Evidenced-based Cardiology

The value of angiotensin converting enzyme inhibitors for the treatment of patients with left ventricular dysfunction, heart failure or after acute myocardial infarction

K. Swedberg* and N. Sharpe†

*Department of Medicine, Östra University Hospital, Göteborg University, Göteborg, Sweden; †Department of Medicine, University of Auckland, New Zealand

Introduction

Chronic heart failure, despite optimal therapy, is a disorder with both high mortality and morbidity[4,5]. The incidence of chronic heart failure has been increasing during the last decade[6-8] and congestive heart failure is one of the most frequent diagnoses among hospitalized patients. There is a spectrum of myocardial failure from asymptomatic left ventricular dysfunction to severe congestive heart failure. Studies of patients with left ventricular dysfunction have shown that the prognosis is much worse among patients with symptomatic failure compared with those who are asymptomatic, although the degree of left ventricular dysfunction may be similar[6-8]. When assessing the prognosis for patients with heart failure, it is important to establish the degree of left ventricular dysfunction together with clinical symptoms.

Angiotensin converting enzyme (ACE) inhibitors have been introduced for the treatment of heart failure within the last decade. Their potential value was suggested by studies showing improved symptomatology[9], haemodynamics[10,11] and survival[12]. It was hypothesized that ACE inhibitors might attenuate left ventricular remodelling after myocardial infarction[13,14] and thus possibly reduce left ventricular dilatation and the progression to symptomatic heart failure. Neuroendocrine activation has been shown to be of prognostic importance[15] and ACE inhibitors have the potential of modulating this activation[16]. Several studies have reported results on the effects of ACE inhibitors on survival in patients with clinical heart failure, following acute myocardial infarction generally and following myocardial infarction with left ventricular dysfunction or heart failure in particular.

Key Words: ACE inhibitor, myocardial infarction, heart failure.

Treatment objectives

The objectives of treatment of patients with acute myocardial infarction, ventricular dysfunction or heart failure are to: improve survival; reduce morbidity which can be related to hospital admission rate or medication for heart failure; improve symptomatology as shown by increased physical capacity; improve haemodynamics; prevent progression of myocardial dysfunction; prevent progression of atherosclerotic disease; improve cost-effectiveness.

This review will discuss the value of ACE inhibitors for treatment of patients with acute myocardial infarction or heart failure in relation to these objectives. We will grade the importance of the information available in January 1995 from published trials and present our interpretation of this with a clinical overview.

Methodology

Trial data included in the review cover patients with acute myocardial infarction, left ventricular dysfunction or congestive heart failure. The primary or secondary objectives of these trials included some of the objectives for therapy which have been listed above. 'Major' trials are those which have been randomized, controlled and were of moderate size (≥100 patients). For more extensive details there are several reviews available[11,17]. Table 1 lists the trials included.

We have graded the trial evidence in relation to the treatment objectives into three categories: (1) Proven indication. Always acceptable; (2) Acceptable indication but of uncertain efficacy and may be controversial; (3) Not proven. Potentially harmful (contraindicated).

Cost-effectiveness was not a primary goal of our review, but considering the relevance of cost to clinical decision making, we have included comments on this important aspect.
Table 1  ACE inhibitor trials in acute myocardial infarction, left ventricular dysfunction and heart failure included in the review

