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 theory⁸ and in practice⁹ 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.
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- 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.
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- 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-III 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-III 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.
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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

that evidence for this mechanism remains circumstantial.¹ This may be so but it is also very strong. Thirty years ago, in the *British Heart Journal*, Corrin described two cases in which there was necropsy evidence of thrombus protruding through the patent foramen ovale.² Remarkably he was able to review a further 52 "verified cases" in which there was systemic embolisation, a source of thrombus in the veins, and a clot found in situ in a patent foramen ovale—surely the thrombotic equivalent of a smoking gun! He pointed out that the foramen ovale rather than a pathological shunt was the most commonly reported route for paradoxical embolism.

The sequence of events seems less unlikely if one considers that venous return from the inferior vena cava streams directly onto the fossa ovalis—the direction of the fetal circulation—so that thromboemboli arising in the lower half of the body bombard the valve of the foramen ovale while those that fly further to the pulmonary arteries transiently raise the right heart pressures, forcing the valve to open from right to left.

Thus any systemic embolism occurring around the time of a pulmonary infarction should alert us to the possibility of paradoxical embolism.

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- 1 Prakash A, Chambers J, Holt P. Near miss paradoxical embolism. *Br Heart J* 1994;72: 293.
- 2 Corrin B. Paradoxical embolism. *Br Heart J* 1964;26:549–53.

NOTICES

The 1995 Annual Meeting of the **British Cardiac Society** will take place at the

Conference Centre, Harrogate, North Yorkshire from 23 to 25 May.

The first international meeting of the Working Group on Heart Failure (**Heart Failure '95**) will take place on 1–4 April 1995 in Amsterdam, The Netherlands. It will be sponsored by the European Society of Cardiology. For further information, please contact: Holland Organising Centre, Parkstraat 29, 2514 JD The Hague, The Netherlands (tel +31 70 365 78 50; fax: +31 70 361 48 46).

A meeting on **Neurohormones, Kinins and Endothelial Function in Ischaemia. Effects of ACE Inhibition**, sponsored by the International Society of Cardiovascular Pharmacotherapy, will take place in Versailles, France on 19–20 May 1995. For further information, please contact: Dr Willem J Remme, Sticares, Cardiovascular Research Foundation, PO Box 52006, 3007 Rotterdam, The Netherlands (tel: +31 10 485 51 77; fax: +31 10 485 48 33).