How do ACE inhibitors reduce mortality in patients with left ventricular dysfunction with and without heart failure: remodelling, resetting, or sudden death?

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The benefits of ACE inhibitors as standard treatment for patients with overt heart failure due to ventricular dilatation and systolic dysfunction are proved beyond reasonable doubt, at least when a diuretic has been used to control symptoms. More recent studies have suggested that ACE inhibitors may delay or prevent the onset of heart failure requiring diuretics in patients with obviously impaired ventricular function.1 2 However, although the benefits of ACE inhibitors in clinical practice are well established, the mechanisms underlying the beneficial effect at the cellular, organ, and clinical level are poorly characterised. Other articles in this supplement have dealt with the more basic mechanisms underlying ACE inhibitor action. In this article we re-evaluate the clinical nature of left ventricular remodelling and consider to what extent it accounts for the beneficial effects of ACE inhibitors on outcome in patients with established ventricular dysfunction with or without heart failure.

Left ventricular remodelling, cardioprotection, and cardiorepair

Although the introduction of neologisms without good reason is generally to be deplored, some new terms have been coined that have helped our understanding of how the heart responds to ventricular damage and to beneficial interventions. These terms and proposed definitions are shown in table 1.

Progressive ventricular remodelling is complex, entailing changes at many levels, and is associated with a poor prognosis.3 4 Remodelling after myocardial infarction has been intensively studied as the process occurs rapidly in response to dramatic changes in ventricular function5; remodelling in hypertension and chronic heart failure is slower.6 7 At the cellular level changes in the function, morphology, and distribution of the cardiac myocytes7 occur, as well as changes in the type, structure, and amount of collagen8; an inflammatory cell infiltrate is common.9 In the myocardium both contractility and relaxation are impaired and hypertrophy occurs.10 In the ventricle volume is increased,11 the shape becomes more globular,12 and hypertrophy occurs, though the latter is rarely enough to normalise wall stress.13 Ventricular compliance increases,8 possibly reflecting changes in collagen structure or the increased wall stress associated with ventricular dilatation.

Remodelling after infarction may affect the scar, the peri-infarction zone, and non-infarcted regions of the heart. Attempts to interfere with the process of remodelling itself may be deleterious. Thus indomethacin and steroids reduce the inflammatory infiltrate in infarcted areas of myocardium, but they result in further thinning and expansion of the scar and ventricular dilatation.11 14 Indeed, ventricular remodelling may be a useful adaptation to haemodynamic stress; ventricular dilatation allows stroke volume to be maintained with less myocardial fibre shortening, and increased ventricular compliance will delay increases in filling pressures.15 Failure of appropriate remodelling to haemodynamic stress may account for the worse prognosis of older patients with heart failure or myocardial infarction, or both, in whom gross ventricular dilatation is rare.

How common is remodelling?

Theoretically, many aspects of remodelling should be a continuous response to the changing demands on the ventricle in health and disease. However, progressive ventricular remodelling does not seem to occur after all myocardial infarctions or in all cases of heart failure. In many cases ventricular volumes remain stable for years.3 4 This will reflect technical difficulties with the reproducibility of measurements in some patients and a lack of or a reduction in ventricular haemodynamic stress in others. After myocardial infarction an acute period of dilatation may be followed by a reduction in volumes towards baseline due either to the functional recovery of stunned myocardium or to the contraction of myocardial scars.16 Myocardial fibrosis probably contributes to the lack of obvious ventricular dilatation in many elderly patients with heart failure.

Remodelling is more likely to occur with larger infarcts, especially in the anterior...
territory.\textsuperscript{18} Thrombolytic treatment attenuates left ventricular dilatation after infarction,\textsuperscript{19} probably by reducing infarct size, but re-perfusion may also be important in itself.\textsuperscript{20} Additional angioplasty does not seem to confer greater benefit.\textsuperscript{21} Whereas establishing early patency of the infarct related artery may reduce the size of the myocardial infarction and seems to be associated with improved survival,\textsuperscript{22, 23} the importance of late infarct related artery patency in preventing remodelling is unclear. A poor collateral supply\textsuperscript{24} and persistent occlusion of the infarct related artery\textsuperscript{25} are associated with a poorer prognosis. However, late patency may not be intrinsically important to the dilating process as completed transmural infarcts require little coronary blood flow and the lack of requirement for a blood supply may lead to the disappearance of the vessel. Thus, the relation between remodelling and late infarct related artery patency may be one of association rather than cause and effect.

