Nifedipine and conventional therapy for unstable angina pectoris: a randomized, double-blind comparison*

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ABSTRACT To characterize the potential of nifedipine in the therapy of unstable angina pectoris we implemented a blinded, randomly assigned, titrated schedule of conventional therapy (propranolol, if not contraindicated, and isosorbide dinitrate) or nifedipine for 14 days in 126 patients hospitalized in a coronary care unit for ischemic chest pain of less than 45 min duration. There were no significant differences between conventionally and nifedipine-treated patients with regard to (1) the time to relief of pain as judged by life table analysis, (2) the decrease in anginal attacks per 24 hr from day 0 to day 2 (−2.5 ± 0.4 for conventional therapy vs −2.8 ± 0.3 for nifedipine), (3) the decrease in the number of nitroglycerin tablets consumed per 24 hr (−2.0 ± 0.5 for conventional vs −2.1 ± 0.4 for nifedipine therapy), (4) the percentage of patients requiring morphine on day 1 (13% for conventional vs 21% for nifedipine therapy), or (5) the percentage of patients who developed infarction (14% in both groups). Among the 27 patients who did not respond to initial conventional (n = 13) or nifedipine therapy (n = 14), five in each group became pain free when the opposite therapy (either nifedipine or conventional therapy) was added. In the subgroup of 67 patients who were receiving propranolol before randomization, addition of nifedipine was more effective in controlling pain than was an increase in conventional therapy (p = 0.026). In the subgroup of 59 patients not receiving prior propranolol, initiation of conventional therapy produced more rapid pain relief than initiation of nifedipine therapy alone (p < .001), which tended to increase heart rate. Thus, for the study population as a whole therapy with nifedipine alone was equivalent to conventional therapy for unstable angina, although this overall equivalence may result from a combination of superiority of nifedipine therapy in patients previously receiving β-blocker therapy and superiority of β-blocker therapy in patients not previously receiving β-blockers.


UNSTABLE ANGINA, a syndrome intermediate in severity between stable angina pectoris and acute myocardial infarction, is well recognized. Heberden, in his classic description of angina pectoris, noted that in some cases the pain occurred in patients at rest. Herrick, in describing myocardial infarction, noted that the event was often preceded by an increase in the severity of angina. Specific attention was focused on unstable angina by Feil and Sampson and Elias in 1937, all of whom emphasized its tendency to progress to myocardial infarction. The therapy for this condition, which was established about a half century ago and has persisted to the present, includes bed rest, sedation, and nitrates. Anticoagulation was often recommended in the 1960s, but was less frequently used in the 1970s with the increasing use of β-adrenergic blockade and/or coronary artery bypass grafting (CABG). The relative roles of initial medical and surgical therapy for unstable angina were well defined by the National Cooperative Unstable Angina Study,8

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*All editorial decisions for this article, including selection of reviewers and the final disposition, were made by a guest editor. This procedure applies to all manuscripts with authors from the Washington University School of Medicine.
and as a result it is now accepted practice to begin treatment with medical therapy and to proceed to CABG only in those patients whose conditions are resistant to intensive medical management.

The keystone of conventional medical therapy for the control of unstable angina pectoris is a combination of nitrate therapy and, if not contraindicated, β-blockade.10-12 However, the objective evidence supporting the use of these drugs is surprisingly meager and is not based on results of randomized, double-blind, placebo-controlled studies.10,11 To complicate matters, it has been suggested that in many patients bed rest alone is adequate therapy,13 that anticoagulants may prevent progression to transmural infarction,13 and that β-blockade may actually exacerbate coronary artery spasm,14,15 which is now considered a more frequent cause of unstable angina than previously recognized.16

The widespread availability of calcium-channel blocking drugs has added new promise, and new complexity, to the selection of proper medical therapy for unstable angina.17,18 These drugs are extremely effective against coronary artery spasm.19-23 Nifedipine, the drug we investigated in this study, has been shown to be superior to placebo for therapy of stable angina pectoris24 and Prinzmetal’s angina.22,23 Early uncontrolled studies suggest that nifedipine may relieve pain in many patients with unstable angina who do not respond to conventional therapy.25-27 In a large group of patients with unstable angina, including patients with and without ST segment elevation during pain, nifedipine has been found to be superior to placebo for control of pain after the acute episode when added to conventional therapy.28

The present study was undertaken to provide in a double-blind, randomized manner an estimation of the efficacy of initial therapy of unstable angina with the calcium-channel blocker nifedipine and to compare it with that of initial treatment with propranolol and/or nitrates, i.e., conventional therapy. The trial was begun in 1979 and conducted by investigators from six institutions (see Appendix). Primary end points were the control of anginal pain and the incidence of progression to myocardial infarction.

