

## VIEWPOINT

## ACE inhibitors after myocardial infarction: patient selection or treatment for all?

H S J Lindsay, A G Zaman, J C Cowan

It is now clear that angiotensin-converting enzyme (ACE) inhibitors have an important role in the management of patients after myocardial infarction. Several clinical trials have shown statistically significant reductions in mortality (SAVE, AIRE, GISSI-3, ISIS-4).<sup>1-4</sup> Some may argue that the weight of evidence favours wide, if not universal, use of ACE inhibitors among post-infarct patients. Does this argument withstand closer scrutiny? If not, what criteria should be used to identify which patients should be treated?

### Rationale for postinfarction ACE inhibition

After infarction, infarct expansion and ventricular remodelling lead to increasing ventricular volume. This has a powerful adverse effect on prognosis.<sup>5,6</sup> There is clear evidence that ACE inhibitors reduce dilatation in patients at high risk of progressive ventricular dilatation.<sup>7-10</sup>

Not all patients with infarction will develop ventricular dilatation. About a third do; but in a third ventricular volumes are unchanged and in the final third ventricular volumes may actually improve as the myocardium recovers from stunning.<sup>11</sup> Dilatation, when it occurs, is initially adaptive and volumes stabilise in some patients, but in about 20% of those with infarct dilatation is progressive and may ultimately lead to heart failure.<sup>12</sup>

Should treatment be confined to those who undergo adverse remodelling or are there additional benefits, perhaps of lesser magnitude, to be gained in treating all patients? While a complete answer to this question is not possible at present, useful information can be derived by comparing the differing strategies and results of treatment with ACE inhibitors in recent studies of mortality after myocardial infarction.

### Selection strategies and clinical trials

To date five major trials on the effects of ACE inhibitors on mortality after infarction have been reported. Three strategies have been used: selection based on clinical evidence of ventricular impairment (AIRE), selection based on radionuclide evidence of ventricular impairment (SAVE), and a strategy of unselective universal treatment (GISSI-3, ISIS-4, CONSENSUS II).<sup>3,4,13</sup>

The selective strategies showed unequivocal benefit. In the AIRE study, where selection was based on clinical criteria of ventricular impairment, there were striking benefits with a reduction of 27% in mortality at a median follow up of 15 months. The investigators estimated that 15-20% of patients after myocardial infarction fulfilled study entry criteria. In the SAVE study selection was based on a radionuclide ejection fraction of <40%. Just under 40% of the population screened for the investigation fulfilled this criterion.<sup>14</sup> Benefit was not seen for the first nine months of follow up but by 42 months mortality was reduced by 19%. Benefit was seen regardless of Killip class at entry, suggesting that the benefits of ACE inhibition may extend beyond patients with clinical evidence of heart failure.

By contrast the benefits of a strategy of global unselected treatment are much less striking. In the one negative study of ACE inhibition after myocardial infarction (CONSENSUS II) ACE inhibitors were given very early and intravenously to unselected patients. No effect on outcome was shown. This was true across all subgroups. The initial fears that this trial engendered about the safety of early ACE inhibition were largely dispelled by the ISIS-4 and GISSI-3 studies in which oral ACE inhibitors given within 24 hours of infarction were associated with small but statistically significant reductions in mortality at 5 and 6 weeks respectively. ISIS-4 showed an overall benefit of 5 lives per 1000 patients treated. This compares with a benefit of 30 lives per 1000 patients treated at a comparable time point in the AIRE study.

Some evidence supports the hypothesis that ISIS-4 and GISSI-3 demonstrate the same effect as AIRE, namely a benefit of ACE inhibition in the 15-20% of patients with heart failure that is diluted by a neutral effect in the 80-85% of patients without heart failure. Subgroup analysis within ISIS-4 shows a trend towards greater benefit among the 13% of patients considered to be in heart failure at the time of randomisation. The GISSI-3 study offers stronger support for this view. Among patients without evidence of heart failure at entry (Killip class I), ACE inhibition reduced mortality by a mere 3 per 1000, compared with a 30 per 1000 reduction among patients with clinical evidence of

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failure (Killip class II and above).<sup>15</sup> There was, therefore, a 10-fold greater reduction in mortality among patients with heart failure on presentation.

