

## Do All Patients Deserve Treatment With ACE Inhibitors After Myocardial Infarction?

### An Argument to Treat Only High-Risk Patients

Based on a presentation by Stephen G. Ball, PhD

#### **Presentation Summary**

Whether angiotensin converting enzyme (ACE) inhibitors should be given to all patients after myocardial infarction (MI) or only to a particular subset of patients has sparked controversy. Recent major trials, such as the third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) and the Fourth International Study of Infarct Survival (ISIS-4), have shown only minor benefit of limited certainty. In contrast, large and certain benefit has been observed consistently in trials of selected patients, such as those with left ventricular dysfunction after MI.

Findings from recent trials in which patients with impaired left ventricular function were treated with ACE inhibitors are consistent in demonstrating the beneficial effects of these drugs in limiting damage and prolonging life. This benefit is seen early after treatment is

started, with decreases in mortality often apparent within 24 hours, and is maintained and enhanced with continued treatment.

A clinical assessment that takes into account the patient's age, history of ischemic damage, size and site of the current infarction, and absence of overt heart failure and an objective assessment of left ventricular function allows rational selection of patients for ACE inhibitor treatment. Arguments for more widespread use of ACE inhibitors after MI have stemmed from observations that these drugs can decrease the likelihood of reinfarction. However, results from ISIS-4 indicate that ACE inhibitors may be harmful in certain MI patients, such as those with low blood pressure or those in whom treatment produces profound hypotension. Large-scale trials in hypertensive patients and other high-risk populations should resolve this important issue.

**T**he proper use of angiotensin converting enzyme (ACE) inhibitors after myocardial infarction (MI) is an important issue facing clinicians who care for these patients. Recent discussions have focused on appropriate candidates for ACE inhibitor therapy after MI. Some experts recommend administering ACE inhibitors to all patients who suffer MI; others recommend more selective use by identifying a subset of patients who derive the greatest benefit from ACE inhibitors after an MI.

Stephen G. Ball, PhD, provided his insights into the controversy by reviewing and interpreting recent clinical trials

in which the utility of ACE inhibitors in post-MI patients was examined. "We have a lot of evidence to help guide our choice. Further placebo-controlled trials

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will be unlikely so we must make up our minds now on how we are going to treat our patients," said Dr. Ball, Professor of Cardiology, Institute for Cardiovascular Research, University of Leeds, England.

Recent major trials, such as the third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) and the Fourth International Study of Infarct Survival (ISIS-4), have shown only minor benefit of limited certainty. "Patients after an MI are a heterogeneous group and it seems unlikely that a single treatment will benefit all, and certainly not equally; some may even be harmed," said Dr. Ball. "After a heart attack, patients are faced with a multitude of options and it behooves the physician to tailor treatment for the individual."

**Recent Post-Myocardial Infarction Trials**

Recent trials in which the use of ACE inhibition after MI was studied include the second Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II), GISSI-3, ISIS-4, Chinese

**CONSENSUS II.** At 103 Scandinavian centers, 6,090 patients with acute MI were randomly assigned to treatment with enalapril or placebo. In the treatment group, therapy was started with an intravenous infusion of enalapril (enalaprilat) within 24 hours of the onset of chest pain, followed by administration of oral enalapril. Mortality at 1 and 6 months was not significantly different between the treated patients and placebo recipients. Early hypotension occurred in 12% of the enalapril group. The CONSENSUS II study was stopped prematurely because of a fear that enalapril treatment would harm the patients (heart failure worsened in 30% of the placebo group and 27% of the enalapril group). The lack of effect with enalapril was consistent across a number of prespecified subgroups studied.

