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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.*<sup>1</sup> needs to be set in the wider context of stratification of risk after MI according to therapeutic outcome.<sup>2</sup> 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),<sup>3</sup> significantly surpassing even exercise induced segment depression<sup>4,5</sup> in its prognostic accuracy. By analogy with the therapeutic outcome of coronary artery bypass surgery in poorly controlled chronic stable angina,<sup>6</sup> 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,<sup>6</sup> 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 study<sup>1</sup> 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,<sup>2</sup> 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.<sup>3</sup>

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 RNVG<sup>4</sup> 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.<sup>5-6</sup> 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,<sup>7</sup> 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.<sup>8</sup>

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.<sup>1-3</sup> 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.<sup>3,4</sup> Hence, even in large clinical trials of fibrinolytic therapy the effects on a composite outcome of death and/or some 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.<sup>5</sup> 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.<sup>6</sup> 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 trials<sup>6</sup>). 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