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

*REPORT OF THE HOLLAND INTERUNIVERSITY NIFEDIPINE/METOPROLOL TRIAL (HINT) RESEARCH GROUP†*

From the Netherlands Interuniversity Cardiology Institute, Utrecht, the Netherlands

**SUMMARY** A multicentre, double blind, placebo controlled, randomised trial of nifedipine, metoprolol, and nifedipine and metoprolol combined was conducted in a group of 338 patients with unstable angina not pretreated with a β blocker and in 177 patients pretreated with a β blocker. The main outcome event was recurrent ischaemia or myocardial infarction within 48 hours. Trial medication effects were expressed as ratios of event rates relative to placebo. In patients not pretreated with a β blocker the event rate ratios with associated 95% confidence intervals were 1-15 (0-83, 1-64) for nifedipine, 0-76 (0-49, 1-16) for metoprolol, and 0-80 (0-53, 1-19) for nifedipine and metoprolol combined. In patients already on a β blocker the additive effect of nifedipine was beneficial (rate ratio 0-68 (0-47, 0-97)). Equal numbers of patients developed myocardial infarction and reversible ischaemia. Most infarctions occurred early, within six hours of randomisation. In patients not already on a β blocker the nifedipine rate ratio for infarction only was 1-51 (0-87, 2-74).

These results suggest that in patients not on previous β blockade metoprolol has a beneficial short term effect on unstable angina, that fixed combination with nifedipine provides no further gain, and that nifedipine may be detrimental. On the other hand, the addition of nifedipine to existing β blockade when the patient’s condition becomes unstable seems beneficial.

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Patients admitted to a coronary care unit with acute chest pain present a spectrum of signs and symptoms ranging from those that are characteristic of acute myocardial infarction to chest pain without myocardial ischaemia. Within these two extremes a subgroup of patients can be identified who have symptoms that are atypical of myocardial
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infarction but characteristic of myocardial ischaemia—anginal pain at rest not severe enough to suggest myocardial infarction, combined with changing electrocardiographic findings compatible with ischaemia but not directly diagnostic of infarction. This syndrome is usually called unstable angina. Patients with this diagnosis at admission to the coronary care unit may be in the process of sustaining a myocardial infarction. Alternatively, the infarction may not yet have occurred, and the patient should be considered at risk for recurrent and possibly irreversible ischaemia.1–3

After initial pain relief the aims of early treatment are the prevention of recurrent ischaemia or myocardial infarction and the restoration of a stable condition. Calcium antagonists and β blockers are among the agents that have been advocated as being useful in this respect.4–8 Calcium antagonists are thought to increase oxygen supply by coronary vasodilation and β blockers are assumed to reduce oxygen demand by decreasing heart rate and myocardial contractility.9 10 However, β blockers have also been implicated as a potential cause of increased coronary vasomotor tone,11 12 and calcium antagonists in the coronary steal phenomenon.9 13 Furthermore, several cases of severe congestive heart failure have been reported in patients treated with both drugs.14 15

In 1980 the Holland Interuniversity Nifedipine/metoprolol Trial (HINT) research group initiated a randomised, double blind, placebo controlled, multicentre trial to assess the role of calcium antagonists and β blockers in the treatment of unstable angina. At that time this role had not been defined.16 The objective of the trial was to determine whether nifedipine (a calcium antagonist) and metoprolol (a β blocker) could prevent recurrence of ischaemia or progression to myocardial infarction when given either alone or in combination to patients diagnosed as having unstable angina at admission to the coronary care unit. The trial was confined primarily to an observation period of 48 hours, although long term follow up continues. The protocol was designed to follow established cardiological practice as closely as possible. In particular, patients were admitted to the trial as soon as unstable angina was suspected before myocardial infarction could be excluded by enzyme measurements.

The trial was carried out under the auspices of the Interuniversity Cardiology Institute, in which all academic cardiology departments in the Netherlands participate. The trial was funded by the Dutch Ministry of Education. In addition, it was supported by grants from Bayer GmbH, Wuppertal, Germany, and Hässle AB, Mölndal, Sweden.

The first patient was enrolled on 1 February 1981.

On 30 October 1984 enrolment was discontinued because an interim analysis suggested that the risk of myocardial infarction was higher in patients assigned to nifedipine than in patients treated with the other trial medications. The data on which this decision was based are reproduced in appendix I. Both Bayer and Hässle and the Dutch health authorities were informed of the decision but not of the actual data. This report deals with the main findings on the efficacy of nifedipine and metoprolol in preventing recurrent ischaemia and myocardial infarction in the 515 patients who were eventually available for analysis.

Patients and methods

Organisation

Eight university and three non-university cardiology departments participated. Before the start of the trial the protocol was approved by the Scientific Council of the Interuniversity Cardiology Institute and by the principal investigators of participating non-university hospitals (together they formed the Executive Committee) and by the ethics committees at each participating centre. A Policy Advisory Board of acknowledged experts in related fields, not otherwise associated with the trial, also approved the protocol and adopted the task of progress monitoring. Until the decision was taken to discontinue the trial only this board was informed of the interim results.

Data were processed by the Clinical Epidemiology Unit of the Thoraxcentre in Rotterdam, which also provided overall coordination. Its staff was kept unaware of the patient medication assigned and interim results until the trial was discontinued.

The clinical course, electrocardiograms, and laboratory data of each patient up to 48 hours after start of trial medication were reviewed by a committee of three experienced cardiologists. This Classification Committee, which was unaware of the trial medication assignment and findings at subsequent angiography, determined which clinical events had taken place up to 48 hours after randomisation, according to predefined guidelines.

Patient recruitment and inclusion criteria

At admission to hospital patients were screened for immediate inclusion before the results of the enzyme measurements were known. Chest pain (if present) was treated with sublingual glyceryl trinitrate (maximum two 0·5 mg doses) and if it persisted an intravenous injection of glyceryl trinitrate (maximum 1 mg in 10 ml 5% glucose) or fentanyl (0·05 mg) was given.

