JACC Vol. 25, No. 7 (Supplement)
June 1995:47S–51S

Indications for Immediate Angiotensin-Converting Enzyme Inhibition in Patients With Acute Myocardial Infarction

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When initiated a few days after myocardial infarction, angiotensin-converting enzyme inhibition exerts beneficial effects on survival and morbidity in patients with asymptomatic left ventricular systolic dysfunction or symptomatic heart failure. During the acute phase of a myocardial infarction, angiotensin-converting enzyme inhibition appears to be well tolerated, to prevent the development of heart failure in patients with asymptomatic left ventricular systolic dysfunction and to improve the hemodynamic and clinical variables of heart failure when present. Accordingly, early angiotensin-converting enzyme inhibition is clearly indicated in patients with acute myocardial infarction associated with asymptomatic left ventricular dysfunction or clinical evidence of heart failure. Angiotensin-converting enzyme inhibition may also be beneficial when thrombolytic agents fail to restore coronary patency in patients with acute myocardial infarction.

(J Am Coll Cardiol 1995;25[Supplement]:47S–51S)

Over the past 15 years, angiotensin-converting enzyme inhibitors have been found to be increasingly beneficial in patients with chronic congestive heart failure (1). Initially, angiotensin-converting enzyme inhibitors were evaluated in patients with severe symptoms of congestive heart failure who were in New York Heart Association functional class III or IV (2,3). Later, angiotensin-converting enzyme inhibition was considered for patients with milder symptoms compatible with functional class I or II and, more recently, for patients with asymptomatic left ventricular systolic dysfunction (4–6). Although the prevention arm of the Studies of Left Ventricular Dysfunction (SOLVD) trial (5) failed to show a benefit of long-term administration of enalapril on mortality, morbidity, in terms of development of congestive heart failure or hospital admission for congestive heart failure, was substantially reduced in patients receiving enalapril compared with those receiving placebo.

While the indications for angiotensin-converting enzyme inhibition in patients with chronic left ventricular systolic dysfunction with or without congestive heart failure were widening, the role of angiotensin-converting enzyme inhibition was being evaluated in patients with recent acute myocardial infarction (7). Because congestive heart failure in North America is most often related to coronary artery disease, acute myocardial infarction and the resulting left ventricular systolic dysfunction are a clear therapeutic target if one has it in mind to significantly alter the natural history of congestive heart failure (8).

Large Randomized Studies of Angiotensin-Converting Enzyme Inhibitors in Patients With Acute Myocardial Infarction

In 2,231 patients with a left ventricular ejection fraction <40% and without noticeable symptoms of congestive heart failure, the Survival and Ventricular Enlargement (SAVE) trial (9) clearly demonstrated the benefits of long-term administration of captopril on overall mortality and prevention of symptomatic congestive heart failure and recurrent myocardial infarction over that observed in patients receiving placebo (Table 1). Administration of captopril or placebo was initiated on average 11 days after the acute event, once the eventual need for coronary angioplasty or bypass surgery had been assessed and performed if needed. In that regard, data from the SAVE trial are pertinent to asymptomatic patients in the convalescent phase of an acute myocardial infarction and do not help to define the indications for immediate angiotensin-converting enzyme inhibition in patients with evolving myocardial infarction. Of note, the benefit of captopril on mortality became apparent only after 12 months and was highly significant after an average follow-up period of 42 months.

A double-blind, placebo-controlled trial of similar size to that of SAVE recently reported (10) the benefits of angiotensin-converting enzyme inhibition with ramipril on mortality and morbidity in patients with acute myocardial infarction and transient evidence of heart failure. The Acute Infarction

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0735-1097/95/$9.50
0735-1097(95)00103-B

Table 1. Clinical Characteristics and Main Outcomes in the SAVE, AIRE, SMILE, CONSENSUS II and GISSI-3 Trials