**GISSI-3.** More than 19,000 acute MI patients seen within 24 hours of

**Table 1.** Recent Trials of Angiotensin Converting Enzyme Inhibitors in Post-Myocardial Infarction

| Trial        | Treatment                | Treatment Duration | Mortality Endpoint | Mortality   |          | RR (%) |
|--------------|--------------------------|--------------------|--------------------|-------------|----------|--------|
|              |                          |                    |                    | Control (%) | Drug (%) |        |
| CONSENSUS II | Enalapril (IV then oral) | 6 months           | 1 month            | 6.3         | 7.2      | --     |
|              |                          |                    | 6 months           | 10.2        | 11.0     | --     |
| GISSI-3      | Lisinopril               | 6 weeks            | 6 weeks            | 7.1         | 6.3      | 11     |
| ISIS-4       | Captopril                | 4 weeks            | 5 weeks            | 7.7         | 7.2      | 7      |
|              |                          |                    | 12 months          | 12.5        | 12.0     | 5.4    |
| SMILE        | Zofenopril               | 6 weeks            | 6 weeks            | 6.5         | 4.9      | 25     |
|              |                          |                    | 12 months          | 14.1        | 10.0     | 29     |
| SAVE         | Captopril                | 42 months          | 42 months          | 25          | 20       | 19     |
| AIRE         | Ramipril                 | 15 months          | 15 months          | 23          | 17       | 27     |
| CCS-1        | Captopril                | 4 weeks            | 4 weeks            | 9.6         | 9.1      | 0.53   |
| TRACE        | Trandolapril             | 26.5 months        | 12 months          | 42.3        | 34.7     | 22     |

CONSENSUS II = second Cooperative New Scandinavian Enalapril Survival Study; GISSI-3 = third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico study; ISIS-4 = Fourth International Study of Infarct Survival; CCS-1 = Chinese Cardiac Study; SMILE = Survival of Myocardial Infarction Long-term Evaluation study; SAVE = Survival and Ventricular Enlargement study; AIRE = Acute Infarction Ramipril Efficacy study; TRACE = Trandolapril Cardiac Evaluation study; RR = risk reduction.

Cardiac Study (CCS-1), Survival of Myocardial Infarction Long-term Evaluation (SMILE) study, Survival and Ventricular Enlargement (SAVE) study, Acute Infarction Ramipril Efficacy (AIRE) study, and Trandolapril Cardiac Evaluation (TRACE) study (Table 1).

symptom onset were randomly assigned in a factorial design to 6 weeks of treatment with oral lisinopril or open control as well as nitrates or open control. When started within 24 hours of acute MI symptoms, lisinopril (5 mg initial dose followed by 10 mg daily) decreased overall mortality by 11%. The survival

curves of the patients treated with lisinopril and the control patients separated by day 1 and continued to diverge throughout the following 6 weeks of treatment. Lisinopril also decreased the combined endpoint of mortality and severe ventricular dysfunction by about 10%.

"The confidence limits in GISSI-3 were very close to no benefit," commented Dr. Ball. "The results are disappointing when you review the data to 6 months—the benefit appears to be halved and it is no longer significant. But the course of treatment was only during the first 6 weeks."

**ISIS-4.** ISIS-4 was done in a 2 x 2 x 2 factorial design in which 58,000 patients were randomly assigned within 24 hours of the onset of suspected acute MI to receive either captopril or placebo. (Patients were also randomly assigned to receive either nitrates or placebo as well as magnesium sulfate or placebo.) Captopril was started at 6.25 mg and titrated up to 50 mg twice daily. Five-week mortality was 7% lower in the patients treated with captopril compared with those receiving placebo. In certain higher-risk groups, such as those with previous MI or a history of heart failure, captopril was associated with about 10 fewer deaths per 1,000 patients treated. At 12 months, the survival advantage with captopril was maintained, although the advantage over placebo at 1 year was no longer significant.

Captopril was associated with an increase in hypotension severe enough to require termination of the study medication in 10% of patients, compared with 4.8% of patients in the placebo group. About half of the cases of hypotension with captopril were observed by day 1. Entry systolic blood pressure less than 100 mm Hg appeared to be a significant risk factor for termination of study treatment because of hypotension. A slight excess of cardiogenic shock and renal dysfunction also was noted in patients treated with captopril. Captopril was not associated with an increase in early death among patients with low blood pressure at entry.

The investigators concluded that ACE inhibitors started early in acute MI save about 5 lives per 1,000 patients treated for 1 month. They subsequently recommended that all patients be given an oral long-acting ACE inhibitor shortly after MI, with continuing ACE inhibitor treatment for 6 weeks.

**CCS-1.** Oral captopril was compared with placebo in 13,634 patients with suspected acute MI seen up to 36 hours after onset of symptoms. Patients were randomly assigned to 1 month of treatment with either oral captopril (6.25 mg initially titrated up to 12.5 mg three times daily) or placebo. At 4 weeks, captopril was associated with a 10% decrease in mortality, although this result did not reach statistical significance. Patients treated with captopril had a significant excess of hypotension, but this was not associated with an increase in mortality, even among patients who were hypotensive at study entry. These researchers concluded that treating every patient after acute MI with an ACE inhibitor saves approximately 5 lives per 1,000 patients treated.

