Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison*

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ABSTRACT  Preliminary clinical and laboratory observations suggest that nifedipine might prevent progression of threatened myocardial infarction by reversing coronary spasm or might limit necrosis during the course of acute myocardial infarction. We screened 3143 patients with ischemic pain of > 45 min duration and randomly assigned 105 eligible patients with threatened myocardial infarction and 66 with acute myocardial infarction to receive nifedipine (20 mg orally every 4 hr for 14 days) or placebo plus standard care. Treatment was started 4.6 ± 0.1 hr after the onset of pain. Infarct size index was calculated by the MB-creatine kinase (CK) method and expressed as CK-geq/m² ± SE. The incidence of progression to infarction among patients with threatened myocardial infarction was not significantly altered by nifedipine (36 of 48 [75%] for placebo-treated and 43 of 57 [75%] for nifedipine-treated patients). Furthermore, infarct size index was similar among placebo- and nifedipine-treated patients (16.9 ± 1.5 MB-CK-geq/m², n = 65, and 17.0 ± 1.5 MB-CK-geq/m², n = 68, respectively) with threatened myocardial infarction who exhibited infarction and for those with acute myocardial infarction. Among the 171 eligible patients randomly assigned to drug or placebo, 6 month mortality did not differ significantly (8.5% for placebo vs 10.1% for nifedipine, NS), but mortality in the 2 weeks after randomization was significantly higher for nifedipine-treated patients (0% for placebo compared with 7.9% for nifedipine, p = .018). There were no significant differences in 2 week and 6 month mortalities in the group of all participating patients, which included 10 patients randomly assigned therapy but retrospectively determined to be ineligible. Two week mortality for this group (n = 181) was 2.3% for placebo- and 7.5% for nifedipine-treated patients and 6 month mortality was 11.4% for placebo- and 10.8% for nifedipine-treated patients. Thus, nifedipine therapy did not prevent progression of threatened myocardial infarction to the acute event or limit infarct size in patients who experienced infarction. There was a statistically significant increase in 2 week mortality with nifedipine in the group of eligible patients randomly assigned to a regimen, but mortality was balanced when results were analyzed for all patients taking part in the randomization protocol.


CALCIUM CHANNEL-BLOCKING drugs are effective in the treatment of Prinzmetal’s angina and chronic stable angina. They may also be of prophylactic or therapeutic value for acute myocardial infarction (AMI). Their potent spasmolytic properties may reverse the coronary spasm that is thought, in some cases, to initiate myocardial infarction. In addition, calcium blockers may limit the quantity of ischemic myocardium that eventually becomes necrotic whether or not flow is increased via the compromised vessel of supply. This beneficial effect may result from a decrease in oxygen demand through reduction of afterload, an increase in oxygen supply through improved coronary collateral flow, and/or metabolic benefits in cells exposed to a given ischemic insult.

Accordingly, in 1979 we initiated a trial of nifedipine for patients with threatened myocardial infarction (TMI) and AMI. The purpose of the trial was to determine if nifedipine therapy could prevent progression of TMI and/or limit necrosis in patients with infarction.
Methods

The trial involved investigators from six medical institutions.* Patients were considered to have TMI if they had prolonged pain due to ischemia but no enzymatic or electrocardiographic (ECG) evidence of infarction. The primary end points in this group were progression to and extent of infarction, as determined by analysis of plasma MB-creatine kinase (CK) values. Patients were considered to have had an AMI if they had prolonged ischemic pain and either enzymatic or ECG evidence of necrosis at the time of randomization. The primary end point in this group was infarct size, which was determined enzymatically.

Selection of patients. Patients were screened for entry into the study if they had one or more episodes of chest pain greater than 45 min duration thought by the investigator to originate from myocardial ischemia. Patients were then identified who met both of the following inclusion criteria:

(1) Six hours or less elapsed time from the onset of the qualifying episode of severe ischemic pain to randomization.