Trial*	No. of Pts	Clinical Characteristics	ACE Inhibitor	Follow-Up Duration	Risk Reduction in All-Cause Mortality	Risk Reduction in Severe CHF	Risk Reduction in Recurrence of MI
SAVE (9)	2,231	11 d post-MI; no ischemia or failure; EF ≤40%	Captopril	42 mo	19%	22%	25%
AIRE (10)	2,006	5 d post-MI; clinical or radiographic heart failure	Ramipril	15 mo	27%	19%	NS
SMILE (11)	1,556	1st 24 h of ant MI; SBP >100 mm Hg	Zofenopril	6 wk	NS	49%	NS
GISSI-3 (12)	19,394	1st 24 h; all comers	Lisinopril	6 wk	11%	NA	NA
CONSENSUS II (15)	6,090	1st 24 h; all comers	Enalaprilat	6 mo	NS	29%	NS

*Numbers in parentheses are reference numbers. ACE = angiotensin-converting enzyme; AIRE = Acute Infarction Ramipril Efficacy trial; ant = anterior; CHF = congestive heart failure; CONSENSUS II = Cooperative New Scandinavian Enalapril Survival Study; d = days; EF = ejection fraction; GISSI-3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; MI = myocardial infarction; NA = not applicable; Pts = patients; SAVE = Survival and Ventricular Enlargement trial; SBP = systolic blood pressure; SMILE = Survival of Myocardial Infarction Long-Term Evaluation trial.

Ramipril Efficacy (AIRE) study investigators found that ramipril reduced overall mortality by 27% and resistant congestive heart failure by 19% compared with placebo. Of interest, the benefit of ramipril on mortality became apparent as early as 30 days after the acute event and was highly significant after 15 months of follow-up.

Administration of ramipril or placebo was initiated from 3 to 10 days after the acute event. Thus, as noted with the SAVE trial, data from the AIRE study are pertinent to the convalescent phase of myocardial infarction for patients who, at one point, had clinical or radiographic evidence of heart failure.

More recently, the effects of early angiotensin-converting enzyme inhibition with zofenopril on the prevention of severe congestive heart failure were evaluated in 1,556 patients with an acute anterior wall myocardial infarction by the Survival of Myocardial Infarction Long-Term Evaluation trial (SMILE) investigators (11). Administration and dose titration of the study drug were done with great care to avoid systemic hypotension, that is, systolic blood pressure <100 mm Hg. During the 6 weeks of double-blind treatment, 34 patients (4.3%) developed severe congestive heart failure in the placebo group, and 17 patients (2.2%) did so in the zofenopril group, with a risk reduction of 49% (95% confidence interval [CI] 11% to 171%, p = 0.018). In agreement with the findings of the SAVE investigators after 42 months and the AIRE investigators after 15 months, the overall mortality tended to be decreased in patients in the zofenopril group compared with that in the placebo group, that is, 50 versus 60 deaths, respectively, with a risk reduction of 22% (95% CI −12% to −48%, p = 0.171). Administration of zofenopril or placebo was started within the first 24 h of onset of acute myocardial infarction. Although the incidence of systolic blood pressure <100 mm Hg was greater in the zofenopril group, the rate of discontinuation of the study drug because of significant hypotension was not increased in the zofenopril group compared with that for the placebo group (3.8% vs. 2.7%, p = NS).

In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) trial (12), patients with acute myocardial infarction in Killip class 1 or 2 who were treated within 24 h of symptoms with lisinopril had a lower mortality rate at 6 weeks than those treated with placebo (6.3% vs. 7.1%, p = 0.03). Of interest, these findings were observed in a population intensively exposed to recommended treatments, including thrombolysis, beta-blockade and aspirin. Finally, preliminary results from the Collaborative Group Fourth International Study of Infarct Survival (ISIS-4) (13,14) also indicate a lower mortality rate at 35 days in patients with acute myocardial infarction treated with captopril than that noted in patients receiving placebo (7.1% vs. 7.6%, p < 0.02).