Methods

Patient selection. Over the 39 month course of the study, 1388 patients were screened for eligibility. All had been admitted to one of the four participating coronary care units (CCUs) and had experienced one or more episodes of pain of less than 45 min duration that were thought by the investigator to be caused by myocardial ischemia. A total of 682 patients was identified as fulfilling both of the following inclusion criteria:

1. Pain considered characteristic of unstable angina pectoris within 24 hr of randomization. Unstable angina may have been present for any interval but no more than 24 hr could have elapsed between the last episode of pain and randomization, and no episode of pain within the previous 24 hr could have exceeded 45 min in duration. The pattern of angina could be one of the following: (a) Progressive angina, i.e., progressive increases in intensity, frequency, duration, ease of provocation, or difficulty of relief with nitrates, either soon after the initial onset of angina pectoris or manifest as a change in the pattern of longstanding stable angina. (b) Angina at rest, including nocturnal angina.

2. Either of the following markers of coronary artery disease: (a) Electrocardiographic (ECG) evidence of reversible myocardial ischemia in any lead of a standard 12-lead ECG with any attack of pain. This could have been either new or presumably new ST segment elevation or depression of at least 0.05 mV that had begun to return, or that had already returned, toward normal or a known baseline, or T waves that inverted and became isoelectric or began to resume their original polarity after cessation of the episode. (b) Documented coronary artery disease manifest by either prior myocardial infarction, or at least 70% luminal diameter narrowing of at least one coronary artery detected by a prior coronary angiogram.

Among the patients who satisfied the inclusion criteria, a total of 489 were excluded for the reasons listed in table 1, leaving 193 eligible patients of whom 133 were willing to participate in the study.

After informed consent had been obtained, patients were assigned to group A (additional propranolol acceptable) or

### TABLE 1

<table>
<thead>
<tr>
<th>Reasons for ineligibility in 1388 screened patients</th>
<th>Percent</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria not met</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anginal pain within the 24 hr before screening</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>No ECG signs or other evidence of myocardial ischemia</td>
<td>49</td>
<td>682</td>
</tr>
<tr>
<td>All inclusion criteria met</td>
<td>49</td>
<td>682</td>
</tr>
<tr>
<td>Exclusion criteria met</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG evidence of new infarction or LBBB</td>
<td>29</td>
<td>408</td>
</tr>
<tr>
<td>Age &lt; 21 or &gt; 80 years</td>
<td>7</td>
<td>96</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>Prior participation in this study or current or previous nifedipine therapy that could not be discontinued</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>Other major illness</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>Physical or psychological inability to cooperate</td>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>Treatable cause for angina such as severe anemia or arrhythmias</td>
<td>3</td>
<td>46</td>
</tr>
<tr>
<td>Systolic arterial pressure &lt; 100 mm Hg</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>MI within 21 days</td>
<td>3</td>
<td>48</td>
</tr>
<tr>
<td>Elevated CK-MB level (local)</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Serum CK &gt; 2 × normal (local)</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>Childbearing potential</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>All inclusion criteria met and no exclusion criteria met</td>
<td>14</td>
<td>193</td>
</tr>
</tbody>
</table>

LBBB = left bundle branch block; MI = myocardial infarction.

*Total exceeds 100% because a patient could be ineligible for more than one reason.*
group B (additional propranolol contraindicated). Contraindications to addition of propranolol and the number and percentage of patients with each are listed in table 2. Randomization to conventional or nifedipine therapy was conducted separately within group A and group B. The randomization scheme was balanced for each clinical unit.

Prerandomization propranolol (which had been ineffective in controlling pain) was continued as background therapy for group A and group B patients, unless one of the contraindications to propranolol listed in table 2 was present or developed. In group A, 50 of 92 patients had received propranolol therapy in the 24-hour period before randomization (mean dose 116.8 ± 15.8 mg/24 hr); in group B, 17 of 34 had taken propranolol (mean dose 110.0 ± 22.1 mg/24 hr). Prerandomization therapy with calcium-channel blockers or nitrates was discontinued at the time of randomization. The treating physician did not give consent to randomization if he or she believed that discontinuation of nitrates or calcium-channel blockers would be detrimental to the patient. The results of coronary angiography were not used to guide selection of therapy.

