be targeted for interventions such as treatment with angiotensin converting enzyme inhibitors after myocardial infarction, perhaps even irrespective of criteria generally implemented in other post-myocardial infarction subgroups.

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1 Choy AM, Darbar D, Lang CC, *et al.* Detection of left ventricular dysfunction after acute myocardial infarction: comparison of clinical, echocardiographic, and neurohormonal methods. *Br Heart J* 1994;72:16–22.
2 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarcto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986:i;397–402.
3 ISIS–(Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected myocardial infarction. *Lancet* 1988:ii;349–60.
4 Schechtman KB, Capone RJ, Kleiger RE, *et al.* Risk stratification of patients with non–Q wave myocardial infarction: The critical role of ST segment depression. *Circulation* 1989; 80:1148–58.
5 Wilich SA, Store PH, Muller JE, *et al.* High–risk subgroups of patients with non–Q wave myocardial infarction based on direction and severity of ST segment deviation. *Am Heart J* 1987;114:1110–19.

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

SIR,—As Dr Jolobe states in his letter, the adverse prognostic significance of ST segment depression in patients with non-Q wave myocardial infarction is well recognised. In our study, however, the patient group was representative of all patients admitted with myocardial infarction (MI). Of 57 patients whose admission and follow up electrocardiograms were available for analysis 13 (23%) had a non-Q wave MI and of these six presented with ST segment depression. The mean left ventricular ejection fraction (LVEF) in those patients with non-Q wave MI and ST depression was 37·5% compared with 45·7% in those who presented with non-Q wave MI and ST elevation. It is notable that the mean modified Peel index, which includes a score for post-infarction angina, was 10·7 in the ST depression group and 7·3 in ST elevation group. In the patients who had a Q-wave MI, 17 patients had no ST depression on the admission electrocardiogram, 20 had reciprocal ST depression, and 2 had ST depression alone. The mean LVEF in those with no ST depression was 42·5% compared with 40·5% in the group with reciprocal ST depression.

In the light of current evidence, the decision on whether to start an ACE inhibitor after MI should be based on clinical and/or echocardiographic evidence of left ventricular dysfunction.[1 2] Although our findings are consistent with previous reports of the association between ST depression and left ventricular dysfunction in non-Q wave MI, this association does not seem to apply in most patients with Q wave MI. Thus it does not seem that the addition of ST segment analysis to sorting methods such as the modified Peel index would significantly improve their sensitivity in the detection of left ventricular dysfunction, except possibly in the subgroup of patients with non-Q wave MI.

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1 Pfeffer NA, Braunwald, LA, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992; 327: 669–77.
2 The AIRE Study investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821–8.

Will serum enzymes and other proteins find a clinical application in the early diagnosis of myocardial infarction?

SIR,—Dr Timmis discussed the limitation of early biochemical diagnosis of acute myocardial infarction in guiding thrombolytic therapy.[1]

The mortality of infarct patients in Newham General Hospital who present without ST elevation is only a third that of those with ST elevation, none the less about one in 20 of such patients died. In addition, in infarct patients who present with predominant ST depression one year mortality is high (31%).[2] De Wood *et al*'s angiographic study of non-Q wave infarction was performed up to 24 hours after acute myocardial infarction[3] and the patency rate caused by spontaneous coronary re-canalisation would be expected to be higher than in the first 12 hours, the time window when thrombolytic therapy is believed to be effective.[4] Even so, 26% of these patients had occluded coronary arteries and might have benefited from re-vascularisation treatment. The result of the ISIS-2 trial suggests that patients without ST elevation (except bundle branch block) would not benefit from thrombolytic therapy.[5] However, the inclusion criteria of ISIS-2 raise the possibility that an appreciable number of these patients may not have had a myocardial infarction at all. No definitive data are currently available to guide treatment in patients with early biochemical confirmation of acute myocardial infarction, though the LATE study[4] did include patients with old or equivocal electrocardiographic changes and raised concentrations of cardiac enzymes. The LATE study showed a significant reduction in mortality in patients treated with alteplase when thrombolysis was started 6–12 hours after onset of symptoms. Other treatments such as β blockers, ACE inhibition, and aspirin have been shown to be useful in the early management of acute myocardial infarction.[5 6] Early biochemical diagnosis may be useful in guiding this treatment.

Furthermore the use of rapid assays may offer advantages in terms of efficiency; patients with atypical chest pain may be discharged earlier after negative results. None the less, to exclude acute myocardial infarction, myoglobin should be measured 4–6 hours after the onset of chest pain and creatine kinase MB 6–8 hours after the onset of chest pain.[7]

Rapid biochemical diagnosis of acute myocardial infarction may be useful in guiding treatment and the more efficient management in coronary care units of patients who present with chest pain.