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study drug</th>
<th>Study size</th>
<th>Treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (&lt;24 h) non-selective approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS II&quot;</td>
<td>Enalapril</td>
<td>6090</td>
<td>6 months</td>
</tr>
<tr>
<td>ISIS 4&quot;[19]</td>
<td>Captopril</td>
<td>58 050</td>
<td>5 weeks</td>
</tr>
<tr>
<td>GISSI 3[20]</td>
<td>Lisinopril</td>
<td>18 895</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Early (&lt;24 h) selective approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMILE[22]</td>
<td>Zofenopril</td>
<td>1556</td>
<td>6 weeks</td>
</tr>
<tr>
<td>CATS[23]</td>
<td>Captopril</td>
<td>298</td>
<td>3 months</td>
</tr>
<tr>
<td>Delayed (days) selective for left ventricular dysfunction</td>
<td>Captopril</td>
<td>2231</td>
<td>42 months</td>
</tr>
<tr>
<td>SAVE[23]</td>
<td>Trandolapril</td>
<td>1749</td>
<td>24-50 months</td>
</tr>
<tr>
<td>Delayed (days) selective for heart failure</td>
<td>Ramipril</td>
<td>2006</td>
<td>15 months</td>
</tr>
<tr>
<td><strong>Asymptomatic left ventricular dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLVD prevention[24]</td>
<td>Enalapril</td>
<td>4228</td>
<td>37 months</td>
</tr>
<tr>
<td><strong>Chronic heart failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS[12]</td>
<td>Enalapril</td>
<td>253</td>
<td>6 months</td>
</tr>
<tr>
<td>SOLVD[26]</td>
<td>Enalapril</td>
<td>2569</td>
<td>41 months</td>
</tr>
<tr>
<td><strong>Trials on exercise capacity</strong></td>
<td>Benzopril, Captopril, Cilazopril, Enalapril, Lisinopril, Ramipril</td>
<td>1607</td>
<td>3 weeks-6 months</td>
</tr>
<tr>
<td><strong>Haemodynamics</strong></td>
<td>Enalapril</td>
<td>15</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Decarlo 1983[10]</td>
<td>Captopril/Enalapril</td>
<td>100</td>
<td>1-3 months</td>
</tr>
</tbody>
</table>

**ACE inhibitors after acute myocardial infarction**

*Early (<24 h) non-selective approach*

In the CONSENSUS II trial, 6090 patients with acute myocardial infarction were randomly allocated to treatment with enalapril or placebo at 103 Scandinavian centres[18]. Treatment was initiated intravenously, using enalaprilat, within 24 h of the onset of infarction. The duration of treatment varied between 41 and 180 days due to the premature termination of the study. Mortality after the first month was 7.2 and 6.3%, and after 6 months 11.0 and 10.2%, in the enalapril and placebo groups respectively. The differences between the groups were not statistically significant. Heart failure was associated with the index infarction in 1109 patients (18%). There was no difference in survival between the two treatment groups in this subgroup of patients. Hypotension (systolic blood pressure below 90 mmHg or diastolic blood pressure below 50 mmHg) was more frequent in the enalapril group than in the placebo group (12% vs 3%). Mortality was higher among patients given enalapril who had hypotension after the first dose (17%) than among patients on placebo who had hypotension (12%). Treatment was changed because of new or worsened heart failure in 30% of the placebo group and 27% of the enalapril group (P<0.006). It is not known whether enalaprilat treatment was harmful among patients with first dose hypotension or whether the drug merely identified patients at high risk of death.

In ISIS-4, the largest cardiovascular study to date, 58 050 patients were randomly assigned to treatment with placebo or captopril (as well as nitrates and magnesium in a 3 x 2 factorial design), within 24 h of onset of a suspected or definite acute myocardial infarction[19]. There was a significant 7% reduction in mortality at 5 weeks from 7.69 to 7.19% (P=0.002) which corresponds to an absolute difference of 4.9 ± 2.2 fewer deaths per 1000 patients treated for one month. The benefits appeared larger in certain high risk groups such as those with a history of previous myocardial infarction or with heart failure. Captopril was associated with an increase in profound hypotension being observed in 20.9% patients vs 11% in the placebo group.