The presence or absence of enzymatic evidence of a prerandomization myocardial infarction were determined in a blinded fashion on the basis of serum samples analyzed by the creatine kinase (CK) core laboratory. The ECG core laboratory, while blinded to treatment group and outcome, verified that ECG eligibility criteria had been met.

Application of these criteria led to a final study population of 126 patients (92 in group A; 34 in group B).

Therapy

Standard care. Standard therapy for unstable angina consisted of bed rest, inhalation of supplemental O₂, and sedation. The protocol stipulated that intra-aortic balloon counterpulsation (IABC) and CAGB should not be performed unless the patient (1) had demonstrated continuing unstable angina while receiving the highest tolerated level of conventional (β-blockade and nitrates) and nifedipine therapy (see below), (2) had been pain free for 48 hr, or (3) had completed the evaluation at 14 days after randomization. With these guidelines, decisions regarding the need for IABC and CABG for management of unstable angina were made by the treating physician.

Experimental therapy. In group A (additional propranolol acceptable), nifedipine was compared with a combination of propranolol and isosorbide dinitrate. In group B (additional propranolol contraindicated), nifedipine was compared with isosorbide dinitrate alone. Comparison of the experimental regimens was made in a double-blind fashion. Blinded comparison of the titration of one drug (nifedipine) with two drugs (propranolol and isosorbide dinitrate) was accomplished with the equivalent, graduated levels of therapy shown in table 3. Separate placebo were produced and administered for each of the three drugs under study.

As in standard clinical practice, the dosage of either therapy was gradually increased if the attacks of angina were not eliminated and if no adverse effects occurred (such as systolic arterial blood pressure greater than 85 mm Hg or 30 mm Hg less than known baseline values with evidence of vital organ hypoperfusion, heart rate < 40 beats/min, new or worsening left ventricular failure, asthma, PR interval > 0.24 sec, or second- or third-degree atrioventricular block). The level of therapy was increased only if an episode of pain occurred after more than 2 hr had been allowed for absorption and distribution of the drug. Angina during the period of increase in dosage of the experimental drug was treated initially with sublingual nitroglycerin, in the dose and frequency deemed necessary by the treating physician. If nitroglycerin was ineffective, morphine was given. Thus, advances to higher levels of therapy were dictated by the continued anginal attacks.

The primary randomized comparison of the study was between conventional and nifedipine therapy at levels 1, 2, and 3, as shown in table 3. If angina recurred despite maximal conventional or nifedipine therapy at level 3, the alternative therapy was added in a graduated fashion (levels 4, 5, and 6). By the time patients reached level 6, they had received identical ther-

### TABLE 2

Contraindications to the administration of β-blocker therapy in 38 patients in group B

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percent</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate &lt; 55 beats/min currently or &lt; 40 beats/min before anticholinergic therapy</td>
<td>43</td>
<td>15</td>
</tr>
<tr>
<td>Moist rales ≥ one-third of the way up the lung field that do not clear with coughing</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Asthma, either by history or by examination</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Systolic arterial pressure more than 50 mm Hg below known baseline levels</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary edema (documented by chest x-ray, if available)</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>First degree AV block with PR interval &gt; 0.24 sec, or second- or third-degree block present before anticholinergic therapy</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

AV = atrioventricular.

### TABLE 3

Type of experimental therapy used in group A

<table>
<thead>
<tr>
<th>Level</th>
<th>Initial conventional therapy</th>
<th>Initial nifedipine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20 mg PRO; 10 mg ISDN; N placebo</td>
<td>PRO placebo; ISDN; 20 mg N placebo</td>
</tr>
<tr>
<td>2</td>
<td>40 mg PRO; 10 mg ISDN; N placebo</td>
<td>PRO placebo; ISDN; 20 mg N placebo</td>
</tr>
<tr>
<td>3</td>
<td>60 mg PRO; 20 mg ISDN; N placebo</td>
<td>PRO placebo; ISDN; 30 mg N placebo</td>
</tr>
</tbody>
</table>