(2) New or presumably new ST segment elevation or depression of at least 0.1 mV or new or presumably new Q waves of at least 30 msec width and 0.2 mV depth in one of the following lead combinations: (a) at least two of the three diaphragmatic leads (II, III, aVF), (b) at least two of the six precordial leads, or (c) I and aVL.

Exclusion criteria and the percentage of patients to whom they were applied are listed in table 1. The four criteria that excluded the largest number of patients were left bundle branch block, age under 21 or greater than 80 years, systolic arterial pressure less than 110 mm Hg, and having undergone previous coronary artery bypass grafting.

After informed consent had been obtained, eligible patients were assigned randomly in a double-blind fashion to receive either nifedipine or placebo, with concomitant standard therapy for myocardial infarction in both groups. Within 8 weeks of randomization, patients were categorized with regard to either TMI or AMI at the time of randomization by personnel blinded to the treatment modality and using criteria developed prospectively. Patients were considered to have had an AMI if the centrally analyzed MB-CK value obtained at randomization exceeded 12 IU/l or new or presumably new Q waves were present before randomization. Patients without any of these findings were considered to have TMI.

Therapy

Standard care. All patients received standard therapy in the coronary care unit in accordance with guidelines formulated by the study group. It was agreed at the outset that systematic use of drugs with potential but unproven value to limit infarct size, such as β-blocking drugs or nitroglycerin, would be avoided. Therefore, the use of nitrates, β-blockers or calcium-channel blockers (other than those specified in the experimental drug regimen) was not permitted during the 72 hr interval after randomization in patients who evolved AMI. For patients already receiving β-blocker therapy before enrollment, the total daily dose during the 72 hr after randomization could not exceed their prior total daily dose. Prior nitrate therapy was discontinued. Patients in the TMI group who did not exhibit AMI as judged by ECG data or plasma MB-CK values could receive β-blockers and nitrates 24 or more hr after the qualifying episode of presumed angina pectoris.

Experimental regimen. Patients were randomly assigned to oral treatment with either two nifedipine capsules (20 mg total)

<table>
<thead>
<tr>
<th>Criteria description</th>
<th>Percenta</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria not met</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than or equal to 6 hr elapsed time between onset of pain and randomization</td>
<td>41</td>
<td>1278</td>
</tr>
<tr>
<td>ECG evidence of TMI or AMI</td>
<td>56</td>
<td>1752</td>
</tr>
<tr>
<td>Chest pain less than 45 min in duration</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>Number of patients for whom inclusion criteria were met</td>
<td>20</td>
<td>633</td>
</tr>
<tr>
<td>Exclusion criteria met</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>13</td>
<td>424</td>
</tr>
<tr>
<td>Age &lt; 21 or &gt; 80 years</td>
<td>10</td>
<td>305</td>
</tr>
<tr>
<td>Systolic arterial pressure &lt; 110 mm Hg</td>
<td>7</td>
<td>203</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>6</td>
<td>201</td>
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<tr>
<td>Other major illnesses</td>
<td>5</td>
<td>144</td>
</tr>
<tr>
<td>Physical or psychological inability to cooperate</td>
<td>4</td>
<td>111</td>
</tr>
<tr>
<td>Previous participation in NAMIS or received current or previous nifedipine</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td>Signs of cardiogenic shock</td>
<td>3</td>
<td>82</td>
</tr>
<tr>
<td>Myocardial infarction within 21 days</td>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>Childbearing potential</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Number of patients for whom inclusion criteria were met and exclusion criteria not met</td>
<td>8</td>
<td>243</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass; NAMIS = nifedipine angina myocardial infarction study.