In the GISSI-3 study, 18 895 patients were randomly assigned to treatment with lisinopril or open control within 24 h from the onset of acute myocardial infarction. Using a 2 x 2 factorial design the efficacy of transdermal glyceryl trinitrate was also assessed. After 6 weeks treatment, mortality was significantly reduced from 7.1% among patients receiving placebo to 6.3% among patients receiving lisinopril; risk reduction, 11%[20]. There were fewer patients in the lisinopril group with left ventricular ejection fraction ≤ 35%, estimated by two dimensional echocardiography at the end of the study period (4.8% vs 5.3%) although the frequency of clinical heart failure was similar in both groups.
The Chinese captopril study (CCS study) allocated 13,634 patients within 36 h of onset of a suspected myocardial infarction to captopril or placebo. The study continued for 4 weeks during which period all patients were kept in hospital. The mortality was reduced from 9.59% to 9.05% (P=0.324).

**Early (<24 h) selective approach**

In the SMILE (Survival of Myocardial Infarction Long-term Evaluation) study, 1556 patients with acute anterior myocardial infarction who were not eligible for thrombolytic therapy were enrolled within 24 h of onset of symptoms as judged by echocardiography). There were 253 patients in NYHA class IV randomized to placebo or enalapril. After a follow-up of 6 months (primary objective), there were 14-8% in the enalapril group was 15-8% compared to 16-7% in the placebo group; risk reduction, 22%. The patients were then included in a random controlled trial for 3 months. Left ventricular volumes increased in both the placebo and captopril groups but the dilatation tended to be attenuated among captopril treated patients.

**Delayed (days) selective approach for left ventricular dysfunction**

In the SAVE trial, 2231 patients with an ejection fraction of 40% or less, but without overt heart failure or symptoms of myocardial ischaemia, were randomly assigned treatment with captopril or placebo within 3 to 16 days after myocardial infarction. The patients were followed during an average of 42 months. Mortality from all causes was 20% in the captopril group and 25% in the placebo group; risk reduction 19% (P=0.019). The proportion of patients who needed hospitalization due to congestive heart failure was higher in the placebo group (17%) than in the captopril group (14%); risk reduction, 22% (P=0.019). Furthermore, the risk of developing a fatal or non-fatal myocardial infarction was reduced by 25% (P=0.015) with captopril.

The TRACE (TRAndolapril Cardiac Evaluation) was a multicentre, Danish study where 1,749 patients with left ventricular dysfunction (wall motion index ≤ 1.2 as judged by echocardiography) were randomly assigned treatment with placebo or the ACE inhibitor trandolapril. Treatment was initiated 3-7 days from the onset of myocardial infarction. This trial has the largest proportion of screened patients randomized (25%). Patients were followed for a minimum of 2 years. All cause mortality in the placebo group was 42.3% and 34.7% with trandolapril, a 22% relative reduction of mortality (P=0.00065).

**Delayed (days) selective approach for heart failure**

In the AIRE study, 2006 patients with clinical evidence of heart failure at any time after the index infarction, were randomly allocated to treatment with ramipril or placebo on the 3rd to 10th day from the onset of infarction. Clinical evidence of heart failure was defined as at least one of the following: signs of left ventricular failure on chest X-ray, bilateral auscultatory crackles extending at least one-third of the way up the lung fields in the absence of chronic pulmonary disease, or auscultatory evidence of a third heart sound with persistent tachycardia. The average follow up time was 15 months with a minimum of 6 months. Mortality from all causes at the end of the study was 17% in the ramipril group and 23% in the placebo group; risk reduction, 27% (P=0.002).

**ACE inhibitors in patients with asymptomatic left ventricular dysfunction**

The SOLVD Prevention trial evaluated 4228 patients with left ventricular ejection fraction <35% who were not receiving therapy for heart failure. Patients were randomized to receive placebo or enalapril. The average follow-up was 37-4 months. The mortality in the placebo group was 15.8% compared to 14.8% in the enalapril group. The risk reduction of 8% was not statistically significant. Enalapril significantly reduced the number of hospitalizations for heart failure and the incidence of heart failure. There were also significantly fewer patients observed to develop myocardial infarction, 9.7% vs 7.6% (P=0.01); risk reduction 24%.