Preliminary reports of the TRACE study offer further support for the merits of a selection policy. Patients were selected for randomisation to ACE inhibition or placebo on the basis of an echocardiographic assessment of regional wall motion abnormalities.<sup>16</sup> Over a median follow up of 3 years a highly significant 22% reduction in mortality was seen.

In conclusion it seems probable from the post-infarction trials that there is a heterogeneity of ACE inhibitor benefit, that benefit does not necessarily apply to all patients, and that benefits may be greatest in those patients with clinical evidence of heart failure.

#### **How do ACE inhibitors reduce mortality?**

The question of how ACE inhibitors reduce mortality is central in determining an optimal strategy for patient selection. There are several possible mechanisms. Firstly, by extrapolation of the CONSENSUS<sup>17</sup> and SOLVD<sup>18</sup> data, treating those patients with heart failure may of itself lead to an improvement in prognosis. This clearly is one possible explanation for the dramatically positive results of the AIRE investigation and the suggestion in ISIS-4 and GISSI-3 that benefits may be greater in patients with heart failure.

A second possible mechanism of benefit is the limitation or prevention of adverse ventricular remodelling. Although the prevention of adverse remodelling provided the rationale for the use of ACE inhibitors after infarction, the evidence that prevention of remodelling underlies the consequent reduction in mortality is surprisingly limited. The best available evidence comes from a substudy of the SAVE investigation.<sup>10</sup> In this study, a strong association was seen between adverse cardiac events and ventricular dilatation. Overall, ACE inhibitors reduced both the extent of ventricular dilatation and the number of patients showing adverse events. Among those patients manifesting adverse events, ACE inhibitors failed to prevent dilatation. This finding offers some rather weak, circumstantial evidence that reduction in mortality is achieved through a reduction in the number of patients who undergo ventricular dilatation and are thereby at risk of adverse events.

The third potential benefit of ACE inhibitors after myocardial infarction is the prevention of recurrent infarction. Such a benefit might apply to all patients after infarction, irrespective of ventricular function, and might indicate a need for universal treatment. The SAVE and SOLVD studies<sup>19</sup> have shown that ACE inhibitors reduce the incidence of reinfarction among patients with ventricular impairment. However, in both studies the analysis leading to this conclusion has been questioned.<sup>20,21</sup> The AIRE study did not substantiate this effect. Similarly, the ISIS-4 and

GISSI-3 investigations have shown no evidence of an effect on reinfarction, suggesting that if such a benefit exists it can only result from long-term treatment.

Further studies are needed to address the issue of ACE inhibition and reinfarction. Assuming that such a benefit may exist, the most important question would then become whether this benefit applied to all patients—remodellers and non-remodellers alike. If prevention of reinfarction applied only to the adverse remodelling group, the goal would remain the identification of these patients. Conversely a benefit in non-remodellers would be a strong argument for universal treatment. The reduction in reinfarction seen in the SAVE study was independent of ejection fraction at entry, suggesting that benefits might be universal. In our opinion, however, there is currently insufficient evidence to justify the rationale of treating all patients to prevent reinfarction.

It is of course possible that the reduction of mortality with ACE inhibitors is unrelated to the proposed benefits and arises in hitherto unrecognised ways. However, in the light of current knowledge, there does not seem to be a mechanistic mandate for universal treatment, and a selective approach to treatment seems the most rational strategy.

#### **Timing of ACE inhibition**

The timing of the start of ACE inhibition is central to determining strategies of selection. If, for example, ACE inhibitor benefits could be optimised by starting treatment on day 1, the need for early treatment would leave little option but to pursue a strategy of universal treatment.

Here, as elsewhere, uncertainty still prevails. On the one hand, early ACE inhibition is clearly desirable to minimise adverse remodelling.<sup>22</sup> On the other, there continues to be concern that individual patients may be disadvantaged by starting an ACE inhibitor in the earliest phase of acute myocardial infarction. This is illustrated by the GISSI-3 study. Treatment with lisinopril was, as might be anticipated, accompanied by an increased incidence of hypotension. Though in percentage terms, mortality among those with hypotension in the control group was 36% (compared with 20% in the lisinopril group), in absolute terms there were 85 deaths in the lisinopril group compared with 60 in the control group. It therefore remains possible that the hypotension associated with early ACE inhibition may have an adverse effect on mortality. This remains a matter for speculation.