To qualify for admission to the trial the presence of either of the following was required: a chest pain
episode in the hospital accompanied by a varying pattern of ST-T changes suggesting reversible myocardial ischaemia; a history of typical angina at rest or during light activity occurring within 12 hours of admission and lasting > 15 min combined with either ST-T abnormalities, a documented history of myocardial infarction or unstable angina, or at least 50% narrowing of a major coronary artery observed at earlier angiography. Patients who did not qualify at hospital admission were included on the basis of any of the above criteria when chest pain subsequently developed, provided that available enzyme values were below twice the local upper limit for normal.

If pain could not be relieved as described above, the patient was not admitted to the trial. In addition, the following exclusions were applied: age > 70, new Q wave formation on the electrocardiogram, acute myocardial infarction within one week, maintenance treatment with nifedipine, heart rate below 50 or above 120 beats/minute, systolic blood pressure < 100 mm Hg, systolic blood pressure > 170 mm Hg and diastolic pressure > 110 mm Hg, conduction abnormalities other than bundle branch block, anaemia (haemoglobin < 6.5 mmol/l, if known), clinically overt heart failure, congenital or valvar heart disease, cardiomyopathy, serious pulmonary or other non-cardiac disease, and previous participation in this trial. After eligibility had been established, oral informed consent was asked for and if it was obtained the trial medication was started without further delay.

TREATMENT
All patients received routine care for at least 48 hours. Sedatives and anticoagulants were given according to local practice. Oral long acting nitrates were continued if they had been given before admission to hospital; otherwise these drugs were not part of the standard regimen. Antiarrhythmics, digitalis, diuretics, and antihypertensive agents other than β blockers were given on indication only. Previous maintenance treatment with a β blocker was continued; before 13 November 1982 with the same compound and dose as given before, thereafter with two 100 mg doses of metoprolol per 24 hours. Chest pain was initially treated as described above. If pain persisted the decision to use further measures was left to the discretion of the attending physician.

Trial medication was added to the standard regimen as follows. Patients not on previous maintenance treatment with a β blocker for > 3 days were randomly assigned to receive either double placebo, nifedipine six 10 mg doses per 24 hours plus metoprolol placebo, metoprolol two 100 mg doses per 24 hours plus nifedipine placebo, or both drugs. Patients on previous maintenance treatment with a β blocker were randomly assigned to receive placebo or nifedipine six doses of 10 mg per 24 hours. No loading dosages were given. Both nifedipine and metoprolol (or their placebos) were started at the same time. Both randomisation procedures were performed for each clinic separately and in equal proportions.

Unless persistent chest pain developed, the trial medication was continued for at least 48 hours, preferably until catheterisation or discharge. In the event of suspected side effects trial medication was reduced or discontinued. The treatment code could be broken but only if it was considered mandatory by the attending physician. For this purpose a coding envelope was packed with each package of the trial medication.

DATA COLLECTION AND FOLLOW UP
Twelve lead electrocardiograms were recorded every six hours as well as during and after episodes of chest pain over the period from hospital admission until 48 hours after start of trial medication. The extent of ST depression and elevation was coded as described in appendix II in two electrocardiograms recorded before start of trial medication—that is, the last electrocardiogram obtained in the absence of pain (the baseline electrocardiogram) and for patients with pain while in hospital an electrocardiogram made during pain (the pain electrocardiogram).

Blood samples for measurement of activities of creatine kinase or its isoenzymes or both were obtained at least once before start of trial medication and every six hours until 54 hours thereafter. The activities of glutamic oxaloacetic and pyruvic transaminases, lactic acid dehydrogenase, and α-hydroxybutyric acid dehydrogenase were determined every 24 hours. After 54 hours enzyme measurements were left to local routine but were recorded when available. All enzyme determinations were performed locally and were subsequently related to local normal values. Heart rate was recorded every hour and blood pressure every six hours.

Cardiac catheterisation and coronary angiography, unless contraindicated, were performed preferably before discharge but not within 54 hours after start of trial medication.

DEFINITION OF OUTCOME EVENTS AND DATA ANALYSIS
A patient was classified as having "pre-randomisation myocardial infarction" when concentrations of one or more cardiac enzymes measured before the start of trial medication were significantly raised—that is, to more than twice the local upper limit for normal. In this case no outcome classification was defined. For all other patients the following two out-
come events were defined: recurrent ischaemia or myocardial infarction within 48 hours—that is, chest pain with ST-T changes and/or enzymatic evidence of infarction as defined below; myocardial infarction within 48 hours—that is, cardiac death or characteristic serial enzyme pattern with at least one cardiac enzyme significantly raised within 54 hours (as there is an intrinsic delay in the release of enzymes after the onset of myocardial infarction enzyme values until 54 hours after randomisation were taken into account). Myocardial infarction which occurred within the remainder of the first seven days was recorded according to clinical diagnosis. For all cases classified as myocardial infarction within 48 hours the most likely time of onset was determined retrospectively from the complete clinical history. In addition, the time of appearance of a Q wave lasting > 0.03 seconds or of a Q wave equivalent (R > 0.03 seconds in V1 and R/S > 1 in V2) was noted.

Those patients for whom an unequivocal protocol violation occurred before the start of trial medication were excluded from analysis. These exclusions were applied retrospectively by the Classification Committee. Patients were retained, however, if the committee disagreed with the attending physician’s assessment of qualifying ST-T abnormalities or changes. Treatment effects were assessed in terms of the occurrence of the two outcome events defined above. In accordance with the protocol, patients classified as having pre-randomisation myocardial infarction were excluded from this assessment. Treatment effects were expressed as the ratio of the rate of the respective outcome event observed in patients allocated to a specific index trial medication to that observed in patients allocated to a specific reference trial medication. For instance, the effect of nifedipine relative to placebo is the rate of the outcome event in the nifedipine group divided by that in the placebo group. Thus a rate ratio of one indicates that nifedipine has no effect relative to placebo. A rate ratio of < 1 points to a preventive effect and a rate ratio > 1 to a detrimental effect. The 95% confidence intervals of the rate ratio estimates are also given.