Diabetic patients have a worse prognosis after myocardial infarction, which seems to be because of a greater propensity to develop heart failure for any given size of infarct; but it is not known if this is due to a different propensity for remodelling.\textsuperscript{26} Hypertensive patients also have a worse prognosis after myocardial infarction, but this seems mainly because of a greater risk of reinfarction.\textsuperscript{27} The hypertrophied ventricle may be less likely to develop infarct expansion.\textsuperscript{28}

Relation of remodelling to prognosis
Left ventricular dilatation developing after a myocardial infarction is associated with a poorer prognosis.\textsuperscript{12, 13} Similarly, ventricular volume is a major determinant of prognosis in patients with dilated cardiomyopathy.\textsuperscript{29} Not only is a low ejection fraction a bad prognostic sign but a decline in ejection fraction with time indicates a worse outcome.\textsuperscript{4} Ventricular dilatation leads to an increase in wall stress and progressive distension, and this may be a major determinant of outcome. Remodelling may, however, be a marker rather than a cause of worse outcome. The forces leading to remodelling may be the major determinant of prognosis rather than the ventricular dilatation itself. Obvious dilatation is often associated with severe symptoms, high filling pressures, and low cardiac output. However, patients with obvious ventricular dilatation and a good exercise tolerance may have a better prognosis than those with minimally dilated ventricles and severe symptoms associated with appreciable haemodynamic compromise.\textsuperscript{30}

Effects of interventions on ventricular remodelling
Several treatments can alter ventricular remodelling, not all of them beneficially as described above, but ACE inhibitors are the only class of agent that has been well studied. After myocardial infarction there is limited evidence for a favourable effect of nitrates on remodelling,\textsuperscript{11} which has not been supported by clinical evidence of benefit in recent large trials.\textsuperscript{32, 33} Loop diuretics\textsuperscript{8} and digoxin\textsuperscript{34} do not seem to alter remodelling favourably, while captopril,\textsuperscript{13} probably magnesium,\textsuperscript{35} and calcium antagonists\textsuperscript{36, 37} do not reduce the risk of developing heart failure after myocardial infarction. \(\beta\) Blockers reduce the risk of developing heart failure in selected patients after myocardial infarction\textsuperscript{38} and can improve haemodynamics and increase ejection fraction in patients with dilated cardiomyopathy.\textsuperscript{39} Non-pharmacological interventions may also alter the remodelling process. In patients with dilated, poorly functioning ventricles and severe coronary stenoses subverting a large amount of viable myocardium, revascularisation may result in appreciable improvements in volume and function.\textsuperscript{40} Limited data also suggest that other techniques such as haemofiltration\textsuperscript{41} or the correction of sleep apnoea\textsuperscript{42} can improve ventricular function, apparently independent of haemodynamic effects.

Effects of ACE inhibitors on ventricular volume and ejection fraction
The effects of ACE inhibitors on the remodelling process after myocardial infarction are dealt with in this supplement.\textsuperscript{42, 43} Briefly, ACE inhibitors reduce cardiac volumes, and the major impact seems to be through reducing the extent to which anterior scars expand,\textsuperscript{44} with lesser effects on dilatation of the non-infarct zone. Thrombolyis may reduce both the frequency of progressive remodelling\textsuperscript{19, 45} and the impact of ACE inhibitors on left ventricular dilatation,\textsuperscript{46} while persistent occlusion of the infarct related artery may reflect a greater tendency to dilate and a greater benefit from ACE inhibition.\textsuperscript{47} ACE inhibitors reduce both systolic and diastolic ventricular volumes in patients with heart failure, and this effect occurs within six weeks of starting treatment.\textsuperscript{48, 49} These short term changes are readily reversible\textsuperscript{48, 49} and associated with improved haemodynamics; they are therefore not good evidence for remodelling as defined above.

The SOLVD studies used echocardiography and radionuclide ventriculography to show that enalapril reduced ventricular volumes over 3–4 years.\textsuperscript{7, 8, 50} The radionuclide substudy of SOLVD showed, however, that the largest change in volume occurred in the first four months; thereafter there was no apparent difference in the rate of ventricular dilatation. This comparatively short term effect might be termed “resetting” rather than remodelling,\textsuperscript{51} the latter implying a process of continuing improvement. The change in ventricular volumes did not seem to be solely due to an effect of enalapril on haemodynamics because, although ventricular volumes rose after withdrawal of enalapril for two weeks at the end of the study, they were still reduced compared with placebo.

The captopril–digoxin multicentre\textsuperscript{52} and V-HeFT II studies,\textsuperscript{53} the largest radionuclide
ventriculographic studies of ACE inhibitors in heart failure, failed to show a significant long- term effect of ACE inhibitors on ejection fraction. By contrast, the combination of hydralazine and nitrates led to an increase in ejection fraction in the V-HeFT II study. These studies did not provide information on cardiac volumes, and therefore a balanced reduction in systolic and diastolic volumes by ACE inhibitors cannot be excluded.

