review included trials comparing early and late administration. Early administration exceeds the time period associated with emergency department care. In those receiving early therapy the odds of 1 year mortality was (OR 0.93, 95% CI 0.88-0.97) compared with the late therapy group (OR 0.84, 95% CI 0.73-0.97). Based on this study it can not be conclude that delayed administration is associated an increased rate of mortality compared to early administrations.

Level 5, support, fair

Eligible patients were admitted to a coronary care unit. Enalaprilat was administered intravenously within 24 hours of symptom onset. Time from hospital admission to study treatment is not reported. Subgroup analysis revealed that the benefit from enalaprilat was in patients with an anterior myocardial infarction.

Level 5, neutral, fair

This trial enrolled patients in the coronary care unit within 24 hours of an acute myocardial infarction. In those treated with captopril or losartan there was a high rate of asymptomatic hypotension, but no intervention was required.

Level 5 neutral, good

Patients were enrolled in a coronary care unit a mean time of 14 hours from symptom onset. Study drug recommended to be started following reperfusion therapy. Time from presentation to study drug initiation is not reported. This trial was stopped prematurely.

Level 1, support, good

Eligible patients had an anterior myocardial infarction and were treated with streptokinase within 6 hours of symptoms. Patients were randomized to receive captopril immediately following the fibrinolytic infusion. There was no difference in mortality, but a reduction in the rate of heart failure similar to the primary results of the trial. The rate of hypotension was not reported.

Level 1, neutral, good

This metaanalysis included the same patient population at de Kamp (2000) but evaluate a different outcome measure. This analysis showed no difference in mortality compared to palcebo in pateints receiving an angiotensin converting enzyme inhibitor within 2 hours of fibrinolytic therapy. There was a difference in heart failure with an absolute decrease of 6.8% in those treated with an ACE
inhibitors. However there was also an increase in reinfarction in the treated patients of 3.4% (OR 2.0 (95% CI 1.06-3.75). The investigators could not identify a specific subgroup that benefited from early ACE inhibition.


Level 5, support, poor

Eligible patients were admitted to a coronary care unit and had failed reperfusion. All patients underwent primary coronary intervention. Treatment with imidapril was begun within 24 hours of chest pain. This study only contained 20 patients in each randomization group and was underpowered to detect clinical differences.