We used a composite logistic prediction function to determine which baseline characteristics were independently related to the risk of recurrent ischaemia or myocardial infarction within 48 hours. The baseline risk of recurrent ischaemia or myocardial infarction within 48 hours (that is, the probability that such an event would occur) was estimated for each patient separately given individual baseline characteristics and the prediction function. Patients were subsequently divided into three subgroups of low, medium, and high risk.

In the analysis we found that despite random allocation, trial medication groups differed in terms of the distribution of baseline risk. To adjust for this, relative treatment effects, as defined above, were estimated as weighted averages of risk subgroup specific effects. Full details of the analytic methods are given in appendix II.

STUDY SIZE REQUIREMENTS
The protocol stated that trial treatments were to be evaluated in terms of the rates of recurrent ischaemia or myocardial infarction within 48 hours in patients without myocardial infarction at the start of trial medication. If it is assumed that this rate would be 40% in placebo treated patients who were not already on β blockade, that nifedipine and metoprolol alone would reduce this rate to 20%, and that the combination would reduce this further to 10% (that is event rates of 40%, 20%, 20%, and 10% respectively), 70 patients per group are required for a 97% chance of obtaining a statistically significant (p < 0.05) result in a 4 × 2 contingency table χ² test. To allow for lower rates and the possibility that only the combination would be effective, we planned to study 150 patients per group.

Results

RECRUITMENT AND EXCLUSIONS
Between 1 February 1981 and 30 October 1984, 668 patients were enrolled. The median contribution per centre was 50 patients, ranging from seven (for a centre that participated only during the last nine months) to 144. Randomisation by centre resulted in balanced trial medication groups.

Figure 1 shows that a violation of the admission protocol occurred in 131 patients; these cases were excluded. Another 22 patients classified as having pre-randomisation myocardial infarction were left out from trial medication assessment. In 82% of the 515 remaining patients the treating physician’s judgement on qualifying ST-T abnormalities or changes was independently confirmed by the Classification Committee. Figure 1 also shows the overall occurrence of relevant clinical events. All deaths were caused by myocardial infarction.

Figure 2 shows the time of onset in 89 cases of non-fatal myocardial infarction within 48 hours of the start of trial medication. In 43 patients acute myocardial infarction was thought to have occurred before the start of trial medication despite cardiac enzyme concentrations being below twice the upper limit for normal at that time. Figure 2 also shows the time of first occurrence of a significant rise in enzyme concentrations and that of a new Q wave.

Table 1 shows selected baseline characteristics in
Patients randomised

- 131 protocol violations before start trial medication (some patients were excluded for more than one reason)
  - 22 last chest pain > 12 hours before
  - 49 exclusion criterion overlooked
  - 40 chest pain not treated as prescribed
  - 5 glyceryl trinitrate infusion started
  - 5 previous use of β-blockade not properly taken into account
  - 6 not pain free at start
  - 15 other reasons

Patients with unstable angina as defined

- 22 (1 died) pre-randomisation myocardial infarction (MI₀)

Patients available for assessment of trial medication effect

- 92 MI₄₈ (3 died within 48 hours, 1 died between 2–7 days)
- 99 no MI₄₈
- 20 MI between 2–7 days (4 died)

Fig 1 Exclusions from data analysis and overall distributions of outcome events. MI₀, pre-randomisation myocardial infarction; RI/MI₄₈, recurrent ischaemia or myocardial infarction within 48 hours; MI₄₈, myocardial infarction within 48 hours.

Fig 2 Timing of the onset of non-fatal myocardial infarction, the first significant rise in enzyme concentration, and the appearance of Q waves for 89 cases of non-fatal myocardial infarction within 48 hours in 515 patients without enzymatic evidence of infarction at randomisation. The time of the onset of myocardial infarction was determined retrospectively by the Classification Committee from the complete clinical history. The upper dotted line represents the cumulative distribution of the time of onset of myocardial infarction—that is, it represents for each point in time after randomisation the total number of patients with an onset before that time. In 43 cases the onset was judged to have taken place before randomisation; the upper line thus starts at 43. Similarly the middle broken line represents the cumulative distribution of the time of first rise in enzyme concentration to over twice the local upper limit of normal and the lower solid line the time of first appearance of a Q wave on the electrocardiogram.
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Table 1 Baseline characteristics and corresponding outcome event rates