Effects of ACE inhibitors on ventricular hypertrophy
Hypertrophy in response to an increase in ventricular wall stress or neuroendocrine mediators, or both, is a characteristic feature not only of hypertension but also of heart failure.53 As ventricular dilatation is usual in heart failure, hypertrophy is usually eccentric and is therefore less obvious on imaging. ACE inhibitors are effective in reducing hypertrophy in hypertension,54 but what happens in heart failure is less clear. Rather than a regression of hypertrophy the SOLVD study indicated that enalapril prevented ventricular mass from increasing.55 Therefore, cardiac volumes fall either before or to a greater extent than the decline in ventricular hypertrophy. This may be because haemodynamic stress rather than neuroendocrine activation is the dominant factor in determining ventricular hypertrophy in heart failure. The preferential and earlier reduction in volume means that the ratio of mass to volume increases with concomitant reductions in wall stress that should have beneficial effects on ventricular function and possibly survival.

Effects of ACE inhibitors on ventricular compliance
Although myocardial compliance is decreased in heart failure, ventricular compliance is paradoxically increased, reflecting the increase in wall stress secondary to dilatation. Data from the SOLVD study suggest that long term ACE inhibition reduces filling pressures to a lesser extent than ventricular diastolic volume: thus for a given ventricular volume, filling pressure tends to rise.54 This implies that ACE inhibitors reduce ventricular compliance towards normal.

Doppler studies in patients with chronic ventricular dysfunction do not indicate an important effect of ACE inhibitors on ventricular filling patterns,55 although studies in patients with heart failure have suggested an improvement in the early rapid filling phase.56 ACE inhibitors used in the short term after myocardial infarction also seem to improve Doppler filling characteristics long term.57 Improvements in ventricular filling under some circumstances may be due to direct effects on the myocardium but could also be due to changes in ventricular loading conditions.

Effects of ACE inhibitors on peripheral vascular structure
Studies in hypertension have highlighted the structural changes that occur in arterioles. Experimental evidence from animal studies suggests that the histological changes induced by hypertension may be reversed by ACE inhibitors,58 though this awaits confirmation in humans.

In heart failure maximal vasodilatation induced by drugs or metabolic stress is reduced, suggesting that structural changes in the systemic vasculature may be important in regulating blood flow.59 Alveolar-capillary membrane dysfunction leading to a decline in pulmonary diffusing capacity in heart failure may represent similar structural changes in the pulmonary vasculature.60 Although ACE inhibitors reduce vascular resistance both at rest and during exercise, it is unclear how much of this is due to a beneficial effect on vascular remodelling.

Effects of ACE inhibitors on recurrent infarction
Recurrent infarction causes progressive ventricular damage and confers a greater risk of developing heart failure or dying. The arguments for and against a significant impact of ACE inhibitors on reinfarction have been discussed previously.61 The results of QUIET (quinapril ischaemic heart failure) trial, investigating the effects of quinapril on recurrent ischaemic events in patients with coronary disease but no substantial ventricular dysfunction, will be critical in resolving these arguments.

Effects of ACE inhibitors on salt and water balance
ACE inhibitors are believed to reduce sodium and water retention, though this assumption is based mostly on experiments in animals or in normal and hypertensive human subjects.

By contrast, patients with heart failure commonly retain salt and water in the first few days after taking an ACE inhibitor.61 This suggests that the fall in renal perfusion pressure, glomerular filtration rate, and atrial natriuretic peptide concentration in response to ACE inhibition prevents any potentially natriuretic effect due to a decline in angiotensin II and aldosterone concentrations. However, salt and water retention is generally self limiting and not accompanied by clinical deterioration, presumably because central haemodynamics improve. Over 6–8 weeks sodium retention is reversed and returns to pretreatment values.62 63 Thirty four studies have compared the effects of ACE inhibitors and placebo on symptoms in patients with heart failure, but weight was recorded in only 11. Only two studies showed a reduction in weight, suggesting that most of the patients studied did not show diuresis.

Effects of ACE inhibitors on arrhythmias
Whether ACE inhibitors exert a beneficial effect on arrhythmias remains controversial. Several small studies64 65 66 and the V-HeFT II65 and SAVE studies67 suggest that
ACE inhibitors reduce arrhythmias, but the SOLVD study did not.\textsuperscript{65} ACE inhibitors improve ventricular loading conditions, reduce volumes and retard progressive hypertrophy, increase serum potassium concentrations and parasympathetic tone, and reduce sympathetic activity, so it would not be surprising if they reduced arrhythmias.\textsuperscript{66} The reason why the smaller early crossover studies were successful in showing a modest decrease in the frequency of ventricular extrasystoles may reflect the fact that hypokalaemia was common at baseline. The reduced intraindividual variability in ectopic beats in patients with a high frequency of arrhythmias probably also contributed to the ability of these studies to show an effect of ACE inhibitors.