*aThe total of percentages exceeds 100% because a single patient could be ineligible for multiple reasons.

or two identical-appearing placebo capsules every 4 hr for 14 days. The regimen was continued for 14 days, even in patients in whom infarction did not evolve, unless complications considered to have been caused by calcium blockade developed. If headache refractory to acetaminophen developed, the dosage was reduced to 10 mg every 4 hr (or equivalent placebo) and then eliminated if severe symptoms persisted. If significant hypotension developed (systolic arterial blood pressure of less than 85 mm Hg and clinical evidence of vital organ hypoperfusion with a drop in systolic arterial pressure of 30 mm Hg or more from baseline), the treatment regimen was terminated although data collection was continued. If hypotension (systolic arterial pressure < 85 mm Hg) without symptoms or signs of hypoperfusion developed, the dose of the experimental agent could be halved by the treating physician. Such alterations in regimen were made in a blinded fashion unless the treating physician decided that the patient's medical care would be altered based on knowledge of the agent being given.

Data collection and follow-up. Data collection and testing were continued in all patients regardless of modification or discontinuation of the experimental regimen. Blood samples for determination of total CK and MB-CK levels by central analysis were drawn every 4 hr starting immediately before implementation of the experimental regimen until 72 hr after randomization, and then every 24 hr through the fourteenth day after randomization or until discharge from the hospital if that was in less than 14 days. If the patients were thought to have developed an AMI any time later than 72 hr after randomization, plasma samples for determination of CK and MB-CK levels by central analysis were collected on an every-4-hr basis for a total of 72
hr, then every 24 hr until 14 days after randomization or until hospital discharge if that was in less than 14 days. Infarct size index (ISI) was calculated by the MB-CK method.12

Twelve-lead ECGs were obtained daily for the first 3 days after randomization and then every other day until the fourteenth day or discharge from the hospital if earlier than 14 days. Sites on the chest wall for placement of the precordial ECG leads were delineated with indelible ink to ensure comparability of recordings. Myocardial necrosis was assessed by analysis of loss of R wave voltage.13 The R wave voltage at sites with \( \geq 0.15 \text{ mV} \) ST segment elevation was measured at randomization and 72 hr later. R wave loss was expressed as a reduction in voltage from randomization to 72 hr later.

Pertinent information on the present illness, past medical history, and physical examination and routine laboratory study results were entered on standardized forms. Each patient had a 12-lead ECG recorded and was evaluated 14 days after randomization. A health status check was made by telephone 6 months after randomization.

For TMI patients the primary end point was the occurrence of myocardial infarction during the 24 hr after randomization, which was determined by ECG and plasma CK findings. For TMI patients who progressed to infarction, a secondary end point was infarct size estimated enzymatically (CK and MB-CK) and by ECG (R wave loss) criteria. For AMI patients infarct size was the primary end point. Secondary end points for both studies were mortality within 14 days and within 6 months after randomization and apparent side effects of therapy.

**Organization of the study.** A common protocol was developed by the investigators from the participating institutions listed on p. 739. Core laboratories were established for analysis of CK and ECG data. An external policy board reviewed the data at yearly intervals. Investigators were blinded to results of the study, which were maintained by a data coordinating center.

**Statistical methods.** Student’s t test14 was used to compare the patients’ baseline characteristics that had underlying continuous distributions such as ISI and R wave loss. For ISI a logarithmic transformation was used to normalize the distribution. The Kolmogorov-Smirnov test15 was used to compare overall distributions of ISI in placebo- and nifedipine-treated groups. The Yates corrected chi-square test and Fisher’s exact test were used to compare treatment groups for baseline characteristics that were discrete, including incidence of myocardial infarction within 24 hr, incidence of untoward effects, and mortality. Mortality was compared after stratification of patients by age with the use of a small-sample version of the Mantel-Haenszel test.16 The variability around mean values was expressed as \( \pm \text{SE} \).

