REVIEW

Should angiotensin converting enzyme (ACE) inhibitors be used routinely after infarction? Perspectives from the Survival and Ventricular Enlargement (SAVE) Trial

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Left ventricular remodelling after infarction

Many factors influence the survival of patients after myocardial infarction, but the single most important clinical determinant is left ventricular function.¹⁻³ Left ventricular function correlates closely with the size of the region of myocyte necrosis in human and in animal infarction models.^{4,5} Recently, the cellular processes occurring soon after acute myocardial infarction have become better understood. Viable myocytes adjacent to the necrotic area can remain dysfunctional or stunned for a long time.⁶ Within the first 72 hours the infarct zone stretches owing to slippage of necrotic myofilaments before the tensile strength of the infarct becomes altered by the deposition of collagen.⁷ Expansion of the infarction zone results in left ventricular dilatation, increased wall stress, and a fall in ejection fraction.^{4,8} Increased wall stress is a potent stimulus for left ventricular hypertrophy. When the hypertrophy is sufficient to normalise the increased wall stress, the left ventricular ejection function is restored towards normal. When the hypertrophy is insufficient to counteract the increased wall stress, however, left ventricular dilatation progresses and further deterioration in contractile function leads to early congestive heart failure and a poor outcome. This combination of left ventricular dilatation, hypertrophy, and alteration in cavity configuration, which has been termed left ventricular remodelling, begins early and may continue for months or even years.⁸ The impact of raised plasma concentrations of noradrenaline, renin/angiotensin, atrial natriuretic peptide, and a range of other neurohormones on left ventricular remodelling after infarction is currently under intensive investigation.⁹

Limitation of infarction size by restoration of flow

Over the past decade there have been many attempts to improve survival after acute myocardial infarction by limiting the size of the initial infarction, which lessens subsequent left ventricular dilatation and reduces the incidence of heart failure. These studies used two basic therapeutic strategies: first, early restoration of flow to the infarct-related coronary artery by thrombolysis or mechani-

cal intervention¹⁰⁻¹³ and secondly, early controlled reduction of left ventricular loading conditions.¹⁴ Because treatment with thrombolytic agents improved both early and late mortality after infarction in several multinational trials,¹⁰⁻¹³ it has become standard cardiological practice. Thrombolysis in re-establishing flow in the infarct-related coronary artery within the first few hours limits initial infarct size and lessens the extent of left ventricular remodelling.¹⁵ Patency of the infarct-related coronary artery or collateral flow to the infarct territory in the presence of total occlusion of the infarct-related artery plays an important but unexplained part in limiting left ventricular dilatation compared with infarcts of a similar size where there is total occlusion of the infarct artery and no collateral flow.¹⁶ Patency of the infarct artery has been associated with improved survival.¹⁷ The early use of aspirin after infarction has also increased survival.¹¹

Infarct limitation by alteration of left ventricular loading

Modification of left ventricular loading conditions produced by reducing mean arterial pressure in the immediate post-infarction period significantly limited infarct expansion, lessened ventricular dilatation, and improved ejection fraction in humans and laboratory animals.¹⁴ In humans these beneficial effects on left ventricular remodelling have translated into prolonged survival.¹⁴ Non-specific rather than specific adrenergic receptor blockers have also reduced mortality and reinfarction rates in several post-infarction trials, the presumed mechanism being a combination of reduction in left ventricular loading conditions, their negative chronotropic effects, and antidysrhythmic properties.^{18,19} The widespread use of calcium channel antagonists after infarction with equipotent effects on left ventricular loading conditions has not had beneficial effects on mortality, re-infarction rate, or left ventricular remodelling,²⁰ except in the Danish Acute Infarction Trial with Verapamil (DAVIT II) in patients without congestive heart failure.²¹ Use of either verapamil or diltiazem in patients with heart failure after infarction is associated with increased adverse cardiovascular events.^{21,22} The next logical step was to investigate the

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effect of angiotensin converting enzyme inhibitors on left ventricular remodelling after infarction, because they combined afterload reduction with the potentially useful blocking action on neurohormonal activation, including direct effects upon angiotensin II and indirect effects on noradrenaline and vasopressin.