Animal studies have subsequently confirmed that ACE inhibitors have antiarrhythmic effects. These models suggest that modulation of the cardiac sympathetic system or the bradykinin-prostaglandin system may be important in mediating the electrophysiological effects of ACE inhibitors.\textsuperscript{67} Studies of ACE inhibitors in human heart failure have suggested only subtle electrophysiological effects, but these may, none the less, be important.\textsuperscript{68}

**Effects of ACE inhibitors on sudden death**

Results from both small and large trials have suggested that ACE inhibitors may affect sudden death as well as death due to progressive heart failure.\textsuperscript{1, 53 69-71} Sudden death should no longer be equated with death from arrhythmias in heart failure. The frequency of documented recurrent myocardial infarction in patients with heart failure and the adverse effect on prognosis suggests that many such sudden deaths are vascular rather than arrhythmic in origin.\textsuperscript{72} Postmortem studies indicate that in 74\% of patients with ischaemic heart disease who die suddenly death is associated with fresh thrombus in the coronary artery.\textsuperscript{73} As ACE inhibitors may reduce the risk of recurrent infarction a reduction in the number of sudden deaths might also occur by this mechanism.\textsuperscript{74}

The first study to report on the influence of ACE inhibitors on the mode of death was the captopril multicentre trial, which indicated a striking reduction in the number of sudden deaths, though numbers were small.\textsuperscript{75} Several large studies of heart failure, with the exceptions of the CONSENSUS\textsuperscript{76} and the SOLVD treatment trial,\textsuperscript{77} have recorded sudden death, either with or without progression, as the most common mode of death.

The CONSENSUS study the patients had severe heart failure. The more severe the heart failure the greater the likelihood that death will be classified as progressive heart failure.\textsuperscript{78} This may indicate that the real mode of death is influenced by the severity of heart failure, which is entirely plausible. Alternatively, if patients already confined to bed by symptoms die suddenly it is likely that the death will be recorded as progressive heart failure rather than sudden death. In the SOLVD treatment trial the investigators chose to report death due to progressive heart failure and sudden death in the context of worsening heart failure as one and the same. This may be why sudden death accounted for only about 20\% of deaths in that study. Distinguishing sudden death in the context of worsening heart failure from death due to worsening heart failure alone is important not only because it would provide a more accurate view of the clinical course of heart failure but also because sudden death may be amenable to other treatment strategies, which may be important in, for instance, patients awaiting cardiac transplantation. However, the SOLVD studies suggested a reduction in both sudden death and myocardial infarction\textsuperscript{72}—an effect that was not significantly different from the effect on the combined sudden death/progressive heart failure group. Interestingly, enalapril reduced mortality even during the run in period.\textsuperscript{73} As it would be surprising if patients with rapidly deteriorating heart failure were considered for a randomised study, one possible explanation for the positive effect of enalapril during this phase was a reduction in sudden death.

In the V-HeFT II study the effect of enalapril was entirely due to a reduction in sudden death with or without a concomitant deterioration in symptoms.\textsuperscript{79} It is possible that the combination of hydralazine and nitrate may increase the risk of sudden death and that the use of an active comparator rather than placebo led to the apparent beneficial effect on sudden death, but this is unlikely as the vasodilator combination probably has a beneficial effect on survival.\textsuperscript{77} Alternatively, the conventional vasodilator combination could have selectively reduced death from the combined sudden death/progressive heart failure group. It would be reduced death by either mechanism; this cannot be discounted. The SAVE study also showed a reduction in mortality due to progression of heart failure alone and sudden death with or without progressive heart failure.\textsuperscript{1}

In summary, the landmark studies have failed, so far, to convincingly identify the mechanism by which ACE inhibitors reduce mortality from heart failure. Undoubtedly, ACE inhibitors reduce ventricular volumes, but it is unclear whether the principal reason for this is an acute reduction of volumes mediated primarily through reduced haemodynamic stress; retardation of progressive remodelling through alterations in ventricular stress and inhibition of neuroendocrine activation; or prevention of recurrent ischaemic damage to the left ventricle (table 2).

<p>| Table 2 Mechanisms by which ACE inhibitors might reduce progressive ventricular dilatation |</p>
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<th>Mechanism</th>
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<tr>
<td>Reduction in ventricular preload and afterload</td>
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<td>Resetting of ventricular volumes (possibly secondary to the above)</td>
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<tr>
<td>Remodelling (secondary to haemodynamic and neuroendocrine effects)</td>
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<tr>
<td>Reduction in recurrent ischaemia and infarction</td>
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