**Results**

**Study population.** Of the 9994 patients admitted to the four coronary care units during the study, 3143 had pain characteristic of TMI or AMI and were screened for eligibility. As indicated in table 1, application of inclusion criteria identified 633 potentially eligible patients. After application of the exclusion criteria 243 eligible patients remained (table 1). One hundred eighty-one of these 243 eligible patients were randomly assigned to a regimen (110 TMI, 71 AMI). The reasons that 62 randomizable patients did not participate were lack of consent by the treating physician (26 patients), lack of consent by the patient (27 patients), and lack of notification or unavailability of the investi-

gator (nine patients). The TMI protocol was initiated 6 months before initiation of the AMI protocol. During this interval five of the 19 patients randomized to the TMI protocol were found by the CK core laboratory to have sustained an AMI at the time of randomization; these five patients were therefore considered ineligible and excluded from the primary analysis. Five of the 71 AMI patients were excluded from primary analysis because they were found by the ECG core laboratory not to have met ECG criteria at the time of randomization. Thus, the total eligible study population participating in randomization consisted of 171 patients (105 TMI, 66 AMI). The results of the study, with the exception of those for 2 week mortality, were not altered by the outcomes in the 10 ineligible patients who were randomly assigned to treatment or placebo. Therefore, the results that follow, other than mortality, are presented only for the eligible patients that participated; mortality results are presented both including and excluding data from the 10 ineligible patients.

**Adherence to protocol and untoward effects.** Although there were no statistically significant differences in baseline parameters in the placebo- compared with nifedipine-treated group, age greater than 60 years, a variable associated with poor prognosis, applied to 47% of patients in the nifedipine group and to 38% of patients in the placebo group (NS; table 2). The mean age was 56.7 \( \pm \) 1.2 years for placebo-treated and 58.0 \( \pm \) 1.2 years for nifedipine-treated patients (NS).

There were no statistically significant differences in the frequency of development of hypotension, headache, nausea, or vomiting between placebo and nifedipine groups (table 3). The frequency of hypotension (systolic arterial pressure < 85 mm Hg) severe enough to cause discontinuation of experimental therapy was almost identical in the control group (15%) and the nifedipine-treated patients (16%) (\( p = \text{NS} \)); it was classified by blinded observers as a severe side effect in four placebo- and six nifedipine-treated patients. Regimens required alteration because of headache refractory to acetaminophen in one (1%) placebo-treated and one (1%) nifedipine-treated patient. Unblinding for clinical reasons before 14 days of therapy was necessary in two (2%) patients in the placebo and two (2%) in the nifedipine group.

Heart rates before randomization determined from the ECGs analyzed in the core laboratory were not significantly different in the placebo- and nifedipine-treated patients (76.9 \( \pm \) 2.2 beats/min, \( n = 81 \), and 77.1 \( \pm \) 1.7 beats/min, \( n = 89 \)). On the second day after randomization heart rate increased by 4.7 \( \pm \) 2.5 beats/min (\( n = 77 \)) in the placebo-treated group and by...
TABLE 2
Characteristics of study patients at baseline by treatment group
(TMI and AMI)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 82)</th>
<th>Nifedipine (n = 89)</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>31 38</td>
<td>42 47</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>64 78</td>
<td>74 83</td>
<td>NS</td>
</tr>
<tr>
<td>Time interval from onset of qualifying episode of pain to randomization &gt; 3 hr</td>
<td>60 73</td>
<td>73 82</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, treated</td>
<td>28 34</td>
<td>30 34</td>
<td>NS</td>
</tr>
<tr>
<td>Documented previous MI</td>
<td>14 17</td>
<td>16 18</td>
<td>NS</td>
</tr>
<tr>
<td>Documented history of CHF</td>
<td>4 5</td>
<td>1 1</td>
<td>NS</td>
</tr>
<tr>
<td>Angina &gt; 3 weeks before this episode</td>
<td>25 30</td>
<td>20 22</td>
<td>NS</td>
</tr>
<tr>
<td>Nitroglycerin or nitropaste or other nitrates within 24 hours of randomization</td>
<td>35 43</td>
<td>43 48</td>
<td>NS</td>
</tr>
<tr>
<td>Antihypertensive medications</td>
<td>27 33</td>
<td>23 26</td>
<td>NS</td>
</tr>
<tr>
<td>CHF present</td>
<td>9 11</td>
<td>13 15</td>
<td>NS</td>
</tr>
<tr>
<td>Highest heart rate (beats/min)</td>
<td>88.0 ± 2.0</td>
<td>87.3 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Highest systolic arterial pressure (mm Hg)</td>
<td>150.7 ± 2.4</td>
<td>151.7 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Lowest systolic arterial pressure (mm Hg)</td>
<td>123.5 ± 2.5</td>
<td>124.5 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.06 ± 0.03</td>
<td>1.08 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Hours from onset of pain to randomization</td>
<td>4.71 ± 0.14</td>
<td>4.43 ± 0.15</td>
<td>NS</td>
</tr>
</tbody>
</table>

