

Myocardial Infarction and Heart Failure
The Common Ground

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During the past decade, the management of myocardial infarction and heart failure has merged as a result of clinical research efforts. In the setting of acute coronary care, it is established that thrombolysis can limit infarct size, improve ventricular remodeling, and reduce the likelihood of heart failure and mortality. During the same period, interest was focused on earlier intervention in clinical congestive heart failure. Despite demonstrable improvements in heart failure treatment and the introduction of angiotensin converting enzyme inhibitors in particular, the prognosis for heart failure still remained poor, principally because patients usually had severe ventricular dysfunction by the time clinical congestion was manifest. Improved understanding of the processes leading to progressive ventricular dilatation and dysfunction and realization of the prognostic importance of ventricular volumes have led to a preventive approach to heart failure treatment following myocardial infarction.

Intervention to prevent heart failure may be considered at varying stages following myocardial infarction. The timing of intervention is important as different processes are amenable to treatment at different times. The initial emphasis with thrombolytic treatment is to restore infarct artery patency and limit infarct size. However, once coronary occlusion has occurred and infarction has evolved, treatment is directed toward optimizing oxygen supply and demand and reducing ventricular wall stress. Prevention of ongoing ischemia, recurrent infarction, arrhythmias, and sudden death are related aims that are relevant in the long term.

Following experimental and clinical studies that demonstrated that converting enzyme inhibition was effective in reducing ventricular dilatation following myocardial infarction,1-4 large trials were commenced to determine the effects of such treatment on the later occurrence of heart failure and mortality. Several of these studies5-7 together with the initial clinical studies2-4 and other data related to the ventricular remodeling process, including that provided by Gaudron and colleagues in this issue of Circulation,8 allow a clear clinical perspective and treatment guidelines.

The Survival and Ventricular Enlargement (SAVE) trial8 included patients with definite myocardial infarction and ejection fraction of <40%. Treatment with the converting enzyme inhibitor captopril for a minimum of 2 years reduced total mortality from 25% in the placebo control group to 20% with active captopril treatment (19% reduction; 95% CI, 3-32%; p = 0.019). Cardiovascular mortality was reduced to a similar extent in the treatment group, heart failure requiring open converting enzyme inhibitor treatment or hospital admission diminished by 37% and 22%, respectively, and recurrent myocardial infarction was reduced by 25%. Importantly, patients with continuing myocardial ischemia required investigation and consideration of coronary revascularization or angioplasty before randomization (which occurred 3-16 days after myocardial infarction).

The Studies of Left Ventricular Dysfunction (SOLVD) prevention trial9 was similar in that it included symptom-free patients with reduced ejection fraction (<35%). However, not all had ischemic heart disease, and randomization was months after myocardial infarction in many cases. Although enalapril treatment significantly reduced the incidence of heart failure and hospital admission, and a trend toward reduced mortality was observed, this was not significant, possibly due to the later intervention.

The Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II)7 assessed the effects of early administration of enalapril intravenously and then orally, beginning within 24 hours of the onset of symptoms of infarction. Mortality after 6 months' treatment was similar in treated and control groups. This neutral outcome raised the possibility that such immediate intervention may have had harmful effects that offset any later benefit from treatment. Early hypotension and reduced coronary perfusion could worsen ongoing ischemia in some cases. Neurohormonal activation may be truly compensatory initially although deleterious later, and thus acute neurohormonal blockade may not necessarily be advantageous. However, the observation from the SAVE trial8 that treatment benefit was not demonstrated until after 6 months suggests that a longer treatment or observation period in CONSENSUS II may have produced a positive outcome.

