Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after 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 (founders), 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 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.1 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 1.1).

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" studies.2 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 DE BONO
Department of Cardiology, University of Leicester
Clinical Science Wing, Glenfield General Hospital, Leicester LE3 9QP

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

Sir,—Dr Massel takes us to task for not connoting 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 connoting 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 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 colleagues 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.

Incessant atrial tachycardia accelerated by pregnancy


David de Bono, Peter Calvert, Tim Wilton, and the Editorial Board welcome 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).