End of randomized comparison

<table>
<thead>
<tr>
<th>Level</th>
<th>Initial conventional therapy</th>
<th>Initial nifedipine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Level 3 plus PRO placebo; ISDN; 20 mg N placebo</td>
<td>Level 3 plus PRO placebo; ISDN; 10 mg N placebo</td>
</tr>
<tr>
<td>5</td>
<td>Level 3 plus PRO placebo; ISDN; 20 mg N placebo</td>
<td>Level 3 plus PRO placebo; ISDN; 10 mg N placebo</td>
</tr>
<tr>
<td>6</td>
<td>Level 3 plus PRO placebo; ISDN; 30 mg N placebo</td>
<td>Level 3 plus PRO placebo; ISDN; 20 mg N placebo</td>
</tr>
</tbody>
</table>

ISDN = isosorbide dinitrate; PRO = propranolol; N = nifedipine.

*Therapies used in group B differ only in that propranolol was not included.*
THERAPY AND PREVENTION—CORONARY ARTERY DISEASE

apties (nitrates, propranolol, and nifedipine) despite differences in their initial random assignment in levels 1 to 3. Drugs were administered every 6 hr from randomization until the 14 day evaluation (even if myocardial infarction occurred after randomization) unless an adverse effect of therapy developed or CABG was performed.

Study organization. A standardized protocol for the study was developed by the investigators from the participating institutions listed in the Appendix. Core laboratories were established for the analysis of CK and ECG data. An external policy board reviewed the progress of the study at yearly intervals. Investigators were blinded to the results of the study, which were maintained by a data coordinating center at the Harvard Medical School.

Data collection and follow-up. Blood samples for determination of total CK and CK-MB for central analysis were drawn every 8 hr for 72 hr after randomization and then every 12 hr through the seventh day (or until discharge from the hospital). The frequency of collection of samples was increased to every 4 hr for 72 hr in patients who developed clinical evidence of infarction after randomization. Infarct size was assessed with a method recently validated in comparisons with postmortem measurements of infarct size.29, 30 The number of episodes of anginal pain, their average duration, and their intensity were recorded on special data forms by observers blinded to the type of therapy being administered.

Twelve-lead ECGs were obtained daily for the first 3 days after randomization, and then every other day until the fourteenth day or until discharge from the hospital. All patients were evaluated by a physician 14 days after randomization, after which therapy with propranolol and/or isosorbide or nifedipine was discontinued and the patients' treatment assignments were unblinded. Vital status was determined by a telephone call 6 months after randomization.

Details of the present illness, the past medical history, and physical examination and routine laboratory test results were entered on standardized forms. Pulse and blood pressure determinations were recorded at baseline and at least once during each level of therapy.

Statistical methods. The Yates corrected chi-square test was used to compare the two treatment groups within groups A and B separately for all baseline characteristics other than the dose of \( \beta \)-blocker. The patients were compared with respect to dose of \( \beta \)-blockers by the two-sample t test after application of a logarithmic transformation to better normalize the underlying probability distributions. The Yates corrected chi-square test was used to compare the incidence of side effects in the two treatment groups within groups A and B, respectively. In those instances in which expected cell frequencies were <5, Fisher's exact test was used.

The log-rank method of life table analysis was used to compare the time to relief of pain for at least 48 hr during levels 1 to 3 of therapy between treatment groups, both overall and within the subgroups of patients who did and did not receive prior \( \beta \)-blockade. Similar analyses were performed comparing time to relief of pain in those with and without new ST segment elevation, and time to relief of pain in those with three-vessel disease vs those with 0, one-, or two-vessel disease among those undergoing coronary angiography. All other end points were analyzed with the use of either the Yates corrected chi-square test (or Fisher's exact test) for binary outcomes or the two-sample t test for continuous outcomes. Variations from mean values are expressed as \( \pm \) SE.

Results

Study population. A total of 9994 patients was admitted to the four CCUs during the study; of these 1388 (14%) had pain characteristic of unstable angina and were screened for eligibility. Of these 682 met inclusion criteria (table 1). Subsequent application of exclusion criteria resulted in the identification of 193 eligible patients. The most common cause for exclusion of a screened patient was failure to demonstrate ECG changes or other evidence of ischemic heart disease (49% of those screened).

