

Correspondence

Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both

Sir,

The study on the early treatment of unstable angina in the coronary care unit by the Holland Inter-university Nifedipine/Metoprolol Trial (HINT) Research Group (1986;56:400-13) requires comment.

(a) *The study was terminated too soon*

The HINT study suggested that although the addition of nifedipine to routine treatment could be "detrimental" to patients not previously on β blockers, the addition of nifedipine to existing treatment with β blockers was "beneficial". The trial was ended too early, probably because an interim analysis suggested that the risk of myocardial infarction was greater in patients assigned to nifedipine. The reason for this decision does not appear in the discussion and is poorly documented in the appendix. The analysis only demonstrates the well known fact that an unplanned interim analysis without correction of α error may produce a significant difference.

(b) *Imbalance in the monotherapy groups and the inability of the investigators to differentiate between onset of acute myocardial infarction and unstable angina*

When the Steering Committee made its decision it had not been informed of the clear imbalance of risk at baseline between the study groups. The authors admit that the onset of myocardial infarction in patients presenting with symptoms of unstable angina is uncertain and that they may have miscalculated by more than six hours. Under clinical conditions the use of enzyme determinations for the diagnosis of myocardial infarction is an inaccurate and, at times, an inconsistent indicator of infarction. The higher incidence of myocardial infarctions in the group assigned to nifedipine monotherapy may be explained by the possible (pre) existence of myocardial infarction; and in these circumstances it would be incorrect to use the term "detrimental". Indeed, the recent TRENT study on a much larger

group of patients with confirmed acute myocardial infarction did not show any "detrimental" effects of nifedipine.¹

Later in the HINT study it was found that 43 patients had already had an infarction before treatment but these cases were not excluded even though they no longer fulfilled the inclusion criterion for "unstable angina" and the therapeutic aim, "treatment of unstable angina pectoris", could no longer be achieved. The uniformity of all the groups was not examined and a table showing these data should be published so that the comparability of the treatment groups and the individual centres can be checked.

(c) *Baseline risk differed considerably in the various treatment groups*

The "high baseline risk" of recurrent ischaemia or myocardial infarction within 48 hours was 18% in the nifedipine group and 5% in the metoprolol group. An attempt was made to overcome this imbalance by logistic regression. Since angiography was not available to assess the severity of the underlying coronary artery disease and there is no information on the distribution of these high risk patients among the participating centres, further analysis of these groups on the basis of equal prior risk and equal prior treatment is indicated.

(d) *Nifedipine responders were excluded but metoprolol responders were not*

Patients taking nifedipine maintenance treatment or admittance were excluded whereas those on β blockade maintenance treatment were not. Both medications were probably prescribed for the same indication and it is likely that the exclusion of patients on nifedipine maintenance treatment probably unbalanced the study in favour of metoprolol.

(e) *The term "placebo" is misleading*

"Placebo" suggests that only a placebo was given. In part A of the analysis placebo is the term used for

Correspondence

“conventional” treatment and no details of this are given; however, 87% received long acting nitrates, 76% anticoagulants, and 40% diuretics. Is it possible that a combination of these medications led to a pronounced hypotensive state in those assigned to monotherapy with nifedipine. Further details of the influences of concomitant medication are required, and we need to know the distribution of this concomitant treatment, especially in those patients who progressed to myocardial infarctions. In part B the term “placebo” group indicates treatment with metoprolol and “nifedipine” placebo.

(f) *Confidence limits in patients not pretreated with β blockers are too wide and differences in efficacy so small that statements like “beneficial” and “detrimental” indicate trends rather than statistically significant differences*

In general combined treatment with nifedipine and β blockers had a positive effect both in the pretreatment and no pretreatment groups. This supports the current practice of treating patients with unstable angina with a combination of β blocker and nifedipine. The authors should state this fact instead of branding nifedipine as “detrimental”.

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Reference

1 Wilcox RG, Hampton JR, Banks DC, *et al*. Trial of early nifedipine in acute myocardial infarction: the TRENT study. *Br Med J* 1986;293:1204–8.

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

Sir,
The issues raised by Weihrauch *et al* are covered in an article that is to appear in the *European Heart Journal*. Our answers are summarised below.

(a) *The study was terminated too soon*
The decision to terminate the study was taken by the Executive Committee and was based on the

unanimous recommendation of the Policy Advisory Board. The interim data on which this recommendation was based are given in appendix I of our paper. Interim data such as these are not usually disclosed for trials that have been terminated ahead of time.

Even in retrospect, we regard it inconceivable that we could have reached any other decision about nifedipine monotherapy, even if the final effect estimates had been available. In terms of efficacy the distinction between “no effect” and “negative effect” (or equivalently, “detrimental effect”) is of no real importance. On the other hand, we would view it as unethical to continue such a trial in the face of a negative trend just to establish the distinction between “no effect” and “negative effect” beyond reasonable doubt. Decisions about the other treatments might have been different had a more detailed analysis been available to us.

As regards Weihrauch *et al*'s comments on “statistical significance” and the possibility of an α error, we must point out that as we do not subscribe to the traditional notion of calculating p values and declaring differences to be statistically significant or not, the issue of adjustment of p values in the context of multiple tests therefore does not arise. In fact the positive effect of nifedipine in patients on previous maintenance treatment with a β blocker was the only difference that was statistically significant. Therefore, when Weihrauch *et al* state that “an unplanned interim analysis without correction of α error may produce a significant difference” they suggest that this positive effect of nifedipine may be spurious.

(b) *Differentiation between acute myocardial infarction and unstable angina*

For the 43 cases with myocardial infarction with a probable onset before randomisation, we have (in keeping with current practice) adhered to the intention to treat principle. This approach accords with ordinary clinical diagnosis, which is by definition based on past and present symptoms and not on those that may or may not develop in the future. All patients entered in the HINT, including these 43 patients, were diagnosed as having unstable angina based on symptoms and signs present just before randomisation; they all had enzyme values below twice the upper limit for normal. Thus patients who were later classified as (probably) having the onset of infarction before randomisation also satisfied the HINT definition of unstable angina.

The TRENT study was of patients with symptoms and signs of acute myocardial infarction. Whether nifedipine does or does not promote the development of myocardial infarction in patients with symptoms and signs of unstable angina cannot