Of further interest from these studies is the finding that both the SAVE8 and SOLVD trials9 showed a similar significant reduction of ~25% in recurrent myocardial infarction, and also in unstable angina in the case of the SOLVD trial.9 This suggests an additional
protective vascular and possible antiatherosclerotic role for converting enzyme inhibition that is supported by basic experimental\textsuperscript{10–12} and animal studies.\textsuperscript{13,14}

Summation of all these clinical data now allows the recommendation of converting enzyme inhibitor treatment for selected patients following myocardial infarction. Although the results of the SAVE trial\textsuperscript{6} with captopril are most definitive, it is likely that the treatment effect is a “class effect,” and the differences among the mortality studies are attributable to patient selection, timing of intervention, and duration of treatment follow-up. Very early (immediate) treatment could theoretically confer maximum benefit in preventing initial infarct expansion and ventricular dilatation, but such a generalized, nonselective approach may exacerbate hypotension in some cases, and coadministration of thrombolysis and other treatments may be difficult. Also, many patients destined to have small infarcts with no subsequent ventricular dilatation will receive the treatment unnecessarily. In the study by Gaudron and colleagues,\textsuperscript{8} left ventricular dilatation (defined as an increase in radionuclide end-diastolic volume index of $\geq 8\%$ from the preceding assessment) was progressive, i.e., continued beyond 6 months, in only $20\%$ of a series of patients without clinical heart failure after a first myocardial infarction. A further $26\%$ had “limited” dilatation to 6 months, which then stabilized, and $54\%$ had no significant dilatation from baseline. This study, although of a small series, is valuable because it distinguished the patterns of dilatation over a longer period than previously studied. Patients with limited (compensatory) dilatation showed early restoration of depressed stroke volume index at 4 weeks, but progressive interval increases in wedge pressure during long-term exercise. With progressive dilatation, stroke volume index was also restored by 4 weeks, but it progressively reduced thereafter. Ejection fraction fell, whereas filling pressures and systemic vascular resistance increased progressively after 6 months.

While considering a more selective delayed intervention approach, it is important to recognize that most of the early ventricular dilatation (i.e., that which occurs during the first 6 months) is present at 1 week and certainly 1 month following infarction.\textsuperscript{2,4} Much of the potential benefit from treatment may be lost if treatment is unnecessarily delayed. Thus, selection of stable patients without ongoing ischemia for treatment after 24–48 hours is most appropriate. Treatment should be considered for patients with larger Q wave anterior infarcts in particular, although infarct size rather than location is the most important determinant of ventricular dilatation. Noninvasive assessment of left ventricular volumes and function should be routine to guide management decisions. While left ventricular volumes are of primary importance, in the absence of reliable quantitation, decisions can reasonably be based on ejection fraction measurement. Patients with ejection fraction of <40–45\% should be considered because benefit from treatment increases greatly with progressively lower ejection fraction. A test dose of $6.25–12.5$ mg captopril according to blood pressure is appropriate and generally well tolerated, increasing gradually to $25–50$ mg t.i.d.

Remaining questions that are the subject of ongoing studies are related to refinement of dosage regimens and timing. Reported studies to date have generally used medium-to-high doses of converting enzyme inhibitors, and it is possible that a low dose may be sufficient for a remodeling effect. The comparative and additive effects of nitrates and converting enzyme inhibitors are also important to assess and should be determined by major studies currently in progress. Nitrates may be a very appropriate alternative to converting enzyme inhibitors early following myocardial infarction, particularly where there are concerns related to ongoing ischemia or hypotension. The choice between converting enzyme inhibition, $\beta$-blockade, and a combination of both following myocardial infarction is a matter for careful clinical judgment. Benefit from $\beta$-blockade alone is clearly proven,\textsuperscript{15} and these treatments may be complementary, providing benefit through different mechanisms. While the benefit of converting enzyme inhibition appears to be additive to $\beta$-blockers,\textsuperscript{9} it is unlikely that this will be formally assessed in a definitive study. For many patients, a low-dose combination may be the optimal treatment but will require careful monitoring and dosage adjustment. It is noteworthy that while the use of converting enzyme inhibitors has been extended from the treatment of heart failure to the period following myocardial infarction, conversely, the potential application of $\beta$-blockers has extended in the opposite direction, and their use in heart failure remains a topic of current clinical research interest.\textsuperscript{16}

References


**KEY WORDS**

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