In contrast to the results of the SAVE, AIRE, SMILE, GISSI-3 and ISIS-4 trials, the results of the Cooperative New Scandinavian Enalapril Study (CONSENSUS II) (15) were negative. The CONSENSUS II trial failed to demonstrate any benefit of enalapril therapy initiated within the first 24 h of acute myocardial infarction compared with placebo. Administration of enalapril or placebo was initiated early in the course of myocardial infarction, first by parenteral form and subsequently by the oral route. The Safety Committee, which had concerns about the possible adverse effects of enalapril in elderly patients with early hypotension, decided to interrupt the trial after a 6-month follow-up, which in view of the relatively small number of patients enrolled compared with megatrials, may have been too short to detect a reduction in mortality with enalapril in all patients with acute myocardial infarction. Surprisingly, the subgroup analysis of the CONSENSUS II findings did not document any benefit of enalapril in the subset of patients with a history of congestive heart failure, pulmonary edema or heart failure after admission. These subsets of patients were quite small (6%, 2% and 18%, respectively).

Positive Studies (SAVE, AIRE, SMILE, GISSI-3, ISIS-4) Versus Negative Studies (CONSENSUS II)

The contrasting findings between the SAVE, AIRE, SMILE, GISSI-3 and ISIS-4 trials on the one hand and the CONSENSUS II trial on the other probably result from multiple factors. The patient population was most likely the most influential factor to explain the differences in outcome between the SMILE and CONSENSUS II trials. Patients enrolled in the SMILE were more likely to develop left ventricular dysfunction and heart failure because of the anterior wall location of myocardial damage than those enrolled in the CONSENSUS II trial, although the timing of study drug adminstration was similar in both trials, that is, the first 24 h. Although the CONSENSUS II, GISSI-3 and ISIS-4 trials are similar with regard to the early administration of angiotensin-converting enzyme inhibition during the course of the myocardial infarction, these studies differ on the number of patients enrolled, which is at least threefold greater in the GISSI-3 and ISIS-4 trials than in CONSENSUS II. The major difference among the SAVE, AIRE and CONSENSUS II trials is obviously the duration of follow-up: a maximum of 42 months versus a minimum of 6 months. In addition, therapy with captopril or ramipril was initiated during the convalescent phase of myocardial infarction in the SAVE and AIRE trials, but enalaprilat and later enalapril were administered very early during the course of myocardial infarction in the CONSENSUS II trial. Thus, acute hypotension induced by angiotensin-converting enzyme inhibition and the resulting risk of exacerbating myocardial ischemia during an evolving myocardial infarction may have occurred in patients enrolled in the CONSENSUS II, but it was less an issue in the patients receiving captopril or ramipril in the SAVE and AIRE trials.

Acute Hemodynamic Effects of Angiotensin-Converting Enzyme Inhibition in Acute Myocardial Infarction

Few investigators have studied the hemodynamic effects of early angiotensin-converting enzyme inhibition in patients with evolving myocardial infarction (16–19). McAlpine et al. (16) evaluated nine with an acute myocardial infarction and left ventricular failure who were treated with captopril within the first 48 h of symptoms. Mean systemic arterial and pulmonary capillary wedge pressures decreased from 84 to 76 mm Hg and from 26 to 20 mm Hg, respectively, although cardiac output did not change. Severe systemic hypotension did not occur. Ray et al. (17) studied the hemodynamic effects of early captopril or placebo administration in 99 hemodynamically stable patients with acute myocardial infarction. Captopril, started between 6 and 24 h after the acute event, was not associated with significant hypotension in patients whose baseline pulmonary capillary wedge pressure averaged 16 mm Hg. The reductions in mean systemic arterial and pulmonary capillary wedge pressures were similar to those noted by McAlpine et al. (16): 8 to 10 mm Hg and 4 to 6 mm Hg, respectively.

In a randomized study of captopril versus placebo in patients with acute myocardial infarction treated with intravenous nitroglycerin, Tranchesi et al. (18) demonstrated that concomitant administration of captopril and nitroglycerin was safe in the early hours of a noncomplicated anterior wall myocardial infarction. However, only patients with a mean systemic arterial pressure >70 mm Hg, cardiac index >2.2 liters/min per m^2 and pulmonary capillary wedge pressure >10 mm Hg were included in the trial. Finally, in a randomized, placebo-controlled trial involving 38 patients with acute myocardial infarction, Nabel et al. (19) reported that simultaneous administration of intravenous captopril and recombinant tissue-type plasminogen activator did not lead to any hemodynamic complications. However, intravenous administration of captopril had to be discontinued in only one patient. Of note, three patients in the captopril group underwent coronary bypass surgery before discharge, but none did in the placebo group.