<table>
<thead>
<tr>
<th></th>
<th>RI/MI48</th>
<th>MI48</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>515 (100%)</td>
<td>191 (37%)</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55 years</td>
<td>183 (36%)</td>
<td>69 (38%)</td>
</tr>
<tr>
<td>55–65 years</td>
<td>248 (48%)</td>
<td>92 (37%)</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>84 (16%)</td>
<td>30 (36%)</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>387 (75%)</td>
<td>149 (39%)</td>
</tr>
<tr>
<td>Female</td>
<td>128 (25%)</td>
<td>42 (33%)</td>
</tr>
<tr>
<td>History of myocardial infarction:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>340 (66%)</td>
<td>134 (39%)</td>
</tr>
<tr>
<td>Yes</td>
<td>175 (34%)</td>
<td>57 (33%)</td>
</tr>
<tr>
<td>History of angina &gt; 4 weeks:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>308 (60%)</td>
<td>116 (38%)</td>
</tr>
<tr>
<td>Yes</td>
<td>207 (40%)</td>
<td>75 (36%)</td>
</tr>
<tr>
<td>Previous maintenance treatment with a β blocker:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>338 (66%)</td>
<td>121 (36%)</td>
</tr>
<tr>
<td>Yes</td>
<td>177 (34%)</td>
<td>70 (40%)</td>
</tr>
<tr>
<td>Pain free interval:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 hour</td>
<td>133 (26%)</td>
<td>82 (62%)</td>
</tr>
<tr>
<td>1–3 hours</td>
<td>186 (36%)</td>
<td>66 (35%)</td>
</tr>
<tr>
<td>&gt; 3 hours</td>
<td>196 (38%)</td>
<td>43 (22%)</td>
</tr>
<tr>
<td>Baseline ECG:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not codable</td>
<td>20 (4%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>No ST depression ≥ 0.1 mV</td>
<td>402 (78%)</td>
<td>136 (34%)</td>
</tr>
<tr>
<td>ST depression ≥ 0.1 mV</td>
<td>93 (18%)</td>
<td>47 (51%)</td>
</tr>
<tr>
<td>Comparison of pain ECG with baseline ECG:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not possible*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same ST coding</td>
<td>82 (16%)</td>
<td>32 (39%)</td>
</tr>
<tr>
<td>More ST depression†</td>
<td>159 (31%)</td>
<td>87 (55%)</td>
</tr>
<tr>
<td>More ST elevation‡</td>
<td>101 (20%)</td>
<td>60 (59%)</td>
</tr>
<tr>
<td>Baseline risk for RI/MI48:‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>303 (59%)</td>
<td>65 (21%)</td>
</tr>
<tr>
<td>Medium</td>
<td>126 (24%)</td>
<td>67 (53%)</td>
</tr>
<tr>
<td>High</td>
<td>86 (17%)</td>
<td>59 (69%)</td>
</tr>
</tbody>
</table>

RI/MI48, recurrent ischaemia or myocardial infarction within 48 hours; MI48, myocardial infarction within 48 hours; ECG, electrocardiogram.

*No pain observed after hospital admission or no (codable) pain free electrocardiogram available for comparison.
†Including 50 patients who had more ST depression as well as more ST elevation.
‡As estimated from previous maintenance treatment with a β blocker, pain free interval, baseline electrocardiogram, and comparison of pain electrocardiogram with baseline electrocardiogram (see appendix II).

There were only small differences between the rates of recurrent ischaemia or myocardial infarction within 48 hours of the start of trial medication for respective categories of age, sex, history of coronary disease, and previous β blockade. Trial medication was started after a pain free interval of less than one hour in 26% of patients and in a further 36% after an interval of between one and three hours. The length of this interval was strongly related to the rate of recurrent ischaemia or myocardial infarction within 48 hours: 62% of patients who had a pain free interval of less than one hour developed recurrent ischaemia or myocardial infarction within 48 hours as opposed to 22% of those in whom the pain free interval lasted more than three hours (table 1). The rate of recurrent ischaemia and myocardial infarction within 48 hours was also related to the presence of ST depression > 0.1 mV on the baseline electrocardiogram. Patients without pain observed while in hospital had a lower event rate than those with pain. In those with pain the event rate was also related to the presence of changes in ST coding during pain.

Of the baseline characteristics listed in table 1, previous use of β blockers, pain free interval before the start of trial medication, and ST coding of electrocardiograms made during and after pain were retained in the logistic function for the estimation of the baseline risk for recurrent ischaemia or myocardial infarction within 48 hours. Based on this estimation, 59% of patients were grouped as "low", 24% as "medium", and 17% as "high" risk. The observed rates were 21%, 53% and 69% respectively. The rate of myocardial infarction within 48 hours was also strongly related to this stratification. Appendix II gives full details of the logistic function.

Comparability of trial medication groups and use of concomitant medication

Table 2 shows the trial medication allocation. Of 338 patients who were not on previous maintenance treatment with a β blocker 84 were assigned to placebo, 89 to nifedipine, 79 to metoprolol, and 86 to the combination. Placebo was added to continued β
Table 2  Distribution of baseline characteristics between trial medication groups

<table>
<thead>
<tr>
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<th>No previous maintenance treatment with a β blocker</th>
<th>Previous maintenance treatment with a β blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Placebo</td>
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<tr>
<td>Number of allocations</td>
<td>515</td>
<td>84</td>
</tr>
<tr>
<td>Age:</td>
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</tr>
<tr>
<td>&lt; 55 years</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>55-65 years</td>
<td>48%</td>
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<tr>
<td>&gt; 65 years</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>Sex:</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>Female</td>
<td>25%</td>
<td>29%</td>
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<tr>
<td>History of myocardial infarction:</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>66%</td>
<td>73%</td>
</tr>
<tr>
<td>Yes</td>
<td>34%</td>
<td>27%</td>
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<td>History of angina longer than 4 weeks:</td>
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<tr>
<td>No</td>
<td>60%</td>
<td>69%</td>
</tr>
<tr>
<td>Yes</td>
<td>40%</td>
<td>31%</td>
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<td>Previous maintenance treatment with a β blocker:</td>
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<td></td>
</tr>
<tr>
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<td>66%</td>
<td>100%</td>
</tr>
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<tr>
<td>&lt; 1 hour</td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>1-3 hours</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>&gt; 3 hours</td>
<td>38%</td>
<td>50%</td>
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<tr>
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<tr>
<td>Not codable</td>
<td>4%</td>
<td>6%</td>
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<td>76%</td>
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<td>18%</td>
<td>18%</td>
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<td>15%</td>
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<tr>
<td>More ST depression†</td>
<td>31%</td>
<td>29%</td>
</tr>
<tr>
<td>More ST elevation†</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Baseline risk of R1/M1†</td>
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<td></td>
</tr>
<tr>
<td>Low</td>
<td>59%</td>
<td>67%</td>
</tr>
<tr>
<td>Medium</td>
<td>24%</td>
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</tr>
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<td>17%</td>
<td>7%</td>
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</tbody>
</table>

R1/M1, recurrent ischaemia or myocardial infarction within 48 hours; ECG, electrocardiogram.