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1 Timmis AD. Will serum enzymes find a clinical application in the early diagnosis of myocardial infarction? *Br Heart J* 1994;71: 309–10.
2 Lee HS, Cross SJ, Rawles J, Jennings K. Patients with suspected myocardial infarction who present with ST depression. *Lancet* 1993;342:1204–7.
3 De Wood MA, Stiffer WF, Simpson CS, *et al.* Coronary arteriographic findings soon after non-Q wave myocardial infarction. *N Engl J Med* 1986;315:417–23.
4 LATE Study Group. Late assessment of thrombolytic efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet* 1993;342: 759–66.
5 ISIS-2 (Second international Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;ii:349-60.
6 Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester intravenous magnesium intervention trial (LIMIT-2). *Lancet* 1994; 343:816–9.
7 Lee HS, Cross SJ, Garthwaite P, Jennings K. Rapid exclusion of acute myocardial infarction in patients without ST elevation using serial cardiac enzyme analysis with novel analyzers—myoglobin, creatine kinase and creatine kinase-MB enzymes [abstr]. *Br Heart J* 1992;68:107.

SIR,—Dr Timmis states correctly that there is doubt about whether the use of serum markers of myocardial damage to confirm myocardial infarction in patients with chest pain but without ST elevation in the electrocardiogram will lead to lives being saved by the use of thrombolytic therapy.[1] However, he overstates the case against the use of serum markers with a misleading discussion of the evidence. The fact is that no large study has yet been published to compare the vascular mortality of thrombolysis and placebo in the subgroup of patients who have a non-diagnostic electrocardiogram (ECG) on admission to hospital, but a confirmed diagnosis of infarction on discharge. The GISSI study enrolled 451 patients with ST depression on the ECG; the mortality in this whole group was 18·4%, and did not differ significantly whether streptokinase or placebo was used.[2] ISIS-2 enrolled 1137 such patients, and again the mortality rate of 18·6% was not improved by streptokinase.[3] The ASSET study distinguished only between normal and abnormal ECGs without distinguishing specific ECG abnormalities.[4] GISSI-2 enrolled patients with ST segment elevation only.[5] In the LATE study, 93% of patients had a discharge diagnosis of definite or possible infarction.[6] In the group of 2544 patients without ST elevation on the ECG, the 35 day mortality was 7·5% in the placebo group and 6·4% in the group treated with alteplase.

About two thirds of patients who present with ST depression or T wave inversion on an admission ECG will have confirmed acute myocardial infarction on discharge.[7] The patients with a discharge diagnosis of infarction are potentially those who would benefit most from thrombolytic therapy.[4] It has been shown in theory[8] and in practice[9] that the use of early immunoassay of creatine kinase MB can achieve 94% sensitivity and specificity for prediction of the discharge diagnosis of infarction.

A subgroup analysis that might yield valuable information could be undertaken by the ISIS-3 coordinators. In ISIS-3, 9158 patients were enrolled as having an "uncertain" indication for thrombolytic therapy; 70% of these had an admission ECG criterion other than ST elevation.[10] Fifty nine per cent of the patients in the whole "uncertain" group had a discharge diagnosis of myocardial infarction. Thirty five day mortality was 8·3% in the whole "uncertain" group and 11·4% in those with a discharge diagnosis of infarction. What was the mortality for thrombolytic treatment and what for placebo in this last group? As far as we are aware these figures have never been published.

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1 Timmis AD. Will serum enzymes and other proteins find a clinical application in the early diagnosis of myocardial infarction? *Br Heart J* 1994;71:309–10.
2 Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI). *Lancet* 1986;i:397–402.
3 Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;ii:349–60.
4 Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet* 1988;ii: 525–30.
5 GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. *Lancet* 1990;336: 65–71.
6 LATE Study Group. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet* 1993;342: 759–66.
7 Yusuf S, Pearson M, Sterry H, Parish S, Ramsdale D, Rossi P, Sleight P. The entry ECG in the early diagnosis and prognostic stratification of patients with suspected acute myocardial infarction. *Eur Heart J* 1984;5:690–6.
8 Marin MM, Teichman SL. Use of rapid serial sampling of creatine kinase MB for very early detection of myocardial infarction in patients with acute chest pain. *Am Heart J* 1992;123:354–61.
9 Gunn IR, Mir NS, Parnham AJ, Caslake CE, Matthews DMM, O'Brien IAD. Emergency serum creatine kinase MB isoenzyme concentration in patients with suspected acute myocardial infarction. *Health Bull (Edin)* 1993;51:166–76.
10 Fibrinolytic Therapy Trialists Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311–22.