**ACE inhibitors in patients with chronic heart failure**

**Survival trials**

In CONSENSUS I, it was demonstrated that survival could be improved in severe heart failure by addition of an ACE inhibitor. There were 253 patients in NYHA class IV randomized to placebo or enalapril. After a follow-up of 6 months (primary objective), there were 40% fewer deaths in the enalapril group (P=0.002) and the overall mortality was reduced by 27% (P=0.003).
Number of days for hospital care was reduced and NYHA classification significantly improved with enalapril.

In the largest study, the SOLVD treatment trial, 2569 patients with symptomatic heart failure NYHA class II–III received placebo or enalapril in addition to conventional heart failure therapy. The average follow-up was 41-4 months. Mortality was significantly reduced by 16% from 39-7% to 35-2% (P=0.0036). Hospitalizations for heart failure were also reduced. The largest reduction in mortality occurred among deaths attributed to progressive heart failure. Symptoms and quality of life assessed by questionnaire were improved.

**Trials on exercise capacity**

There are many trials which have focused on exercise capacity. An extensive review of these trials has recently been published. The conclusion from this review was that studies of ACE inhibitors confirm that these agents do improve the exercise capacity as well as symptoms of patients with chronic congestive heart failure. Study size, duration of follow-up and method of exercise testing appear to be three factors affecting the outcome of the studies. In the overall analysis, changes in exercise capacity are consistent with changes in symptoms. However, the type of exercise test used may be important and treadmill appears more sensitive than bicycle testing in detecting a therapeutic response. As exercise testing is increasingly used in routine evaluation of patients with chronic heart failure and their response to therapy, there is a need for more research into exercise protocols for this purpose.

**Trials on haemodynamics**

ACE inhibitors were documented early to induce beneficial haemodynamic responses. These effects included increased cardiac output, increased stroke volume and reduced pulmonary wedge pressure.

**Trials on prevention**

Reduced incidence of heart failure by ACE inhibitors has been demonstrated in several trials. In SOLVD, as discussed previously, the incidence of heart failure and the number of hospitalizations were reduced and similar findings were reported in SAVE. In an overview of ACE inhibitor trials the preventive potential of ACE inhibitors is clearly demonstrated.

The potential anti-atherosclerotic effect of ACE inhibitors, suggested from experimental animal studies, is supported by observations from the SOLVD and SAVE studies in which the incidence of myocardial infarction and unstable angina were reduced. However, these findings were ad hoc analyses and need confirmation from prospective trials which are ongoing.

**Cost effectiveness**

Enalapril therapy for patients with heart failure (SOLVD) was cost effective and justified by added benefits compared to other vasodilator therapy. In asymptomatic patients with left ventricular dysfunction after an acute myocardial infarction (SAVE) captopril was cost effective in patients 50–80 years of age compared to other interventions. Ramipril therapy for patients with clinical heart failure after acute myocardial infarction appears highly cost effective when assessed using data from the AIRE study.

**Documented value of ACE inhibitors**

**Proven indication. Always acceptable**

(a) Symptomatic chronic heart failure and documented systolic myocardial dysfunction. Improved survival and reduced morbidity has been demonstrated. Symptoms will be attenuated and exercise capacity improved.
(b) Previous myocardial infarction and a significant reduction of systolic function (e.g. ejection fraction with any method <35–40%). Improved survival and reduced morbidity has been demonstrated. Symptoms will be attenuated.
(c) Following acute myocardial infarction with clinical signs of heart failure or significant systolic dysfunction (ejection fraction <40%). Improved survival and reduced morbidity has been demonstrated.
(d) Acute myocardial infarction with haemodynamic stability within 24 h. Improved short-term survival (5–7 weeks) demonstrated.

**Acceptable indication but of uncertain efficacy and may be controversial**

(a) Following myocardial infarction to reduce recurrent myocardial infarction or unstable angina.
(b) Heart failure due to diastolic dysfunction.