Plus or minus values are mean ± SE.
CHF = congestive heart failure; MI = myocardial infarction.

7.1 ± 2.3 (n = 77) in the nifedipine-treated group (NS for the change in the placebo group vs the change in the nifedipine group).

Incidence of myocardial infarction. There was no significant difference in the incidence of myocardial infarction during the 24 hr after randomization in the 105 patients in the TMI protocol randomly assigned to receive placebo or nifedipine. On the basis of the CK core laboratory determination, 36 of 48 (75%) placebo-treated and 43 of 57 (75%) nifedipine-treated patients progressed to infarction in the 24 hr after randomization (NS). Similarly, there was no difference in incidence of infarction between control and treated patients in the subgroup of 43 patients (18 of 21 in the placebo group [86%]; 18 of 22 in the nifedipine group [82%]) treated within 4 hr after onset of symptoms.

There was also no significant difference in the frequency of ECG manifestations of infarction between the two groups in those patients for whom the ECG could be evaluated (42 of 44 [95%] for placebo vs 46 of 50 [92%] for nifedipine, NS). There was an 80% chance of detecting whether the true infarction rate in the nifedipine group was ≤ 52% or ≥ 92% at p = .05 with a one-tailed test.

Size of myocardial infarction. There was no significant difference in the extent of infarction as judged from MB-CK release curves in control and nifedipine-treated patients and there was no significant difference in ISI among the eligible patients participating in randomization who developed an infarction (16.9 ± 1.5 MB-CK–geq/m², n = 65 for control patients and 17.0 ± 1.5 MB-CK–geq/m², n = 68 for nifedipine-treated patients, p = NS). In addition, ISI was computed for all eligible patients randomly assigned to nifedipine or placebo, with an ISI of zero assigned to those patients in the TMI protocol who did not develop an infarction. When expressed in this manner, ISI averaged 14.3 ± 1.4 MB-CK–geq/m² in control and 14.1 ± 1.4 MB-CK–geq/m² in nifedipine-treated patients (p = NS). There were also no significant differences between treatment groups for TMI patients who exhibited infarction (13.9 ± 1.5 MB-CK–geq/m², n = 36 for placebo and 14.6 ± 2.0 MB-CK–geq/m², n = 43 in nifedipine-treated patients, p = NS) and for AMI patients considered separately (20.7 ± 2.7 MB-CK–geq/m², n = 29 for placebo and 21.2 ± 2.2 MB-CK–geq/m², n = 25 for nifedipine-treated patients, p = NS). The distribution of ISI was similar for the two groups.

Kinetics of MB-CK release were comparable in the two groups. The time from onset of pain to peak plasma MB-CK was 19.7 ± 0.7 hr for the control group (n = 61) and 20.6 ± 0.8 for the nifedipine-treated group (n = 69, p = NS).

The percentage reduction of infarct size that could have been detected by this study was calculated with respect to the mean log of MB-CK ISI and its standard

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**TABLE 3**
Untoward effects in both AMI and TMI groups

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Placebo n %</th>
<th>Nifedipine n %</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7 9</td>
<td>11 12</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 17</td>
<td>17 19</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19 23</td>
<td>18 20</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure &lt; 85 mm Hg</td>
<td>15 18</td>
<td>21 24</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Includes effects that were and were not attributable to the study drug.
deviation in the placebo-treated group. For the TMI and AMI studies combined there was an 80% likelihood that a reduction in infarct size of 36% or more could have been detected, if present. Judging from the results, there is a 90% likelihood that a reduction in infarct size, if present, was less than 13.2% and that an increase of infarct size, if present, was less than 27.8% (based on the computation of an upper and lower one-sided 90% confidence interval, respectively).