Use of ACE inhibitors: load reduction and neurohormonal blockade

Pfeffer and colleagues first demonstrated in the rat that early and continued captopril treatment significantly improved survival provided that the myocardial infarction involved less than 50% of the left ventricle.^{23 24} The mechanism proposed to explain this finding was that angiotensin converting enzyme inhibition with captopril prevented progressive left ventricular dilatation and the development of heart failure. Studies were subsequently performed in humans to determine whether captopril lessened left ventricular enlargement after acute myocardial infarction and improved functional capacity compared with placebo,²⁵ and whether the combination of captopril and thrombolysis conferred additional benefit over and above that derived from thrombolysis alone.^{26 27} Though early placebo controlled post-infarction trials with captopril contained only small patient cohorts, they consistently showed that captopril lessened progressive left ventricular dilatation and improved ejection fraction compared with placebo, and these effects were maintained after the drug was stopped.^{28 29} These encouraging results provided the background to test the hypothesis in the Survival and Ventricular Enlargement (SAVE) trial that long-term use of angiotensin converting enzyme inhibition in survivors of acute myocardial infarction would improve survival by reducing left ventricular enlargement.³⁰ Several multicentre trials have subsequently investigated the use of different ACE inhibitors including enalapril in the CONSENSUS II,³¹ zofenopril in the SMILE trial,³² ramipril in the Acute Infarction Ramipril Efficacy (AIRE) trial, captopril in the fourth International Study of Infarct Survival, and the concurrent early use of captopril and thrombolytic agents (streptokinase in Captopril and Thrombolysis in Myocardial Infarction Study) (CATS),²⁷ and tissue plasminogen activator (alteplase) in the CAPTIN trial) in patients early after myocardial infarction. Most of these post-infarction trials are either near completion or their results have yet to be published. All of these trials have exclusively involved survivors of recent acute myocardial infarction and for this reason should be distinguished from heart failure trials such as SOLVD (Studies of Left Ventricular Dysfunction) and V-HEFT II (Veterans Heart Failure Trial II).^{33 34}

The SAVE trial was a placebo controlled, double blind, randomised trial in which the primary objectives were to determine whether captopril reduced mortality and improved the

clinical outcome of survivors of acute myocardial infarction who had left ventricular dysfunction at baseline (defined as an ejection fraction of $\leq 40\%$) but no overt heart failure and no ongoing myocardial ischaemia.³⁰ The predefined clinical end points were cardiovascular mortality, deterioration in left ventricular function, severe heart failure requiring admission to hospital, severe heart failure which despite digitalis and diuretics required open-label ACE inhibition, and recurrent myocardial infarction.³⁰ SAVE differed from other post-infarction trials in several important respects: baseline left ventricular ejection fraction was $\leq 40\%$, randomisation to treatment assignment was between three and 16 days (mean 11 days) after infarction, study medication (captopril or placebo) was titrated to 50 mg three times a day and continued over a minimum of two and a mean of three years follow up. The SAVE trial is the first and so far the only trial to show that angiotensin-converting enzyme inhibition with captopril, started early and continued long-term, significantly reduces (21%) cardiovascular mortality compared with placebo.³⁰ The difference in survival between the captopril and the placebo treated patients only emerged at 10 months, but thereafter became increasingly more apparent with longer follow up. Importantly, the favourable impact upon mortality in survivors of acute myocardial infarction depended on the prolonged and continuous use of ACE inhibitors. The incidence of congestive heart failure requiring admission to hospital or open-label ACE inhibitors in addition to digitalis and diuretics increased with time, but was significantly less common in the patients randomly assigned to treatment with captopril. Captopril reduced the risk of development of progressive heart failure by 36%, the risk of fatal or non-fatal re-infarction by 25%, and the risk of cardiovascular death or major adverse cardiovascular event by 24% compared with placebo.³⁰ There was a similar reduction in the combined end points of cardiovascular death and heart failure by zofenopril in SMILE.³² An important finding was that the efficacy of captopril in reducing cardiovascular mortality and severe adverse cardiovascular events in SAVE was independent of other factors that are well known to influence clinical outcome, including age, gender, baseline ejection fraction, and prior infarction.³⁰ In addition, these beneficial effects occurred in patients whether or not they received thrombolytic, β adrenergic receptor blockers, or aspirin therapy. At least two possible explanations for the improved clinical outcome in the captopril treated patients deserve consideration. First, lessening of left ventricular dilatation, for which evidence is provided in the SAVE echocardiographic sub-study³⁵ and by previous studies.^{26 28 29} Secondly, partial inhibition of the activation of circulating neurohormones, for example renin-angiotensin, noradrenaline and atrial natriuretic peptide. Perhaps the combination of these interacting mechanisms accounts for

the increase in ejection fraction and improved left ventricular diastolic function because the beneficial effects of captopril on the latter appear to be independent of ventricular dilatation.³⁶