*No pain observed after hospital admission or no (codable) pain free electrocardiogram available for comparison.
†Including 50 patients who had greater ST depression and greater ST elevation.
‡As estimated from previous maintenance treatment with β blocker, pain free interval, baseline electrocardiogram, and comparison of pain electrocardiogram with baseline electrocardiogram (see appendix II).

blocker treatment in 81 patients and nifedipine in 96. Table 2 also shows the baseline characteristics for each trial medication group separately. Baseline risk for recurrent ischaemia or myocardial infarction within 48 hours was distributed differently over the trial medication groups. Among patients not on previous maintenance treatment with a β blocker 18% of those allocated to nifedipine were high risk; for the other three trial medication groups this percentage ranged from 5% to 12%. The higher risk of the nifedipine group was due primarily to a relatively large proportion (33%) of patients in whom trial medication was started within one hour after the last attack of pain (a strong indicator of risk, table 1). In

Table 3  Use of trial medication at randomisation and during follow up for each trial medication group

<table>
<thead>
<tr>
<th></th>
<th>Use in relation to randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At randomisation</td>
</tr>
<tr>
<td>Placebo (n = 84)</td>
<td>100%</td>
</tr>
<tr>
<td>Nifedipine (n = 89)</td>
<td>100%</td>
</tr>
<tr>
<td>Metoprolol (n = 79)</td>
<td>100%</td>
</tr>
<tr>
<td>Combination (n = 86)</td>
<td>100%</td>
</tr>
<tr>
<td>Placebo (n = 81)</td>
<td>100%</td>
</tr>
<tr>
<td>Nifedipine (n = 96)</td>
<td>100%</td>
</tr>
</tbody>
</table>
Nifedipine and metoprolol in unstable angina

Table 4 Outcome event rates in trial medication groups stratified for estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours

<table>
<thead>
<tr>
<th></th>
<th>MI0</th>
<th>No MI0</th>
<th>RI/MI48</th>
<th>MI48</th>
<th>MI48 + Q</th>
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</thead>
<tbody>
<tr>
<td><strong>Placebo:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>3</td>
<td>84</td>
<td>31 (37%)</td>
<td>13 (15%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Low risk</td>
<td>56</td>
<td>31 (23%)</td>
<td>2 (5%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>22</td>
<td>13 (59%)</td>
<td>1 (28%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>6</td>
<td>5 (83%)</td>
<td>2 (33%)</td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td>Nifedipine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>4</td>
<td>89</td>
<td>42 (47%)</td>
<td>25 (28%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>Low risk</td>
<td>53</td>
<td>22 (28%)</td>
<td>4 (8%)</td>
<td>6 (8%)</td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>20</td>
<td>14 (70%)</td>
<td>6 (30%)</td>
<td>4 (20%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>16</td>
<td>13 (81%)</td>
<td>1 (6%)</td>
<td>6 (38%)</td>
<td></td>
</tr>
<tr>
<td>Metoprolol:</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
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<td>79</td>
<td>22 (28%)</td>
<td>13 (16%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Low risk</td>
<td>52</td>
<td>10 (19%)</td>
<td>6 (12%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>23</td>
<td>9 (39%)</td>
<td>5 (22%)</td>
<td>3 (13%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>4</td>
<td>3 (75%)</td>
<td>2 (50%)</td>
<td>1 (25%)</td>
<td></td>
</tr>
<tr>
<td>Combination:</td>
<td>7</td>
<td>86</td>
<td>26 (30%)</td>
<td>12 (14%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>All patients</td>
<td>6</td>
<td>12 (18%)</td>
<td>4 (7%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>52</td>
<td>10 (19%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>20</td>
<td>12 (60%)</td>
<td>5 (25%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>10</td>
<td>5 (50%)</td>
<td>3 (30%)</td>
<td>2 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MI0</th>
<th>No MI0</th>
<th>RI/MI48</th>
<th>MI48</th>
<th>MI48 + Q</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>2</td>
<td>81</td>
<td>41 (51%)</td>
<td>16 (20%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Low risk</td>
<td>34</td>
<td>8 (24%)</td>
<td>3 (9%)</td>
<td>2 (6%)</td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>18</td>
<td>12 (67%)</td>
<td>2 (11%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>29</td>
<td>21 (72%)</td>
<td>11 (38%)</td>
<td>4 (14%)</td>
<td></td>
</tr>
<tr>
<td>Nifedipine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>2</td>
<td>96</td>
<td>29 (30%)</td>
<td>13 (14%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Low risk</td>
<td>52</td>
<td>10 (19%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>23</td>
<td>7 (30%)</td>
<td>2 (9%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>21</td>
<td>12 (57%)</td>
<td>7 (33%)</td>
<td>4 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

*MI0, pre-randomisation myocardial infarction; RI/MI48, recurrent ischaemia or myocardial infarction within 48 hours; MI48, myocardial infarction within 48 hours; MI48 + Q, myocardial infarction within 48 hours with subsequent Q wave formation.*

Patients who were on continued β blockade the same was true for patients allocated to placebo, although to a lesser extent.

Oral long acting nitrates had been given to 100 patients at admission to hospital and were continued in 76%. Thus 439 patients did not receive oral long acting nitrates at randomisation. These drugs were later given, on indication, to 11% of these patients. Anticoagulants (coumarins or heparin) were given to 67%. At the start of the trial or during follow up 14% received diuretics, 3% digitalis, and 3% platelet aggregation inhibiting drugs. Medication at hospital admission was not related to the risk of recurrent ischaemia or myocardial infarction within 48 hours.