Irrespective of these concerns, the modest benefits seen in ISIS-4 and GISSI-3 suggest that there is little to be gained by very early ACE inhibition. Moreover, detailed studies of the time course of remodelling have suggested that the extent of ventricular dilatation in the first 48 hours after infarction is minimal.<sup>11</sup> It seems reasonable, therefore, to delay treatment until after the first 48 hours and to start treatment as soon as possible thereafter.

### Who should be treated?

None of the strategies of patient selection used so far can be regarded as an adequate sole basis for treatment. Rather, treatment selection should be based on combining aspects of different strategies.

As discussed above, the current evidence does not justify long-term universal treatment. The ISIS investigators have advocated, as an alternative, short-term universal treatment for 6 weeks, opting for a selective continuation of treatment in patients corresponding to either the AIRE or SAVE treatment groups. We argue against this approach. The difficulty in patient selection is only deferred. Extrapolation of the AIRE or SAVE data to selection at 6 weeks adds an additional element of uncertainty. There is no data on the effects of withdrawing therapy from patients at this time, nor on how existing ACE inhibitor treatment might influence selection criteria. Finally, one can seriously question whether in clinical practice ACE inhibitors would really be stopped at 6 weeks. In our opinion the modest benefits of early ACE inhibition do not warrant such an approach and it seems preferable to make a definitive management decision during the patient's original admission.

Few would argue that all patients with clinical evidence of heart failure early after infarction need treatment. Beyond this several strategies are possible. One possible approach is to base treatment on an estimate of left ventricular function. For example, the SAVE investigation provides a rationale for treating all patients with a radionuclide ejection fraction of <40% measured at a median of 11 days after infarction. This approach necessitates some delay in starting treatment because early assessment of ejection fraction during the first few days after infarction will be confounded by patients with stunned or hibernating myocardium whose left ventricular function may recover. Clearly, the provision of radionuclide studies in all patients early after infarction presents major logistic problems. Furthermore, there is significant variability in results between units.<sup>23</sup> To apply a single, universal treatment threshold based on an ejection fraction of 40% would be meaningless. It is therefore questionable whether a radionuclide ejection fraction should be used as the sole or predominant means of selection.

Echocardiography is more readily available and cheaper than nuclear imaging. It cannot, however, be regarded as equivalent to nuclear imaging in estimating ejection fraction<sup>24</sup> and adds further uncertainties to the use of ejection fraction as a means of patient selection. This is not to deny a role for echocardiography. The recent TRACE study has pointed the way forward, showing the success of a policy of selection based on echocardiographic assessment of regional wall motion abnormalities.

A more rational approach is to consider all factors contributing to ventricular dilatation

including ventricular function. Known predictors of ventricular dilatation include infarct size, infarct site, and the patency of the infarct related artery.<sup>12</sup> Because infarct size and patency of the infarct related artery are difficult to measure in routine clinical practice, the value of surrogate measures such as peak creatine kinase or speed of ST resolution needs to be assessed. Alternative approaches that may provide a more direct measure of ventricular stretch are currently under investigation. Plasma concentrations of brain natriuretic peptide have been shown to correlate with early left ventricular dysfunction and may be predictive of adverse remodelling.<sup>25</sup> High resolution electrocardiography is another approach because the early presence of late potentials has been shown to correlate with subsequent ventricular dilatation.<sup>11</sup>

These and other methods of predicting ventricular dilatation will require further assessment. Until their value is known, we have to be pragmatic about the best means of patient selection. A reasonable approach at present seems to be to base treatment on clinical judgement. This will encompass an assessment of site of infarction, the extent of infarction assessed enzymatically and electrocardiographically, and whether reperfusion therapy has been given and whether it has been successful. A history of previous infarction should also be considered. Clearly assessment may also extend to an echocardiographic or radionuclide assessment of ventricular function and regional wall motion abnormalities.

The weakness of such an approach is its subjectivity. However, with current knowledge, over-reliance on quantitative or semi-quantitative assessments to dictate treatment engenders a false sense of objectivity which may be an even greater shortcoming.

