

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).*

Effect of early intravenous heparin on coronary patency infarct size, and bleeding complications after alteplase thrombolysis

SIR,—In the interpretation of the results of a clinical trial where the null hypothesis has been rejected, it is important to discern whether any systematic biases, especially if unbalanced between treatment groups (confounders), could (partially) explain the results. The European Cooperative Study Group (*British Heart Journal* 1992;67:122–28) contended that early concomitant intravenous heparin therapy improves coronary patency at 48–120 hours in patients treated with alteplase.¹ The difference although small (83% heparin, 74% placebo) was deemed statistically significant. However, fewer patients in the heparin group (83%) showed enzymatic evidence of infarction than in the controls (95%). Indeed, although this difference is larger than that of the patency benefit, conventional statistical significance was apparently not achieved. Using the same statistical technique, I estimate that the relative risk of not sustaining an enzymatic infarction in the placebo group compared with the heparin group was 0.31 (95% CI 0.18 to 0.52), clearly significant.²

Moreover, one might assume that coronary vessels in the non-infarction patients would be patent. If included, they would tend to bias the results in favour of patency benefit with heparin. If you eliminate these patients from table 2 (55 heparin, 17 control) and assume that they also account for the 24 subjects where the infarct related vessel could not be identified (nine heparin, 15 control), the results are very different, less marked and may be due to the play of chance (for TIMI grade 0 or 1 perfusion: heparin 20.1% v placebo 25.5%; relative risk 0.79, 95% CI 0.56 to 1.11).

While analysis based on the intention-to-treat principle is regarded as the method most likely to minimise bias, including patients without the disease of interest seems inefficient and may limit the internal and external validity of the conclusions. This may be more of an issue in explanatory or "efficacy" trials, such as this one, than in pragmatic or "effectiveness" trials.³

I argue that when an adequate dose of aspirin is administered, intravenous heparin has little (if any) effect on coronary patency at

48–120 hours in patients treated with alteplase.

DAVID R MASSEL
Cardiac Care Unit,
Victoria Hospital,
London, Ontario,
Canada

- 1 de Bono DP, Simoons ML, Tijssen J, *et al*. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. *Br Heart J* 1992;67:122–8.
- 2 Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised mortality rates. *Br Med J* 1988;296:1313–6.
- 3 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chron Dis* 1967;20:637–48.

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

SIR,—Dr Massel takes us to task for not confining our comparison of alteplase heparin with alteplase plus placebo to patients with confirmed myocardial infarction. Clearly, it is impossible to be sure that the diagnosis of infarction will be confirmed at the time of trial entry. The difficulty of confining the analysis to patients with a retrospectively confirmed infarct is that it is well known and documented that early effective thrombolytic therapy will prevent the development of Q waves and/or a diagnostic increase in plasma enzyme concentration in a proportion of patients with genuine thrombotic coronary occlusion. To confine analysis to those patients subsequently shown to have infarction would be to introduce an entirely arbitrary bias against whatever in fact was the most effective treatment. The conventional approach in trials of this nature is to enter the patients on the basis of clinical and electrocardiographic criteria (and those we adopted were stringent compared with several other trials) and then to analyse on an intention-to-treat basis.

It could be argued that the reduction in cases of confirmed infarction among the group receiving heparin was indeed a consequence of earlier and better sustained patency in the heparin treated group. However, since this was not one of the a priori end points we refrained from attaching weight to this in our discussion.

DAVID DE BONO
Department of Cardiology,
University of Leicester
Clinical Science Wing,
Glenfield General Hospital,
Leicester LE3 9QP

Incessant atrial tachycardia accelerated by pregnancy

SIR,—Dr Doig and colleagues¹ described their experience with a patient in whom incessant atrial tachycardia developed during pregnancy (*British Heart Journal* 1992; 67:266–8). We have recently seen a similar case and feel that certain observations may be pertinent.

A 34 year old woman was admitted at 38 weeks' gestation with palpitation. This had been present for five days and was noticeable only at rest. She was otherwise well and

denied previous symptoms. She was in her fourth pregnancy; the third had required a caesarean section for placenta praevia. On admission her pulse rate was 200 per minute and her blood pressure was 90/70 mm Hg.

The electrocardiogram showed a narrow QRS complex tachycardia with upright P waves in V1 and a frontal P wave axis of +10°. The PR interval was 160 ms and the RP interval was 200 ms. The electrocardiogram was therefore consistent with atrial tachycardia and 1:1 ventricular conduction. Intravenous verapamil (10 mg) had no effect on the ventricular rate and two hours later she was given disopyramide (150 mg). This caused her blood pressure to fall to 70/50 mm Hg but did not improve the ventricular rate. She therefore underwent elective cardioversion, which also proved unsuccessful despite two shocks of 360 J delivered via standard paddle positions. Her atrial tachycardia showed considerable diurnal variation with pulse rates ranging from 135 when asleep to 215 per minute when awake and being examined. The results of fetal heart monitoring remained normal throughout this period and fetal movements were maintained. Intravenous flecainide succeeded in slowing the atrial rate to 130 per minute and precordial echocardiography showed a dilated left ventricle and impaired left ventricular function. In view of her advanced gestation she underwent elective caesarean section and gave birth to a live female weighing 3180 g who had an Apgar score of 7 at one minute and 10 after five minutes.

After delivery she remained in an atrial tachycardia but during the next week her pulse rate fell progressively and her blood pressure rose. At the time of discharge her pulse rate was 100 beats per minute at rest. At auscultation a murmur of mitral regurgitation and a loud third heart sound were heard. Between three and eight weeks after delivery she reverted to sinus rhythm and the P wave configuration showed a prominent left atrial component. There was T wave inversion in all the precordial leads. Two months after delivery left ventricular function remained mildly impaired. Although these changes may have been secondary to the dysrhythmia, their persistence suggests an underlying cardiomyopathy.

Our own experience accords with that of Doig *et al*. The considerable fluctuations in rate and resistance to both pharmacological and electrical cardioversion are in keeping with an automatic atrial tachycardia. In view of the catecholamine drive (as shown by these fluctuations) we considered β adrenoceptor blockade, but her low blood pressure and impaired left ventricular function precluded this treatment. Late in pregnancy standard paddle positions for cardioversion are difficult to obtain and antero-posterior positioning of the paddles might have helped. Delivery of the baby was followed by progressive resolution of the tachycardia and when the fetal lung is likely to be mature this is perhaps the best treatment for both mother and child. Finally, despite its fast rate, the arrhythmia was remarkably well tolerated whereas antiarrhythmic drug treatment caused a considerable fall in blood pressure.

JEREMY J MURPHY
DAVID J R HUTCHON
Department of Medicine,
Memorial Hospital,
Darlington,
County Durham DL3 6HX

1 Doig JC, McComb JM, Reid DS. Incessant atrial tachycardia accelerated by pregnancy. *Br Heart J* 1992;67:266–8.