Table 3 shows the percentage of patients still on trial medication 6, 12, and 48 hours after randomisation. At 48 hours the percentage of patients still on trial medication ranged from 63% of patients allocated to nifedipine who were not on previous maintenance β blockade to 76% of patients allocated to placebo who were not on previous β blockade. The predominant reasons for discontinuation of trial medication were recurrent chest pain and diagnostic findings of myocardial infarction. In five patients the trial medication code was broken within 48 hours of randomisation.

**Outcome event rates in trial medication groups and relative effects of treatment**

Table 4 shows the number of pre-randomisation infarctions by trial medication group. Also shown are the outcome event rates for patients without pre-randomisation infarction, both overall and according to stratum of baseline risk for recurrent ischaemia or myocardial infarction within 48 hours. The directions of the differences between the trial medication groups were consistent over the risk strata. In patients not on previous maintenance treatment with a β blocker who were treated with nifedipine both event rates were higher than the corresponding ones for those on placebo. This was also true for Q wave infarctions. On the other hand, in patients on metoprolol or on the combination, event rates tended to be lower than the rates for those on placebo. In patients who were already on a β blocker, the nifedipine group tended to have lower event rates than the placebo group.

Table 5 gives the estimated relative effects
expressed as weighted averages of risk stratum specific rate ratios together with the 95% confidence intervals for all choices of index and reference trial medication.

**Discussion**

**CLINICAL SPECTRUM OF UNSTABLE ANGINA DIAGNOSED AT ADMISSION TO CORONARY CARE UNIT**

According to one widely accepted definition patients who have recent onset (effort) angina, worsening angina, or angina at rest are classified as having unstable angina provided there are no signs of acute myocardial infarction. It is generally recognised that the differential diagnosis of such cases may be difficult and that myocardial infarction may have already occurred or may be about to occur. The present trial reports clinical events and their timing in 537 patients in whom unstable angina was diagnosed at admission to the coronary care unit.

This diagnosis was based on a combination of findings—angina at rest, evidence for cause myocardial ischaemia, and absence of signs of acute myocardial infarction such as persistent pain or characteristic electrocardiographic signs (a subcategory of unstable angina as defined above). Not unexpectedly in 4% (22 out of 537, fig 1) there had already been myocardial infarction with an increase in enzyme concentrations. These cases of myocardial infarction could have been diagnosed immediately had laboratory measurements been immediately available. Within a week of the start of the trial myocardial infarction had occurred in 25% (22 + 92 + 20 out of 537, fig 1). Thus there is a considerable risk of myocardial infarction during this period. Similar percentages have been reported before but the time of the onset of infarction (retrospectively determined from the complete clinical history) relative to the time when the diagnosis of unstable angina was made was not given. Figure 2 shows that the onset of myocardial infarction was judged to have occurred before the start of trial medication in 43 cases and that there were 34 further cases within six hours of the start of the trial. Only few infarctions occurred later than six hours after the start of the trial. Thus so far as myocardial infarction occurs in patients diagnosed as having unstable angina, its onset tends to cluster around the time of diagnosis. The clinical implications of this finding are considerable and it shows that treatment which aims at the prevention of progression to myocardial infarction will have a limited effect because in most cases it will come too late.

Despite the high frequency of myocardial infarction, this trial supports the notion that the prognosis in patients with this type of unstable angina is good. Total one week mortality was only 1.7% (9/537, fig 1). Our results indicate that the short term risk of recurrent ischaemia or myocardial infarction is primarily related to the interval since the last attack of pain on the one hand and to the presence of resting ST abnormalities and pain related ST changes on the other (table 1 and appendix II). The first finding is understandable because by definition the condition of patients with a long interval between last pain attack and diagnosis has stabilised. The second finding accords with current views and previous findings on the relevance of electrocardiography in such patients.

We did not attempt to relate the baseline risk of recurrent ischaemia or myocardial infarction within 48 hours to findings at subsequent coronary angiography. Unless there are compelling reasons for an emergency procedure, catheterisation is generally only carried out a few days after hospital admission at the earliest. Thus in most patients catheterisation results are not relevant to the initial management.

Does the clinical spectrum seen in the patients we studied in 1981–84 remain valid today? There does not seem to have been any major change in the initial clinical recognition of unstable angina and its differentiation from myocardial infarction or in the pharmacotherapeutic approach. On the other hand, emergency percutaneous transluminal coronary...
Nifedipine and metoprolol in unstable angina

angioplasty or bypass surgery are now increasingly offered, with good results.\textsuperscript{21} It is unlikely, however, that the more general use of these procedures will have had any great effect on the clinical spectrum because such procedures are usually restricted to patients in whom chest pain persists despite maximal pharmacological treatment. In such cases angioplasty or bypass surgery may prevent the occurrence of myocardial infarction. Of the infarctions in the present trial only the later ones could have been prevented in this way, and there were only a few of these.

EFFECTS OF TRIAL MEDICATION

On the basis of an interim analysis enrolment in the present trial was discontinued (appendix I). This was because continuation of nifedipine monotherapy trial medication was considered to be unethical and, secondly, because there were only small differences between the other groups. The final data as presented here essentially accord with the interim data that led to this decision (tables 4 and 5, and appendix I).

Although the series is large, the trial medication groups are rather small. In a randomised trial with small groups the results may indicate differences in the baseline risk between the groups. Table 2 shows that this was indeed the case. We used an approach developed for non-experimental epidemiological studies\textsuperscript{22} to impose risk stratification based on a composite logistic function of relevant baseline characteristics on our study group and we have expressed trial medication effects as weighted averages of stratum specific rate ratios. This approach ensures that the estimation of trial medication effect becomes independent of the distribution of baseline risk in the groups that are compared. The use of 95% confidence intervals for the rate ratios so obtained provides a better indication of the statistical strength of evidence than the customary significance levels (p values).\textsuperscript{23}

Patients with a pre-randomisation myocardial infarction are no longer at risk of the defined outcome events. Therefore, we excluded these patients before we assessed the trial medication effects. To allow for effect analyses based on other principles the number of pre-randomisation infarctions is also given per treatment group (table 4).

