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

SIR,—The question of selection criteria for angiotensin converting enzyme blockade after myocardial infarction (MI) posed by Lindsay *et al.*¹ needs to be set in the wider context of stratification of risk after MI according to therapeutic outcome.² The latter strategy fully justifies the expense of radionuclide measurement of left ventricular ejection fraction (LVEF) because an LVEF < 40% has emerged as a modifiable risk factor for recurrence of MI (including MI related mortality),³ significantly surpassing even exercise induced segment depression^{4,5} in its prognostic accuracy. By analogy with the therapeutic outcome of coronary artery bypass surgery in poorly controlled chronic stable angina,⁶ the use of coronary angiography should also now supplant the exercise test in the risk stratification of patients with refractory angina after MI because, in the study cited above,⁶ reduction in mortality risk was more significantly correlated with the anatomical distribution of coronary atherosclerosis than with the electrocardiographic stigmata of the exercise test.

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This letter was shown to the authors, who reply as follows:

SIR,—Dr Jolobe argues for the widespread use of radionuclide ventriculography (RNVG) for risk stratification after myocardial infarction. The prognostic significance of a low ejection fraction has long been

recognised but its value has been limited by our inability to modify this risk. The results of the SAVE study¹ have changed this by showing that ACE inhibition can modify prognosis in patients with a low ejection fraction. In SAVE ventricular function was assessed relatively late at a median of 11 days post-infarction. Recent data from GISSI-3 (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) show that much of the benefit of unselected ACE inhibition occurs in the first few days after infarction,² suggesting that treatment needs to be started in the first days after infarction. Indeed this is one the main points in favour of Dr Coats' argument for an unselected approach to ACE inhibitor therapy after infarction.³

Selecting treatment on the basis of ejection fraction in the first days after infarction poses several problems. In the SAVE investigation, ejection fraction was estimated by RNVG. Many hospitals in the United Kingdom would have difficulty in routinely assessing left ventricular function by this method within the first 72 hours of infarction. Proponents of echocardiography would argue that it is an adequate substitute for RNVG with the advantages that it is readily performed at the bedside, that it is widely available, and that it is comparatively cheap. However, it is questionable whether echocardiographic assessment of ejection fraction is comparable to RNVG⁴ and this makes it difficult to choose a cut off value below which ACE inhibition should be started.

Moreover, the role of ejection fraction in selecting treatment in the first days after infarction is uncertain. There are few published reports on changes in ejection fraction in the early days after infarction but it seems that there is some recovery in ejection fraction within the first week.⁵⁻⁶ This makes it difficult to interpret the significance of the ejection fraction measured within the first few days. We have found echocardiographic ejection fraction assessed on day 3 to be a poor predictor of subsequent ventricular dilatation. By contrast, and of particular interest given the findings of the TRACE study,⁷ wall motion index was a powerful predictor of dilatation (unpublished observations). This is consistent with the CATS study where there was a trend towards worse wall motion scores among patients undergoing ventricular dilatation compared with those who did not. There was no such trend for ejection fraction.⁸

Thus, despite its pre-eminence as a prognostic marker after infarction, ejection fraction may not be the optimal means of assessing which patients will undergo ventricular dilatation and who may benefit from ACE inhibition. We do not deny that ejection fraction may be a useful adjunct in decision making, but we reiterate our previous conclusion that there is currently no single variable that uniquely identifies patients likely to benefit from ACE inhibition and that over-reliance on quantitative or semi-quantitative methods for treatment selection engenders a false sense of objectivity.

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Effects of streptokinase in patients presenting within 6 hours of prolonged chest pain with ST segment depression

SIR,—Among patients with ST elevation presenting within 6 hours of the onset of the symptoms of suspected acute myocardial infarction (MI), fibrinolytic therapy has been shown to reduce one-month mortality by about a third.¹⁻³ But, there is little evidence that fibrinolytic therapy reduces the proportion of patients who subsequently develop MI, who have continuing ischaemic pain, or who have a positive exercise test.^{3,4} Hence, even in large clinical trials of fibrinolytic therapy the effects on a composite outcome of death and/or some such secondary outcomes will be less clear than the effects just on the primary outcome of death. It is, therefore, both unsurprising and uninformative that in a trial that involved only 112 patients White *et al* found no significant effect of fibrinolytic therapy on this composite outcome.⁵ The use of the composite measure seems particularly inappropriate since deaths, which are the one component of it that might reasonably be expected from other settings to be reduced by fibrinolytic therapy, made only a small contribution (four deaths, as against 84 other events).