Potential Adverse Effects of Initiating Angiotensin-Converting Enzyme Inhibition in the First Hours of an Acute Myocardial Infarction

The published data indicate that although it is associated with a decrease in mean systemic arterial pressure averaging 10 mm Hg, immediate angiotensin-converting enzyme inhibition is hemodynamically and clinically well tolerated in patients with acute myocardial infarction. The coronary perfusion pressure gradient, which is the difference between distal coronary and left ventricular diastolic pressures, may be preserved or even enhanced by angiotensin-converting enzyme inhibition in patients with an elevated left ventricular diastolic pressure. In these patients, the detrimental effect of a decrease in systemic arterial pressure on the coronary perfusion gradient is likely to be offset by a concomitant reduction in left ventricular diastolic pressure. In contrast, coronary perfusion pressure gradient may decrease in patients with a normal or low left ventricular diastolic pressure. Indeed, besides directly decreasing arteriolar resistances, angiotensin-converting enzyme inhibition may precipitate a decrease in stroke volume as left ventricular diastolic pressures decrease in patients whose left ventricles are operating on the steep part of the Starling curve. Such reduction in coronary perfusion pressure gradient may lead to or exacerbate myocardial ischemia in patients with critical coronary obstruction.

Indications for Early Initiation of Angiotensin-Converting Enzyme Inhibition in Acute Myocardial Infarction

The presence of signs and symptoms of left ventricular systolic dysfunction is clearly an important determinant of the

JACC Vol. 25, No. 7 (Supplement)
June 1995:47S–51S

early use of angiotensin-converting enzyme inhibition in patients with acute myocardial infarction. Immediate angiotensin-converting enzyme inhibition is the pharmacologic intervention of choice in patients who develop clinical heart failure in the early hours of an acute myocardial infarction. The alternative approach, administration of potent loop diuretic drugs, has the disadvantage of further activating the renin–angiotensin–aldosterone system and thereby increasing cardiac afterload and paradoxically promoting sodium retention once the short-lived effects have dissipated (20,21). Potent loop diuretic drugs can also result in substantial intravascular depletion in patients chronically treated with diuretic drugs who, during the course of a myocardial infarction, cannot ingest fluids because of nausea and vomiting. Of note, emergency room administration of excessive doses of loop diuretic drugs can lead to intravascular depletion in patients with acute myocardial infarction who were euvolemic before their acute coronary occlusion. In turn, intravascular depletion and stimulation of the renin–angiotensin–aldosterone system substantially increase the likelihood of symptomatic hypotension when angiotensin-converting enzyme inhibition is initiated shortly after loop diuretic therapy. Thus, in patients who are moderately symptomatic with acute left ventricular dysfunction, oral administration of a short-acting angiotensin-converting enzyme inhibitor at low dose or careful intravenous administration of 1 to 2 mg of enalaprilat is the preferred therapeutic approach. The use of potent loop diuretic therapy should be reserved for patients with acute left ventricular dysfunction who are severely symptomatic, such as those with pulmonary edema, or to patients whose symptoms fail to be relieved by angiotensin-converting enzyme inhibition. When angiotensin-converting enzyme inhibition at low dose is well tolerated, the dose can be progressively increased at 8-h intervals to full angiotensin-converting enzyme inhibition. When systolic arterial pressure is borderline, ranging from 90 to 100 mm Hg, or when symptomatic hypotension occurs, angiotensin-converting enzyme inhibition should be withheld and then resumed when feasible at a low dose.

The indications for early angiotensin-converting enzyme inhibition in patients with acute myocardial infarction with normal or near-normal left ventricular function and without clinical evidence of heart failure have yet to be defined. Multiple factors are responsible for the progressive dilation of the left ventricle after an acute myocardial infarction. The size and location of the myocardial infarction and the patency of the infarct-related artery are probably the most important factors in patients with normal or near-normal left ventricular end-diastolic dimension and ejection fraction (22). Thus, patients with large anterior wall myocardial infarctions in whom thrombolysis or revascularization, or both, was unsuccessful or not attempted should be treated with angiotensin-converting enzyme inhibitors for at least 3 months (23–25). In view of the variability in extent and time of the left ventricular remodeling process after myocardial infarction, two-dimensional echocardiography should be repeated at 3 months, and the need for angiotensin-converting enzyme inhibition should be reassessed (26,27). In contrast to patients with a large myocardial infarction and left ventricular systolic dysfunction, patients with a small myocardial infarction, normal left ventricular dimension and function and a patent infarct-related coronary artery are unlikely to derive substantial benefit from immediate angiotensin-converting enzyme inhibition.