There was no significant difference in the two groups in R wave loss by day 3 at sites with ST segment elevation at the time of randomization. The R wave loss was 0.26 ± 0.03 mV/site for placebo (n = 68) and 0.26 ± 0.03 mV/site for the nifedipine-treated patients (n = 63).

Mortality. Total mortality among the 171 eligible patients during the 6 months after randomization was seven of 82 for placebo (8.5%) and nine of 89 (10.1%) for nifedipine-treated patients (p = NS; table 4). However, the number of deaths among nifedipine-treated patients exceeded that among placebo-treated patients during the 2 weeks after randomization (0 of 82 for placebo [0%] compared with seven of 89 for nifedipine-treated patients [7.9%], p = .018). Cardiogenic shock was responsible for four of the seven deaths and occurred in each case in patients with a history of angina pectoris and myocardial infarction before the index infarction. Of the other three deaths, one was associated with a cerebrovascular accident followed by presumed left ventricular rupture, another with cardiac arrest in the setting of presumed aspiration pneumonia, and another with complete heart block after the patient refused to allow insertion of a pacemaker for newly acquired right bundle branch block. Six of the seven patients who died were more than 60 years old. The significance of the mortality difference was reduced from p = .018 to p = .030 when results were adjusted for the larger number of older patients in the nifedipine-treated group. In the 62 eligible patients who were not randomly assigned to drug or placebo because of lack of consent or availability of the investigator and who did not receive nifedipine, the 2 week mortality was three of 62 (4.8%).

Mortality in the 171 eligible patients participating in the study did not include outcomes in 10 patients who were randomly assigned to drug or placebo but who were retrospectively determined to have been ineligible for the study (five patients in the TMI study were later found to have had a CK elevation at the time of randomization and five patients in the AMI study were found not to have met ECG criteria, as determined by the ECG core laboratory). Two week mortality among all study patients (171 eligible patients undergoing randomization plus 10 ineligible patients undergoing randomization) was two of 88 (2.3%) in the placebo-treated group and seven of 93 (7.5%) in the nifedipine-treated group (p = .19, NS). Six month mortality among all patients was 10 of 88 (11.4%) in the placebo-treated group and 10 of 93 (10.8%) in the nifedipine-treated group (NS).

Discussion

The results indicate that nifedipine did not reduce the likelihood of progression from TMI to AMI. In addition, nifedipine did not limit infarct size in those patients with TMI in whom infarction evolved or in patients in whom infarction was already in progress at the time of randomization. Mortality among all 181 patients (including the 10 patients later determined to be ineligible) was not significantly different for either the 2 week or 6 month interval, although there was a statistically significant excess in 2 week (but not 6 month) mortality in the nifedipine-treated group among the 171 eligible patients participating in randomization.

The effect of the intervention on infarct size was assessed from serial plasma MB-CK values. The method used provides results that correlate well with anatomic infarct size measured at autopsy in patients who die with myocardial infarction. Although reperfusion can alter plasma CK values, there was no evidence that the incidence of reperfusion differed in placebo-

<table>
<thead>
<tr>
<th>Patient group (n)</th>
<th>2 weeks Placebo</th>
<th>2 weeks Nifedipine</th>
<th>6 months Placebo</th>
<th>6 months Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Randomized, eligible</td>
<td>0/82</td>
<td>0.0</td>
<td>7/89</td>
<td>7.9</td>
</tr>
<tr>
<td>All randomized</td>
<td>2/88</td>
<td>2.3</td>
<td>7/93</td>
<td>7.5</td>
</tr>
<tr>
<td>Eligible, nonrandomed</td>
<td>3/62</td>
<td>4.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not identical to placebo group.*
compared with in nifedipine-treated patients. The incidence of infarction was the same in the TMI placebo- and nifedipine-treated groups; furthermore, nifedipine-treated patients with infarction evaluated according to the TMI and AMI protocols did not exhibit earlier peak CK values as compared with controls.