It has been suggested that composite outcome measures might, by increasing the number of events in a study of given size, allow the reliable assessment of treatment without increasing the sample size.⁶ But this is not the case when the treatment under investigation does not actually influence some common component of a composite measure (or, worse still, produces effects in an opposite direction to those of other components: as with the proposed combination of death and haemorrhagic stroke for fibrinolytic trials⁶). Hence, although the study by White *et al* was restricted to patients with ST depression, its composite analysis does not provide useful evidence about the efficacy of

fibrinolytic therapy in such patients. A few thousand such patients have already been randomised in other studies,¹ and if reliable evidence is to emerge then several thousand more such patients will need to be randomised. Until large-scale randomised evidence is available it is dangerous to seek premature conclusions from inappropriate analyses of one very small study.

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This letter was shown to the authors, who reply as follows:

SIR,—Patients presenting with ST segment depression with recent ischaemic chest pain within 6 hours have a different pathophysiology and a different outcome from patients with ST segment elevation. Some present with infarction, whereas others may go on to have an infarct later. An important aim of treatment, therefore, is to decrease the incidence of myocardial infarction. In several trials of thrombolytic treatment for patients with unstable angina (involving a more heterogeneous group than those randomised in our trial), thrombolysis was associated with an increased incidence of myocardial infarction.¹ This may be due to procoagulant effects of thrombolytic treatment,² which may convert non-occlusive thrombus to occlusive thrombus. Given the different pathophysiology it cannot be assumed, as Collins *et al* state, that death "might reason-

ably be expected . . . to be reduced by fibrinolytic therapy". The available evidence from mortality trials of the use of thrombolytic drugs in patients with ST segment depression is not encouraging. Among the 3563 patients in the Fibrinolytic Therapy Trialists' overview the mortality was higher in thrombolytic-treated patients (15.2% *v* 13.8%, odds ratio 1.12, 99% confidence interval 0.88 to 1.44). The chance that subsequent large studies would establish a clinically important mortality advantage for thrombolytic treatment (for example, a 15% reduction) is less than 1%.

We therefore believe that Collins *et al* are not justified in stating that the major benefit of thrombolytic treatment in patients with ST segment depression is likely to be a reduction in mortality. They suggest that the randomisation of several thousand more patients is needed to gain reliable evidence of mortality effects. Although the randomisation of this number of patients may confirm that thrombolytic therapy is *harmful*, it would require tens of thousands of patients to establish that the treatment is in fact effective, and that the adverse results to date have been due to the play of chance. For example, it would require 16 000 patients to show a 15% reduction in mortality from the 13.8% control mortality in the Fibrinolytic Therapy Trialists' overview with 90% power and $P < 0.01$, and a greater effect would be needed to confirm a mortality benefit in a meta-analysis including the previous studies.

We were hopeful that thrombolytic treatment might produce other beneficial effects in patients with ST segment depression, such as a lower incidence of ongoing ischaemia (spontaneous or inducible), recurrent infarction, or need for coronary interventions. We used a combined hierarchical end point in which all events carried equal weight. Although our study was adequately sized to assess moderate differences in the frequency of the combined end point, the numbers are insufficient to assess reliably the frequency of all of the individual components of the combined end point. While Collins *et al* found the lack of difference between the two groups with respect to this end point "unsurprising and uninformative", we think our demonstration that a similarly low proportion of patients was free of these adverse outcomes in both groups is disappointing but clinically useful. We chose a composite of end points that we believe share a common pathophysiology—that is, ongoing plaque instability and thrombosis. We deliberately did not include adverse end points such as haemorrhagic stroke and major bleeding, which were likely to alter in a different direction, because our power to estimate the frequency of these events was

very low and random variation may therefore have unduly affected the composite outcome. This is a different situation from the calculation of "net clinical benefit" in trials which are sufficiently large to permit reliable estimates of the frequency of the individual components of a composite end point.

The primary aim of treatment for patients with ST segment depression and recent ischaemic pain should be to stabilise or "passivate" the plaque medically—that is, decrease thrombogenicity while allowing the fissuring or rupturing of the plaque to heal. Treatments that are able to stabilise unstable plaques may well produce clinical benefits apart from reducing death, and these should be evaluated in clinical trials.

As active members of the ISIS Collaborative Group, we strongly support the role of large multicentre trials to reliably assess the frequency of infrequent outcome events such as death and stroke. Smaller trials also have an important role in defining possible mechanisms of benefit and the patient subgroups to whom large-scale studies are best directed. Unfortunately neither small-scale trials nor the limited data from larger studies suggest that thrombolytic treatment provides an important benefit in patients with ST segment depression.

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NOTICE

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