Of all the treatments studied only the addition of nifedipine to previous maintenance treatment with a \( \beta \) blocker was clearly beneficial. None of the other trial regimens came out as being unequivocally effective. Furthermore, there was a worrying trend towards an increased risk for myocardial infarction in patients assigned to nifedipine alone. What is the explanation for these findings?

We postulate that when nifedipine is given to patients whose condition has become unstable despite maintenance treatment with a \( \beta \) blocker coronary spasm may play a larger role than it does in patients not on \( \beta \) blockade. This would explain the efficacy of additional treatment with a coronary spasmolytic agent such as nifedipine.

We do not believe that the apparent lack of effect of the other trial medications is caused by the selection of already stabilised patients, which would lead to too few potential outcome events. The event rate of recurrent ischaemia or myocardial infarction within 48 hours was considerable and accorded with the a priori design assumptions. Nevertheless, the confidence intervals given in table five do not exclude the possibility that relevant trial medication effects were missed. We believe that the most likely explanation lies in the particular clinical situation that this trial was designed to examine. The trial design assumed that neither ischaemia nor necrosis was present after eligibility had been established. We realised that because there are no specific early electrocardiographic signs of necrosis inclusion of some patients in whom myocardial infarction was already evolving would be unavoidable. Although we appreciated that enzyme concentrations increase within hours of the onset of myocardial infarction, we decided to exclude patients from trial medication assessment only if enzymes were already significantly raised at randomisation. This was decided for two reasons. Firstly, if enzyme measurements obtained after randomisation were used as a basis for exclusion the validity of comparisons between trial medications could be compromised. This would have occurred if any of the trial medications had affected the release of enzymes from necrotic myocardium rather than the amount of necrosis. Secondly, only enzyme measurements known at that time could be relevant to the formulation of treatment guidelines based on the results of this trial. Of patients classified as having recurrent ischaemia or myocardial infarction within 48 hours and retained in the analysis, a considerable proportion (92 out of 197, table 1) sustained a myocardial infarction, generally before the start of trial medication or so soon thereafter that oral treatment could not be fully effective (fig 2). Thus an important fraction of the events on which effect estimation was based is unlikely to be affected by a preventive effect of trial medication, notwithstanding such an effect in another context. To be effective in this context a medication must not only prevent recurrent ischaemia or infarction in patients who are still at risk when treatment becomes effective but must also limit necrosis in those in whom the process of infarction has already progressed to the extent that
an otherwise detectable infarction would become
undetectable by current conventional diagnostic
methods. Neither nifedipine nor metoprolol are
likely to meet these requirements. Nifedipine has not
been shown to reduce infarct size when given to
patients with myocardial infarction. Animal
experiments indicate that nifedipine does not protect
the myocardium when given after onset of
ischaemia. Nor is the effect of β blockade on infarct
size definitively known.

The reason why nifedipine monotherapy increases
the risk of progression to myocardial infarction
cannot be determined from our data. The nifedipine
results may be a chance finding. On the other hand,
they virtually exclude a major preventive effect of
nifedipine used in this way for this indication. We do
not believe that nifedipine's postulated influence on
the release of enzymes explains this finding—there
were more Q wave infarcts in the nifedipine mono-
therapy group than in the placebo group (table 4).
Relative to placebo, nifedipine did not raise the heart
rate substantially but it reduced blood pressure. It is
possible therefore that the temporary rise in heart
rate in combination with a decrease in blood pres-
sure, which has been observed before, plays a role.

Nifedipine is generally accepted to be of particular
value in patients with ST elevation during pain. A
hundred and one patients had these features before
entry (table 1). Subgroup analysis did not show that
these patients especially benefited from nifedipine
alone.

Comparison with other studies
In another trial for which patients were selected at
hospital admission treatment with four 20 mg doses
of nifedipine given over 24 hours was compared with
placebo. Eligibility for the trial, however, required
more prolonged chest pain than in the present trial
and patients with electrocardiographic evidence of
acute infarction were not excluded. Patients were
later stratified into either acute or threatened myo-
cardial infarction groups on the basis of the presence
or absence of increased enzyme concentrations and
Q waves at randomisation. The group with threat-
ened myocardial infarction resembled the patients
that we studied. The rate of progression to myo-
cardial infarction, 75% after 24 hours, was much
higher, however, probably because chest pain had
been present for longer. The progression rate in the
nifedipine and placebo groups was similar, as was
enzymatic infarct size. The number of patients who
were also treated with a β blocker was not reported,
so direct comparison with our results is impossible.
In another trial in patients diagnosed as having
"threatened infarction" treatment with propranolol
was compared with conventional treatment. The
effect of propranolol resembled that of metoprolol in
the present trial.

Treatments in patients with unstable angina after
enzyme concentrations were known to be normal
have been studied in several trials with varying selec-
tion criteria. In one the addition of nifedipine to a
standard regimen of propranolol and long acting
nitrates reduced recurrent ischaemia during a three
month follow up. Nifedipine without concomitant
β blockade was not studied. Another trial compared
a conventional step-up regimen of long acting
nitrates and propranolol with increasing dosages of
nifedipine during a treatment period of 14 days.
Overall there were no differences in recurrent
ischaemia and 14% progressed to infarction in both
groups. Because this trial did not have a placebo
control group it is not possible to tell whether both
regimens were equally effective or equally
ineffective. In the subgroup of patients who were on
maintenance treatment with propranolol the addi-
tion of nifedipine controlled pain more rapidly than
did the addition of nitrates or an increase of the
propranolol dose. On the other hand, in the sub-
group of patients who were not on maintenance
propranolol the administration of propranolol or
nitrates or both controlled pain more rapidly than
did nifedipine. Our results accord with these
findings. Moreover, they provide evidence for a pos-
tive effect of a particular β blocker in patients not
already on such treatment compared with placebo
and for a similar effect of nifedipine in patients
already using a β blocker.