**SMILE.** The ACE inhibitor zofenopril was compared with placebo in this study of 1,500 patients with acute anterior MIs who did not receive thrombolytic therapy. Patients were randomly assigned within 24 hours of symptom onset to treatment with either zofenopril or placebo for 6 weeks. In the zofenopril group, the incidence of death or development of severe congestive heart failure at 6 weeks was 7.1% compared with 10.6% in the placebo group, a 34% reduction in risk with active treatment. After 1 year, the benefit of short-term treatment with the ACE inhibitor was still apparent, with the risk of mortality 29% lower in the zofenopril group.

**SAVE.** The SAVE trial tested the benefit of captopril on mortality and morbidity in patients who had asymptomatic left ventricular dysfunction after MI. The 2,200 patients in this study had ejection fractions of 40% or less but no overt heart failure and were randomly assigned to treatment within 3 to 16 days

of their MI (an average of approximately 11 days after MI). Approximately 25% of the study population had undergone revascularization. The target dosage of captopril was 50 mg three times daily. After an average follow-up of 42 months, the decrease in the risk of mortality with captopril treatment was 19%. Death from cardiovascular causes, development of severe heart failure, hospitalization for congestive heart failure, and recurrent MI were all reduced significantly with treatment. The benefits of captopril were seen in patients treated with thrombolytic therapy, aspirin, or beta-blockers, as well as those who did not receive these treatments.

**AIRE.** The effect of treatment with ramipril was evaluated in 2,000 patients who had clinical evidence of heart failure after acute MI. On days 3 to 10 after

*"The benefit from long-term ramipril treatment was profound and obvious; about 40 lives were saved for every 1,000 patients treated."*

MI, patients were randomly assigned to treatment with either ramipril or placebo. With an average treatment period of 15 months, mortality from all causes was 27% lower in patients receiving ramipril. The risk of a first event (death, severe or resistant heart failure, MI, or stroke) was reduced 19% with ramipril treatment.

"The benefit from long-term ramipril treatment was profound and obvious; about 40 lives were saved for every 1,000 patients treated," said Dr. Ball. Even by 30 days, ramipril appeared to produce a reduction in risk of mortality similar to that in the 15-month study, although the *P* value was of borderline significance at 0.53.

In AIRE, patients had to have evidence of heart failure to be entered into the study, even if the heart failure was only transient. Patients with severe heart failure were excluded. Not all of the patients in AIRE had low ejection

fractions, "but they all did very poorly with placebo treatment—1-year mortality in the placebo group was 20%," Dr. Ball said.

**TRACE.** The findings from the TRACE study were unpublished at the time of Dr. Ball's lecture but some of the data were presented in abstract form at the 68th Scientific Sessions of the American Heart Association held November 1995 in Anaheim, California.

The aims of the trial were to determine whether ACE inhibition with the long-acting ACE inhibitor trandolapril in patients with left ventricular dysfunction shortly after MI could decrease morbidity and mortality. A total of 7,000 patients with acute MI were screened for study entry 2 to 6 days after the MI; 1,749 of these patients had reduced left ventricular function and were randomly assigned to treatment with either trandolapril or placebo 3 to 7 days post-MI. Treatment was continued for 24 to 50 months, with a mean treatment duration of 26.5 months at the time the study results were presented.

A 22% reduction in all-cause mortality with trandolapril was seen in the intention-to-treat analysis, according to the TRACE Study Group. Trandolapril decreased the risk of sudden death (105 cases with trandolapril versus 133 cases with placebo) and cardiovascular death (risk reduction, 25%). "The TRACE findings are similar to those from AIRE, although patient selection in TRACE was done using a wall motion index rather than ejection fraction," said Dr. Ball. In TRACE, patients who had wall motion indices of 1.2 or lower, which corresponds roughly to an ejection fraction of 35% or less, had a 1-year mortality of 34% and a 2-year mortality of more than 40%. Patients who had better ventricular function fared appreciably better.

