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EDITORIAL COMMENT

Angiotensin-Converting Enzyme Inhibitor Treatment After Myocardial Infarction

A Selective Approach for Maximum Benefit*

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Early survival following myocardial infarction (MI) has improved significantly over the past 20 years, due in part to medical treatments including thrombolysis, aspirin and beta-blockade. Now, more MI survivors are at risk from the subsequent development of heart failure (1). The clinical entity of heart failure in such patients is a problem and one to which much research attention, both preventive and palliative, has been directed recently.

Heart failure following MI results from changes in ventricular size, shape and structure due to myocardial damage. This process has been termed ventricular remodeling and though initially adaptive and compensatory, it becomes deleterious over time causing progressive ventricular dysfunction.

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Within days of acute coronary occlusion and MI, remodeling may begin with infarct expansion and compensatory hypertrophy of the noninfarcted regions. This is accompanied or followed by a phase of global ventricular dilatation occurring over months and involving both infarcted and noninfarcted segments. These processes establish a new pressure-volume relationship in the damaged ventricle, preserving stroke volume despite a reduction in left ventricular (LV) ejection fraction and tending to continue the ventricular dilatation.

Central to the process of remodeling and the pathophysiology of heart failure is activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. This occurs early following acute MI, and the resultant vasoconstriction, volume expansion and ventricular dilatation increases wall stress, which is a major stimulus for continued ventricular remodeling.

The degree of remodeling after MI can be determined clinically, by assessing LV size and function using echocardiography or radionuclide ventriculography. Left ventricular volumes, and particularly end-systolic volume, are prognostically important, more so than LV ejection fraction or infarct size (2). Prognosis is most favorable in patients without LV dilation, and thus prevention of remodeling after MI is a major therapeutic objective to improve long-term outcomes.

Appropriately timed interventions such as thrombolysis or therapeutic alterations to reduce LV loading conditions can favorably influence LV remodeling early and late after infarction. Initial measures to limit infarct size using thrombolysis showed the degree of infarct artery perfusion after MI to be more important than infarct size itself in predicting volume change. Occlusion of the infarct-related artery (IRA) was associated with greater LV volumes and a more spherical LV shape despite minor differences in ejection fraction (3). Treatment to reperfuse the IRA should therefore be considered the most effective immediate strategy to prevent LV remodeling and improve subsequent mortality and morbidity (4,5).

Additional measures to limit infarct size and reduce remodeling include the use of nitroglycerin or angiotensin-converting enzyme (ACE) inhibitors. Nitroglycerin can limit infarct size, infarct expansion and remodeling, but large-scale studies have not demonstrated clear mortality benefit following acute MI (6,7). However, clinical trials have shown that ACE inhibitors can improve survival in patients with reduced LV systolic function or heart failure after MI (8,9). Initial evidence that ACE inhibitors attenuated LV dilatation after MI came from studies in selected patients with LV impairment, anterior MI or Q-wave MI (10–12). However, evidence that ACE inhibitor treatment improves LV remodeling in patients with a patent IRA and in studies in which high proportions of patients received thrombolysis has been conflicting (13,14). Benefit from ACE inhibitor treatment thus seems to be greatest in patients at higher risk of LV dilatation due to more extensive infarction, particularly those with anterior or Q-wave infarction with an occluded IRA.

The potential for progressive ventricular dilatation exists from the time of acute coronary occlusion and infarction. Very early treatment may be most effective but will not benefit all patients and is not without hazard. Large intervention trials of ACE inhibitor treatment early and nonselectively after MI showed that approximately one third of the modest survival benefit evident at 35 days was apparent in the first 24 h following intervention (6,7). In CONSENSUS II, however, no mortality benefit was shown when ACE inhibitor treatment was given very early after MI. A possible proischemic effect resulting from hypotension secondary to the treatment was suggested as the likely mechanism offsetting any benefit (15).

Although more than 120,000 patients with MI have been

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involved in clinical trials using ACE inhibitors, important questions remain regarding the use of these agents. Optimal timing of ACE inhibitor treatment after MI and the exact mechanisms of benefit have not been completely resolved. In this context, the article by de Kam et al. (16) provides useful guidance. This group reports a meta-analysis combining three trials in which ACE inhibitor treatment was given very early after anterior MI in patients also receiving thrombolysis, aspirin and beta-blockade. Echocardiography was used to assess LV volume change over the three months following MI. Left ventricular dilation was not significantly affected by ACE inhibitor treatment overall. However, in the subgroup of patients who had "bedside" clinical evidence of lack of reperfusion, LV dilation was significantly attenuated. This article provides additional evidence supporting increased benefit of ACE inhibitor treatment in certain patient groups at high risk of developing LV dilation. The safety of adding ACE inhibitor treatment to the cocktail of drugs currently routinely recommended following acute MI, despite relatively low blood pressure, has also been confirmed by this article.

Previously, very early initiation of ACE inhibitor treatment for all patients without significant hypotension after MI, with a policy of subsequent review of treatment, has been recommended (17). Despite this recommendation, a more selective approach has often been favored as more practical. This meta-analysis helps further to identify high risk subgroups of patients who will benefit most and should be treated with an ACE inhibitor without undue delay. A more targeted policy is now supported for the commencement of ACE inhibitor treatment as soon as practical in patients with large or anterior infarcts, or with clinical evidence of lack of reperfusion, as well as in patients with significant LV impairment or heart failure. This "selective" approach to ACE inhibitor treatment can be reviewed later. Patients with persisting LV dysfunction will require continuation of ACE inhibitor therapy while those with normal LV function and a favorable risk profile following the acute event might discontinue treatment. However, beyond considerations of LV remodeling, the recent demonstration of clear benefits from ACE inhibitor treatment in high risk patients with atherosclerotic disease but preserved LV function (18) indicates additional cardiovascular protective effects from ACE inhibitor treatment and extends the indications for such treatment further.

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