Clinical implications
The present results confirm that with currently
available diagnostic methods it is impossible to
reliably differentiate unstable angina from evolving
myocardial infarction at admission of a patient to a
coronary care unit. Many of the patients with sus-
pected unstable angina have already sustained a
myocardial infarction or are in the process of doing
so.

Initial management must take into account the
possible presence of evolving myocardial infarction.
The first management objective therefore becomes
the reduction of the total number of infarcts even-
tually diagnosed among this subgroup of patients,
irrespective of the precise time of onset relative to the
start of treatment. To achieve this treatment must
both reduce the size of evolving infarctions and pre-
vent those which are about to develop.

Our results indicate that previous use of a β
blocker is an important consideration. They suggest
that in patients not already on a β blocker, a β blocker
is the treatment of first choice. The fixed combina-
tion of metoprolol and nifedipine had no additional
Nifedipine and metoprolol in unstable angina

advantages. Patients with ST elevations during pain did not seem to benefit from nifedipine. Furthermore, nifedipine cannot be recommended as monotherapy because it was associated with a higher incidence of myocardial infarction. On the other hand, patients whose condition has become unstable despite maintenance treatment with a β blocker can be expected to react favourably to the addition of nifedipine to a regimen of continued β blockade.

We acknowledge with gratitude the leadership of the late Dirk Durrer, past chairman of the Executive Committee.

Appendix I

On 27 October 1984 the Policy Advisory Board was presented with the following interim classification results of 593 randomised patients who were included irrespective of protocol violations:

<table>
<thead>
<tr>
<th>MI₀</th>
<th>No MI₀</th>
<th>RI/MI₄₈</th>
<th>MI₄₈</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7</td>
<td>86</td>
<td>30 (35%)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>7</td>
<td>95</td>
<td>41 (43%)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>6</td>
<td>89</td>
<td>28 (31%)</td>
</tr>
<tr>
<td>Combination</td>
<td>7</td>
<td>88</td>
<td>30 (34%)</td>
</tr>
</tbody>
</table>

MI₀, pre-randomisation myocardial infarction; RI/MI₄₈, recurrent ischaemia or myocardial infarction within 48 hours; MI₄₈, myocardial infarction within 48 hours.

For myocardial infarction within 48 hours the nifedipine:placebo rate ratio was 2.0 with a 95% confidence interval (1.1, 3.6). The Policy Advisory Board recommended discontinuation of the trial on ethical grounds because of the observed adverse effect in the group on nifedipine alone and because the effects in the other groups were smaller than expected and would have required a much larger trial for adequate statistical power.

This recommendation was accepted by the Executive Committee, which included the principal investigators of the participating centres.

Measures to discontinue inclusion were put into effect immediately.

Appendix II

The baseline risk for recurrent ischaemia or myocardial infarction within 48 hours is defined as the probability that recurrent ischaemia or myocardial infarction would occur within 48 hours given the patient’s baseline characteristics and trial medication assignment to placebo. To estimate a patient’s base-line risk, a logistic function was fitted to the data. This function relates the probability of recurrent ischaemia or myocardial infarction within 48 hours to a set of baseline characteristics X₁, X₂, …, Xₖ using the logistic function:

\[ P = \frac{1 + \exp \left[ -(a + b₁X₁ + b₂X₂ + \ldots + bₖXₖ) \right]}{1 + \exp \left[ -b₁ \right]}. \]

Coding of baseline characteristics

As a general principle only indicator variables were used—that is variables that assume the value 1 if the property at issue is present and 0 if otherwise.

ST depression and ST elevation (measured 0-8 seconds after the J point) was scored according to the following categories: absent; <0.5 mm; between 0.5 and 1.0 mm; between 1.0 and 2.0 mm; between 2.0 and 5.0 mm; >5 mm. Maximum values were recorded for the following groups of leads: (1) V2; (2) V3–V5; (3) II, III, aVF; (4) I, aVL, V6. Electrocardiographic characteristics were expressed in terms of abnormalities present on the baseline electrocardiogram and of changes in the pain electrocardiogram relative to the baseline electrocardiogram. We used separate codes to indicate that the baseline or the pain electrocardiogram was not available. The latter circumstance is of clinical relevance because this would occur if the patient had arrived at the hospital after chest pain had subsided.

Variable selection

We used data on all patients to fit the logistic function. Variables indicating the patient’s trial medication and pre-treatment with a β blocker were kept in the model all the time.

Baseline characteristics were selected for inclusion in the model on the basis of their overall (statistical) contribution to prediction and on medical plausibility. None of the characteristics related to the patient’s history or medication before admission to hospital was selected. Only the interval since the last attack of chest pain and certain electrocardiographic characteristics proved to be predictive for recurrent ischaemia or myocardial infarction within 48 hours.
The baseline risk function was obtained by setting the variables representing the patient's actual trial medication to values representing treatment with placebo.

Table 6 shows the variables that were eventually retained in the model with their coefficients and standard errors.

**STRATIFIED ANALYSIS**

Patients were ranked on the basis of their calculated baseline risk and were subsequently divided into three strata of low, medium, and high risk. The cutoff points were chosen so that each stratum contained an equal number of patients in whom recurrent ischemia or myocardial infarction within 48 hours had occurred. We calculated rate ratios as weighted averages of the stratum specific rate ratios for each trial medication comparison and for each variable of interest, and thus adjusted for variability of the baseline risk. Confidence limits were calculated accordingly.

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