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 pre-treatment 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


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 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 a 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
be inferred from a study with patients presenting with symptoms and signs of acute myocardial infarction, although there is considerable overlap between the clinical pictures at issue. In any case the TRENT data confirm that in acute myocardial infarction no therapeutic benefit can be expected from nifedipine.

(c) **Differences in baseline risk**
The baseline risk for recurrent ischaemia or myocardial infarction within 48 hours was estimated for each individual patient by a logistic model. The apparent imbalance in baseline risk was corrected for (by stratified analysis) in the adjusted effect estimates presented in table 5 of the HINT paper. This comparison within strata of equal baseline risk reduced the observed negative effect of nifedipine monotherapy from 1.28 (that is an increase of 28%) to 1.15 (an increase of 15%). Subsequent findings at angiography were not and cannot be used as baseline characteristics for acute treatment at hospital admission, because the clinician must decide on early treatment without knowing the angiographic findings. We believe that the analysis of clinical trial data should reflect the clinical situation under investigation, and hence we have not used findings of predischarge angiography. The angiographic data are given in the article that is to appear in the European Heart Journal.

(d) **Exclusion of patients on maintenance treatment with nifedipine**
Giving nifedipine to patients who were already taking nifedipine when unstable angina developed is not an appropriate therapeutic action. Instead, the clinician could add β blocker. The latter option was not investigated in HINT because we expected that only a few of these nifedipine non-responders without a contraindication for a β blocker would present, as nifedipine had only been recently introduced when HINT was designed in 1980. Thus we did not exclude nifedipine responders, rather we omitted a β blocker/placebo comparison in nifedipine non-responders. Therefore, there is no argument for the suggestion that the exclusion of patients already on nifedipine unbalanced the study in favour of metoprolol.

(e) **Use of the term “placebo”**
Our use of the term “placebo” accords with convention—that is a placebo for the drug under investigation, with rules for concomitant medication stipulated in the study protocol. The HINT data indicate that previous medication, which was continued in most instances, was not related to prognosis. Therefore, it is highly unlikely that the observed negative trend for nifedipine monotherapy was caused by interaction with other medications such as long-acting oral nitrates.

(f) **Width of the confidence intervals**
We believe that the wide confidence intervals prevent definite conclusions being based on the HINT data alone. Nevertheless, the HINT data do not support Weihrauch et al’s proposal that combination treatment is the treatment of choice on hitherto untreated patients. Whether the HINT data are conclusive enough to discourage the use of a fixed combination as the initial treatment is another matter. None the less, they do support the current practice of adding nifedipine to the regimen when the initial β blocker fails.

We have stated that the HINT findings “suggest that in patients not on previous maintenance treatment with β blocker... nifedipine may be detrimental”. The word “detrimental” was used to reflect the possibility of negative efficacy. Our conclusion was (and still is) that the HINT data virtually exclude a major preventive effect of nifedipine monotherapy in unstable angina (as defined in HINT).

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**Reference**