The possibility that calcium-channel blockers might prevent progression of TMI through reversal of coronary spasm is based on the observations by Maseri et al.6 indicating that spasm may lead to infarction in certain patients. Early evidence that such spasm may be reversible was provided by Oliva and Breckinbridge,7 who found that intracoronary administration of nitroglycerin to patients with AMI led to reperfusion in six of 15 patients. More recent attempts to achieve coronary reperfusion with vasodilators in larger series of patients undergoing coronary angiography for intracoronary thrombolytic therapy have not demonstrated such high rates of reperfusion.19 The failure of orally administered nifedipine to prevent progression of TMI to AMI or to alter the time to occurrence of peak CK values in this study suggests that coronary blood flow was not reestablished. Even if potentially reversible spasm is an initiating process in many cases of myocardial infarction, it is likely that obstruction can no longer be reversed once fixed thrombosis supervenes.7

Several observations do, however, suggest that even in the presence of a fixed complete occlusion a calcium-channel blocker may have a beneficial effect on infarct size. Reduction of infarct size in dogs with experimental myocardial infarction by nifedipine has been demonstrated by Henry et al.8 and by Selwyn et al.9 Meils et al.20 demonstrated that FR-7534, a light-stable derivative of nifedipine, salvaged myocardium in dogs with hearts rendered ischemic for 2 hr before reperfusion. Reimer et al.21 and De Boer et al.11 observed limitation of infarct size in dogs treated with the calcium-channel blocker verapamil. In animals given nifedipine during the course of experimental myocardial infarction, Weintraub et al.22 and Henry et al.23 demonstrated improved ventricular function after infarction — a result to be expected if significant quantities of myocardium were salvaged. In these studies reduction in infarct size and improved function appeared to result from improvement in coronary flow to the ischemic area, and in some cases from a protective effect of the calcium-channel blocker on cells exposed to a given level of ischemia.8, 22 This myocardial protective effect has also been observed in isolated rabbit hearts exposed to ischemia, and in dog hearts exposed to hypothermic or normothermic ischemia during the course of cardiopulmonary bypass.25 Hamm et al.26 found that the calcium-channel blocker diltiazem was more effective than the β-blocker metoprolol in decreasing enzyme release from ischemic, isolated, working rat hearts.

There are, however, a number of reports in which calcium channel–blocking drugs did not produce salutary results. Although Selwyn et al.9 found a beneficial effect of nifedipine on myocardial perfusion and ECG and CK signs of necrosis in dogs with experimental myocardial infarction, the response was dose dependent; an intravenous dose of 1 µg/kg salvaged ischemic myocardium, but a higher dose of 13 µg/kg decreased mean arterial pressure by 30%, led to a reduction in ischemic zone flow, and increased in myocardial necrosis. Henry et al.23 observed that myocardial salvage was dose dependent and underscored the potentially deleterious consequences of high-dose regimens. Meils et al.21 found that myocardial salvage was 7.5% with FR-7534 alone, but 33.5% when phenylephrine was added to maintain systemic arterial pressure. Investigators who found no beneficial effects of diltiazem in the pig27 or of nifedipine in baboons28 stressed the lack of coronary collateral vessels in these animals as the probable cause for absence of an effect. Experience with other drugs known to limit infarct size indicates that only small amounts of myocardium can be salvaged in animals if the intervention is given more than 4 hr after coronary artery occlusion.29–34

Although the hemodynamic effects of nifedipine in patients with chronic ischemic heart disease have been well described,35–37 the actions of this drug in patients with AMI have not been studied as extensively. Jaffe et al.38 studied 17 patients with AMI given nifedipine a mean of 8.7 hr after onset of pain. The hemodynamic findings were similar to those observed in patients with chronic ischemic heart disease, with a reduction in systemic vascular resistance and an elevation in cardiac index. Other investigators have also found that nifedipine reduced arterial pressure in patients with AMI.39–41