### Conclusion

The statistical success seen in the ISIS-4 and GISSI-3 studies should not be used to justify a strategy of universal ACE inhibition after myocardial infarction. There is evidence that the benefits of ACE inhibition are heterogeneous and that benefits are greatest in patients with clinical evidence of heart failure. Radionuclide estimation of the ejection fraction can be used to define further which patients should be treated, though whether this is an optimal means of selection is open to question. There is currently no single reliable method of predicting ventricular dilatation, but site of infarction, extent of infarction, response to reperfusion treatment, and previous infarction history should all play a part in the clinical decision whether or not to start treatment with an ACE inhibitor.

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## LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

### Antibiotic prophylaxis in permanent pacemaker implantation

SIR,—We thank Aggarwal *et al*<sup>1</sup> for the interest they have shown in our recent trial of parenteral antibiotic prophylaxis in permanent pacemaker implantation.<sup>2</sup> They clearly do not like our message—that parenteral antibiotics should be prescribed routinely—which they feel conflicts with an earlier trial at their centre (Broadgreen)<sup>3</sup> which showed no benefit for parenteral antibiotics.

The Broadgreen trial randomised patients to parenteral antibiotics or not, but unfortunately did not include an antibiotic free control group.<sup>3</sup> All patients received antibiotic prophylaxis in the form of an antibiotic spray into the pacemaker pocket, whether or not they received parenteral antibiotics. Though the absence of additional benefit of systemic over local antibiotics in the Broadgreen trial may, if taken in conjunction with our data, suggest that local antibiotic prophylaxis is as good as systemic, this is not as good evidence as a trial against an antibiotic free control group. We agree with Aggarwal's colleagues' suggestion (first made in their paper in 1984<sup>3</sup>) that prophylactic local antibiotics should be tested within a prospective controlled randomised study. We look forward to seeing these data.

We were surprised at Aggarwal and coworkers' assertion<sup>1</sup> that our data did not

support our conclusions. This is not the case. To reach their position Aggarwal *et al* have performed several unusual manipulations on our results. First they retrospectively altered our trial end points by removing patients with sterile erosions from the analysis. Though we have presented data suggesting that non-infective erosion occurs,<sup>4</sup> our prospectively defined end point for this trial was re-operation for septicaemia, pocket abscess, or erosion. We chose re-operation as a solid end point, necessary in a non-blinded trial. Interestingly, even with this post hoc change in the analysis, the benefit of antibiotic prophylaxis remains statistically significant.<sup>1</sup>

Second, Aggarwal *et al* criticise our exclusion, at the operator's discretion, of many patients with temporary wires. Whereas this prevented us from reaching a meaningful conclusion in this subgroup, it has no effect on the significance of the overall result. Aggarwal and co-workers present non-randomised audit data of patients with temporary wires, a proportion of whom received parenteral antibiotics (against unit policy) in addition to local antibiotic prophylaxis.<sup>1</sup> We congratulate them on the low infection rate in both groups of patients but, in the absence of a randomised step, it is impossible to give a reason for it. The efficacy of antibiotic prophylaxis in patients with temporary pacing electrodes in place remains unproven and we will continue to use parenteral antibiotics in all such patients while we await prospectively randomised, controlled data.

The Broadgreen group's third attack on our data is one that no trial would survive. They change our results. Clearly if the control group's event rate is reduced, a point would be achieved where significance is lost for any given population for any benefit in any trial.

To conclude, we reaffirm our original conclusion that our prospective randomised study showed a statistically significant benefit for parenteral antibiotic prophylaxis in permanent pacemaker implantation. We recommend its routine use.

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## CORRECTION

### ACE inhibitors after myocardial infarction: patient selection or treatment for all? *HSJ Lindsay, AG Zaman, JC Cowan*

The authors of this article (*Br Heart J* 1995;73:397-400) misquoted a figure on page 397 (final sentence of second paragraph, right hand column). The corrected version should read... "This compares with a benefit of 21 lives per 1000 patients treated at a comparable time point in the AIRE study."

## NOTICES

The 1996 Annual Meeting of the **British Cardiac Society** will take place at the Scottish Exhibition & Conference Centre, Glasgow from 7 to 9 May.

The **16th Scientific Meeting of the International Society of Hypertension** will take place in Glasgow from 23 to 27 June 1996. For a copy of the main announcement, registration, and abstract forms, please contact ISH 1996 Meeting Secretariat, Conference Associates and Services International Ltd/THG Group, 4 Cavendish Square, London W1M 0BX, UK (tel: +44 171 499 0900; fax: +44 171 436 8309).