References

1. Armstrong PW, Moe GW. Medical advances in the treatment of congestive heart failure. Circulation 1994;88:2941–52.
2. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory congestive heart failure. J Am Coll Cardiol 1983;2:755–63.
3. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.
4. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
5. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
6. Kleber FX, Niemoller L, Doering W. Impact of converting enzyme inhibition on progression of chronic heart failure: results of the Munich Mild Heart Failure Trial. Br Heart J 1992;67:289–96.
7. Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. N Engl J Med 1988;319:80–6.
8. Kannel WB. Epidemiological aspects of heart failure. Cardiol Clin 1989;7:1–9.
9. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1992;327:669–77.
10. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821–8.
11. Ambrosioni E, Borghi C, Magnani B, on behalf of the SMILE Study Investigators. Effects of the early administration of zofenopril on mortality and morbidity in patients with anterior myocardial infarction. Results of the Survival of Myocardial Infarction Long-Term Evaluation Trial. N Engl J Med 1995;332:80–5.
12. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet 1994;343:1115–22.
13. ISIS-4 Collaborative Group. Fourth International Study of Infarct Survival: protocol for a large simple study of the effects of oral mononitrate, of oral captopril and of intravenous magnesium. Am J Cardiol 1991;68:87D–100D.
14. Lonn EM, Yusuf S, Jha P, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. Circulation 1994;90:2056–9.
15. Swedberg K, Held P, Kjekshus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med 1992;327:678–84.
16. McAlpine HM, Morton JJ, Leckie B, Dargie HJ. Haemodynamic effects of captopril in acute left ventricular failure complicating myocardial infarction. J Cardiovasc Pharmacol 1987;9 (Suppl 2):S25–S30.
17. Ray SG, Pye M, Oldroyd KG, et al. Early treatment with captopril after acute myocardial infarction. Br Heart J 1993;69:215–22.
18. Tranchesi B Jr, Santos RD, Caramelli B, et al. Early administration of captopril and nitroglycerin in combination after acute myocardial infarction: an invasive haemodynamic study. Eur Heart J 1993;14:90–5.
19. Nabel EG, Topol EJ, Galeana A. A randomized placebo-controlled trial of

combined early intravenous captopril and recombinant tissue-type plasminogen activator therapy in acute myocardial infarction. J Am Coll Cardiol 1991;17:467–73.

20. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987;57:17–22.
21. Remme WJ, Look MP, Bootsma M, et al. Neurohumoral activation during acute myocardial ischaemia. Effects of ACE inhibition. Eur Heart J 1990;11 Suppl B:62–71.
22. Gaudron P, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors. Circulation 1993;87:755–63.
23. Cigarroa RG, Lange RA, Hillis LD. Prognosis after acute myocardial infarction in patients with and without residual anterograde coronary blood flow. Am J Cardiol 1989;64:155–60.
24. Stone PH, Raabe DS, Jaffe AS, et al. Prognostic significance of location and type of myocardial infarction; independent adverse outcome associated with anterior location. J Am Coll Cardiol 1988;11:453–63.
25. Hochman JS, Srichai MB, Picard M, et al, for the CAPTIN Investigators. Very early ACE inhibition reduces progressive left ventricular dilation when tPA fails to establish early reperfusion during acute anterior myocardial infarction [abstract]. Circulation 1994;90 Suppl I:I-19.
26. St John Sutton M, Pfeffer MA, Plappert T, et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation 1994;89:68–75.
27. Picard MH, Wilkins GT, Ray PA, Weyman AE. Natural history of left ventricular size and function after acute myocardial infarction. Assessment and prediction by echocardiographic endocardial surface mapping. Circulation 1990;82:484–94.