#### Comparing Results in Selected and Unselected Populations

Why is the effect of ACE inhibitors poor in studies of unselected MI populations, such as GISSI-3 and ISIS-4, when compared with that in trials of

selected MI populations? About 20% to 30% of patients included in GISSI-3 and ISIS-4 were similar to those studied in AIRE and TRACE, noted Dr. Ball. Because the decreases in mortality in GISSI-3 and ISIS-4 were only about one third those seen in AIRE and TRACE, he conjectured that the positive effect of the ACE inhibitor was being diluted in the GISSI-3 and ISIS-4 trials because they treated all post-MI patients, not just those at higher risk.

In ISIS-4, physicians had to indicate whether patients had evidence of heart failure. When the results are stratified according to the presence or absence of heart failure, mortality decreases from 16% in the placebo group to 14.2% in the captopril group among patients with heart failure, although the difference is not significant (Table 2). On the other hand, no difference in mortality is observed between the captopril (6% mortality) and placebo (6.3% mortality) groups in patients without evidence of heart failure.

Other evidence also indicates that only certain patients benefited from ACE inhibitor treatment in the ISIS-4 study. Patients with anterior infarcts had a substantial reduction in mortality with treatment, whereas no evidence of benefit exists for patients with inferior infarcts. In addition, the ISIS-4 results suggest that certain MI patients may be harmed by ACE inhibitor treatment. Patients with low blood pressure who were treated with captopril had a slightly higher mortality rate than those who received placebo. Profound hypotension was noted in 10% of patients in the captopril group compared with only 5% of those in the placebo group. "You do not want to give a patient who has just had a heart attack a drug that produces profound and uncontrolled hypotension," said Dr. Ball. "I suggest that one of the harms produced by dropping blood pressure would be to increase the risk of reinfarction. In fact, there are more reinfarcts in the captopril-treated group than in the placebo group in ISIS-4."

Results from other trials, such as SAVE and the Studies of Left Ventricular Dysfunction (SOLVD), suggest that ACE inhibitors may prevent reinfarction. In SAVE, the risk of recurrent MI was reduced by 25% with captopril treatment. If this benefit can be proved, it may provide the rationale for treating a broader group of patients than just those with left ventricular dysfunction or others at higher risk.

Another potential argument for more widespread use of ACE inhibitors after MI is the observation that decreases in mortality occurred within the first 24 hours of ACE inhibitor treatment in GISSI-3 and ISIS-4. In GISSI-3, 21 fewer deaths occurred on days 0 through 1 in the lisinopril group than the placebo group. Some 27.6% of the lives saved with treatment were saved in the first day after onset of symptoms, and 84% were saved within the first week. Simi-

**Table 2.** Mortality According to Absence or Presence of Heart Failure Before Randomization in Patients Enrolled in ISIS-4

| Heart Failure | Mortality (%) |         | Significance Level |
|---------------|---------------|---------|--------------------|
|               | Captopril     | Placebo |                    |
| Yes           | 14.2          | 16.0    | NS                 |
| No            | 6.0           | 6.3     | NS                 |

ISIS-4 = Fourth International Study of Infarct Survival; NS = not significant

larly for ISIS-4, 44 fewer deaths occurred on days 0 through 1 among patients treated with captopril compared with those given placebo. Almost one third of the lives were saved on the first day of treatment; 56% were saved during the first week after symptom onset.

An intriguing and consistent, albeit post hoc, observation emanating from the ISIS-4 and GISSI-3 findings is that early cardiac rupture may be lessened by administering ACE inhibitors. As early as 1986, the first ISIS trial demonstrated that intravenous atenolol lowered mortality from 4.6% to 3.9%. Virtually all the deaths in ISIS-1 occurred on day 1, which suggests that

atenolol prevented myocardial rupture in some manner. "Perhaps by suppressing sympathetic activity, ACE inhibi-

*"You can be a GISSI or ISIS doctor and treat everybody after an infarct with an ACE inhibitor, or you can be more of a thinking clinician and get more benefit from treatment by choosing your patients carefully."*

tors can prevent rupture of the myocardium in the first 24 hours," Dr. Ball remarked.

Although claims that ACE inhibitors can reduce MI have led to cogent arguments for more widespread use of these drugs, Dr. Ball closed his talk by challenging clinicians to select post-MI patients carefully for ACE inhibitor treatment. "You can be a GISSI or ISIS doctor and treat everybody after an infarct with an ACE inhibitor, or you can be more of a thinking clinician and get more benefit from treatment by choosing your patients carefully." The final answer to appropriate use of post-MI ACE inhibition may come from large-scale trials in hypertensive and other high-risk patient populations.

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