These letters were shown to the author, who replies as follows:

SIR,—The concerns of Lee *et al* are certainly understandable. However, the recent history of cardiac therapeutics is littered with examples of drugs that on theoretical grounds should have been beneficial but which, when put to the test of a randomised trial, have proved unhelpful or harmful. Examples include inotropes in heart failure, calcium antagonists in unstable angina, and type 1 antiarrhythmic treatment in the post-infarction period.[1–3] To this list should perhaps be added thrombolytic therapy in patients with unstable angina and non-Q wave myocardial infarction, following the report of the TIMI-IIIB investigators which concluded that in this group thrombolytic therapy "is not beneficial and may be harmful".[4] In this study presenting ECGs were non-diagnostic in 90% of cases, and in the remainder ST elevation was only transient.

Though I was careful to make implicit in my choice of words that the results of subgroup analyses of randomised trials can provide clues about the likely efficacy of treatment but not proof, Gunn *et al* accuse me of a misleading discussion of the evidence against the need for thrombolytic therapy when the presenting ECG is non-diagnostic. They then go on to request a further subgroup analysis from ISIS-3 that seems unlikely to yield much additional clarification. Nevertheless, they make the good point that a definitive answer will be obtained only from a randomised trial of treatment in patients who present with a non-diagnostic ECG and then go on to infarction. The TIMI-IIIB trial, while not designed to provide that definitive answer, certainly comes close to it. At present, therefore, there seems little justification for selecting patients who present with cardiac chest pain and a non-diagnostic ECG for thrombolytic therapy on the basis of rapid biochemical assays.

Finally, the assertion of Lee *et al* that rapid biochemical assays may increase "efficiency" by permitting early discharge of patients with negative results is potentially dangerous if it encourages premature discharge of patients with unstable angina whose need for coronary care is no less than that of patients with acute infarction.

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1 Packer M, Carver JR, Rodeheffer RJ, *et al* for the PROMISE Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991;325: 1468–75.
2 Holland Interuniversity Nifedipine/metoprolol Trial (HINT) Research Group. Early treatment of unstable angina in the coronary care unit. A randomized double-blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine, metoprolol or both. *Br Heart J* 1986; 56:400–13.
3 The Cardiac Arrhythmia Suppression Trial (CAST) investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomised trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;321:406–12.
4 The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. *Circulation* 1994;89:1545–56.

Haemodynamic deterioration after treatment with adenosine

SIR,—It is well known that non-dihydropyridine calcium antagonists, β blockade, and digitalis can lead to an increase in the ventricular rate and haemodynamic deterioration during pre-excited atrial fibrillation. This is because conduction through the accessory atrioventricular connection is facilitated, and the effect relates to sympathetic activation as well as abolition of retrograde concealed conduction into the accessory pathway. The case reported by Cowell *et al* illustrates that adenosine is no exception, especially if it is given repeatedly.[1]

Although the very high rate during pre-excited atrial fibrillation may have been the primary cause for the haemodynamic deterioration, another possibility is that the patient's condition worsened after the repeat administration of adenosine for the wrong indication (that is, conversion of atrial fibrillation). In our opinion, Cowell *et al* should have stressed this fact more than anything else because it illustrates that too enthusiastic and indiscriminate use of adenosine can kill patients with the Wolff-Parkinson-White syndrome. A Vaughan Williams class 1A agent such as procainamide or a 1C agent, rather than adenosine, is indicated for safely terminating rapid pre-excited atrial fibrillation.[2]

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1 Cowell RPW, Paul VE, Ilsley CDJ. Haemodynamic deterioration after treatment with adenosine. *Br Heart J* 1994;71: 569–71.
2 Crijns HJGM, den Heijer P, van Wijk LM, Lie KI. Successful use of flecainide in atrial fibrillation with rapid ventricular rate in the Wolff-Parkinson-White syndrome. *Am Heart J* 1988;115:1317–9.

This letter was shown to the author, who replies as follows:

SIR,—We agree with Dr Crijns and Dr Lie that repeat administration of adenosine once atrial fibrillation had been established was inappropriate. However, this patient deteriorated haemodynamically after adenosine because a narrow complex tachycardia converted to more rapid pre-excited atrial fibrillation. There was no evidence of a progressive rate increase when administration of adenosine was repeated: the patient deteriorated after the onset of atrial fibrillation. There was no further deterioration at the time of repeat adenosine administration.

We agree that the agents suggested could be used to convert pre-excited atrial fibrillation chemically but emphasise that electrical cardioversion should be used if there is any evidence of haemodynamic compromise.

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Near miss paradoxical embolism

SIR,—In their timely reminder of the importance of a patent foramen ovale as facilitator of paradoxical embolism Prakash *et al* state