The CONSENSUS II trial also investigated the effect of ACE inhibition on mortality and adverse cardiovascular events after acute myocardial infarction, but differed from SAVE in three major respects.³¹ First, enalapril rather than captopril was used. Secondly, all patients with myocardial infarctions regardless of infarct size, location, transmural, and baseline ventricular function were eligible for enrolment. Thirdly, enalapril was administered intravenously within 24 hours of infarction. CONSENSUS II enrolled more than 6000 patients, but in contrast to SAVE did not show any beneficial effects on cardiovascular mortality or recurrent myocardial infarction.³¹ CONSENSUS II was terminated prematurely because life-table mortality rates at one and six months showed no difference between the patients randomly assigned to enalapril or to placebo, and also early hypotensive episodes occurred more frequently in the patients treated with enalapril.³¹

Differences between trials

The discrepancies between the results of SAVE and CONSENSUS II are difficult to reconcile, but are most likely to relate to differences in baseline left ventricular function, in the timing, dosage, route of administration and short versus long duration of action of the two different ACE inhibitors and less likely to relate to major differences in their mode of action. All SAVE patients had severe left ventricular dysfunction (ejection fraction of <40%), whereas left ventricular dysfunction was not a prerequisite in CONSENSUS II. Thus in CONSENSUS II patients with small infarctions and near normal left ventricular contractile function were less liable to develop left ventricular dilatation and therefore less likely to benefit from ACE inhibition with enalapril if its major mode of action was to prevent dilatation. In addition, any beneficial effects of enalapril on left ventricular remodelling in CONSENSUS II patients with moderately large or large infarctions would have been diluted out if most of the patients has small infarctions. In CONSENSUS II patients were randomised to ACE inhibition therapy or placebo within the first 24 hours compared with a mean of 11 days in SAVE: and the ACE inhibitors were administered intravenously and orally respectively. The early intravenous administration of enalapril after infarction was associated with a significantly higher incidence of hypotension, and any potential long-term benefits of enalapril may have been offset by these early unwanted complications. Finally, the efficacy of the effects of captopril on mortality in SAVE did not become apparent until 10 months of continued administration of the drug, whereas the intended duration of CONSENSUS II was six months, which

together with the early termination of the trial may have precluded detection of longer term beneficial effects.

Continuing trials of ACE inhibitors

Several large multicentre trials using various ACE inhibitors are nearing completion. In all of them oral ACE inhibitors were given within the first 48 hours, most have short follow up periods and some are combined with thrombolysis. Whereas the results of these new trials may clarify the dosage, timing, and route of administration of ACE inhibitors in survivors of acute myocardial infarction, their short duration of follow up may leave important questions unresolved. In SAVE a difference in mortality only emerged after 10 months of continuous captopril treatment. In all current ACE inhibitor trials the period of active treatment is much shorter than this and the optimal duration of therapy may not be established. Similarly, the reduction in left ventricular enlargement and reduction in adverse cardiovascular events that occurred in SAVE patients whether or not they were treated with thrombolysis was not reported in CATS, and this may be a function of the duration of ACE inhibitor therapy. Another important issue that remains is whether the use of ACE inhibitors after infarction should be restricted to patients with left ventricular dysfunction (this protocol requires some objective assessment of left ventricular function, which may not be readily available) or whether they should be used in all patients irrespective of infarction size, location, and baseline ventricular function. Should ACE inhibitors simply be added routinely to the growing list of medications that are prescribed after myocardial infarction? Current recommendations from the SAVE trial are clear: that ACE inhibition with captopril should be given orally within the first week to all patients after infarction in whom there is evidence of asymptomatic or symptomatic left ventricular dysfunction (ejection fractions $\leq 40\%$ to reduce mortality and severe adverse cardiovascular events.

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