There is little information available comparing the efficacy of nifedipine, or other calcium channel–blocking drugs, with placebo in randomly selected patients with AMI compared with controls. In a randomized study of verapamil in a relatively small number of patients there were four reinfarctions among 33 control group patients compared with none among 28 verapamil-treated patients by the time of hospital discharge, although infarct size and total mortality were not significantly different.42

The primary cause of the lack of a beneficial effect in our study may have been the unavoidable delay of
4.6 ± 0.1 hr between the onset of chest pain and initiation of therapy with nifedipine. Previously cited results of studies in experimental animals indicate that it is not possible to salvage significant quantities of myocardium when an intervention is initiated more than 4 hr after occlusion. This conclusion has been supported recently by results of clinical studies. Khaja et al. found that reperfusion induced by streptokinase a mean 5.4 hr after onset of pain did not lead to salvage of functional myocardium. However, Anderson et al. observed improvement in ejection fraction and regional wall motion in patients treated with streptokinase a mean of 4.0 hr after onset of pain. In our study the subgroup of patients treated less than 4 hr after the onset of pain was too small to provide adequate statistical power for detection of a modest beneficial effect of nifedipine even if it had been present.

Other possible explanations for the failure of nifedipine to abort infarction or limit infarct size may be inferred from results cited previously from studies in experimental animals. The reason for the lack of beneficial effect may have been the absence of collateral flow in some patients; under such conditions nifedipine could not increase flow in the ischemic area. In other patients the detrimental effects of the reduction in coronary blood flow caused by nifedipine-induced hypotension may have outweighed the beneficial effects of a decrease in afterload produced by the drug.

The excess mortality in the nifedipine-treated patients during the 2 weeks after randomization among eligible patients is difficult to interpret. The probability that such a distribution of deaths could occur by chance is 0.018 if the treatments had an equal effect on mortality and if only one mortality interval were examined. The probability rises to 0.030 if the differences in the distribution of age in the two groups is taken into account, and the probability rises to 0.19 when results are analyzed in the group of all participating patients, which includes 10 patients inappropriately included in the randomization protocol.

A potential mechanism by which nifedipine may have been harmful is that of peripheral vasodilatation leading to hypotension and reduced coronary perfusion. However, systemic arterial hypotension severe enough to evoke discontinuation of treatment (< 85 mm Hg) was not significantly more frequent in either treatment group and only two of the seven nifedipine-treated patients who died were among the 14 in whom such hypotension occurred. If nifedipine increased mortality by decreasing systemic arterial pressure, the deleterious effects of hypotension would be expected to have increased infarct size in a substantial number of patients — an effect that was not observed. It is possible that the four patients in the nifedipine-treated group who developed cardiogenic shock could have been affected adversely by relatively small reductions in systemic vascular resistance, but such a mechanism could not account for the other three deaths.

The interpretation of the excess deaths in the nifedipine-treated group is complicated by the lack of deaths within 2 weeks among the 82 patients with infarction who received placebo, an unexpected finding. Among the 62 patients eligible for this study who did not participate because of lack of consent (and who did not receive nifedipine) there were three deaths (4.8%) during the 2 week period after screening. In other studies of AMI with patients similar to those entered into this study, the early mortality in control patients ranged from 4% to 12%. Although 2 week mortality in our investigation differed in the placebo- and nifedipine-treated groups, 6 month mortality did not. Finally, interpretation is limited by the small numbers of deaths in the entire study, which was not designed to be large enough to determine the effect of nifedipine therapy on mortality during AMI. Nevertheless, the suggestion of a higher early mortality combined with the absence of a statistically significant beneficial effect of nifedipine on infarct size or the incidence of the development of AMI in the patients with TMI suggests that the drug should not be used routinely in patients with TMI or AMI in whom treatment cannot be implemented early (within approximately 5 hr) after the apparent onset of the infarction.

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