**Not proven. Potentially harmful (contraindicated)**

(a) Treatment of patients with significant aortic or mitral stenosis.
(b) Treatment of patients with hypotension (systolic blood pressure <80 mmHg).
(c) Treatment of patients with pronounced renal dysfunction.

**Clinical overview**

**Acute myocardial infarction**

A meta-analysis of the trials discussed has clearly demonstrated that the addition of an ACE inhibitor...
early in the acute phase of an acute myocardial infarction will have a modest beneficial effect on early survival, whereas a delayed selective approach can provide a larger benefit longer term. Thus two strategies could be adopted: one general and one selective.

The general approach would be to treat all patients without hypotension or other contraindications with an ACE inhibitor as early as possible by oral administration of captopril or lisinopril. All patients could start with an ACE inhibitor and then be re-evaluated after 5-6 weeks. In those patients where there is documented left ventricular dysfunction at this follow-up, long-term therapy would be maintained.

In contrast to this general approach, a selective approach could be taken to allow maximal benefit for high-risk patients with long-term treatment and avoid unnecessary treatment in those unlikely to benefit.

A substudy from CONSENSUS II demonstrated a significant attenuation of left ventricular dilatation only in patients with anterior myocardial infarction. A similar finding was observed in the CATS trial which assessed remodelling.

In ISIS 4, anterior infarct involvement or bundle branch block was present in 42% of patients. Fifty-four percent of the entire mortality or 2322 deaths occurred among these patients. Mortality was 9-5% in this group, significantly higher than the 5-9% mortality in the remaining patients. Thus patients with anterior infarction or bundle branch block could be treated early with captopril within the first 24 h. The remaining patients could be deferred and ACE inhibitors reconsidered later. The advantage with this strategy would be avoidance of hypotension. Profound hypotension was noted in 5951 captopril-treated patients while there were 3130 such reactions among the placebo group. It is not possible to divide these reactions by infarct location but a significant number could be avoided by a more selective strategy.

This approach has been challenged by the GISSI and ISIS-4 investigators. In ISIS-4 there were 44 excess deaths during the first day in the placebo group and similarly there were 21 excess deaths in the control group in the GISSI-3 trial. However, many of these patients could still have been identified for treatment with a selective approach.

In CONSENSUS II, likewise a number of hypotensive reactions were noted. The major reason for this was probably the more aggressive ACE inhibition with intravenous administration of enalapril. A possible relationship between these reactions and mortality was observed by the Safety Committee. A more careful introduction of low oral dose ACE inhibitor therapy would very likely reduce this risk.

For practical clinical reasons and for optimal cost effectiveness we advise a selective strategy in patients with anterior infarction, bundle branch block, significant left ventricular dysfunction or clinical heart failure. These patients should be treated without delay once haemodynamically stable and should be re-evaluated after the acute phase during the first 2-3 days following myocardial infarction. If significant left ventricular dysfunction or heart failure becomes evident, ACE inhibitor therapy should be initiated. Therapy should then continue for 2 years and with persisting left ventricular dysfunction life-long therapy should be considered.

**Chronic heart failure and left ventricular dysfunction**

All patients with documented left ventricular systolic dysfunction by any method, in the order of ejection fraction <35-40%, should be considered for treatment with an ACE inhibitor. In symptomatic patients this should be considered first line therapy in addition to a diuretic agent. Treatment should be continued long term. Patients with clinical congestive heart failure should be maintained on ACE inhibitor treatment in combination with a diuretic.

Contraindications to ACE inhibitors include hypotension (in general systolic blood pressure <80 mmHg), pronounced renal dysfunction (serum creatinine >200 μmol l⁻¹), history of angioneurotic oedema and important valve stenosis.

The dosage to be used should be titrated from a low dose and increased to the moderate to high levels employed in clinical trials. If no hypotension or renal dysfunction develops, titration up to enalapril 10 mg b.i.d., captopril 50 mg b.i.d., ramipril 5 mg b.i.d., trandolapril 4 mg qd, quinapril 10 mg b.i.d. will be most effective.

**References**