Of the 193 eligible patients, 155 were placed in group A and 38 were placed in group B because of the presence of contraindications to additional propranolol (table 2). Of the 155 patients in group A, 98 (63%) were randomly assigned to a treatment. The remaining 75 eligible patients did not participate because their treating physician did not consent (35 patients), they did not consent (19 patients), or because necessary personnel were not notified or were not available (three patients). In group B, 35 of 38 eligible patients were randomly assigned a treatment (92%). There was no difference in age or sex distribution between the groups of eligible randomized and eligible nonrandomized patients (61.4 ± 0.9 vs 60.7 ± 1.2 years; NS; 56% male vs 59% male, NS).

Of the 133 patients participating (98 group A; 35 group B), four were identified by the CK core laboratory as having experienced a myocardial infarction immediately before randomization, and an additional three were found by the ECG core laboratory not to have met the ECG criteria. As stipulated by the protocol, data from these seven patients (six group A; one group B) were excluded from subsequent analysis, leaving a total of 126 eligible patients who took part in the randomization protocol (92 group A; 34 group B).

Baseline characteristics, adherence to protocol, and untoward effects. There were no significant differences between treatment groups within either group A or B in any of the baseline variables known to be related to prognosis (table 4). The distribution of patients with regard to type of unstable angina and type of ECG changes is presented in table 5. Data collection for the principal end points of the study (control of pain and occurrence of myocardial infarction within 2 weeks of randomization) was complete for all 126 eligible, randomized patients, including patients for whom experimental therapy was terminated before the 14 day evaluation or before relief of pain for 48 hr. Therapy at levels 1 to 3 was terminated prematurely in nine of 126 (7%) patients and therapy at levels 4 to 6 was terminated in an additional seven (6%) patients. The most frequent reasons for premature termination were hypotension in three and CABG in two patients. Premature unblinding occurred in nine of 126 (7%) patients.

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ed with nifedipine when results in all eligible randomized patients were analyzed (figure 1). The therapies were equivalent when conventional therapy was compared with nifedipine for groups A and B combined as well as when the treatment comparisons were made separately within group A and group B. Similarly, there were no significant differences in the percentage of patients in groups A and B combined who had relief of pain with the therapy to which they were initially randomized at levels 1 to 3 (73% [46/63] for propranolol and/or nitrates, 70% [44/63] for nifedipine; table 6). In four of the patients randomly assigned to conventional therapy and five of those assigned to nifedipine, therapy was stopped prematurely during levels 1 to 3. Thus, 13 patients originally randomized to conventional therapy and 14 originally randomized to nifedipine entered level 4, in which the opposite therapy was added due to failure of the initial therapy. Addition of nifedipine relieved pain in five of 13 patients (38%) who initially received conventional therapy, and addition of conventional therapy relieved pain in five of 14 (36%) initially receiving nifedipine (NS). In four of those in whom nifedipine was added and in three of those in whom conventional therapy was added therapy was withdrawn prematurely. Four of those in whom nifedipine was added and six in whom conventional therapy was added experienced continued chest pain despite receiving all six levels of therapy. Achievement of pain relief at any of the six levels was not significantly different for group A vs group B patients (71/93 [77%] in group A, 29/34 [85%] in group B, NS).

**TABLE 5**
Clinical characteristics of unstable angina patients with regard to time of onset of angina, pain at rest, and ST segment changes

<table>
<thead>
<tr>
<th></th>
<th>No ST segment changes</th>
<th>ST segment elevation</th>
<th>ST segment depression</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive or long-standing angina</td>
<td>28 (22)</td>
<td>21 (17)</td>
<td>39 (31)</td>
<td>76 (60)</td>
</tr>
<tr>
<td>Recent-onset angina</td>
<td>14 (11)</td>
<td>15 (12)</td>
<td>29 (23)</td>
<td>50 (40)</td>
</tr>
<tr>
<td>Episodes of anginal pain</td>
<td>24 (19)</td>
<td>22 (17)</td>
<td>48 (38)</td>
<td>80 (63)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages of 126 eligible patients randomly assigned to a treatment.

A No ST segment elevation or ST segment depression.
B Total is greater than the sum of the three column entries because some patients had both ST segment elevation and depression.
C Angina more than 3 weeks before the qualifying episode.
D Angina ≤ 3 weeks before the qualifying episode.
In addition to the lack of difference in pain relief between conventionally and nifedipine-treated patients, there was no significant difference in the reduction in attacks of angina per 24 hr, the reduction in sublingual nitroglycerin use, or the percentage of patients requiring morphine for relief of pain during the 48 hr after randomization (figure 7).

There were, however, significant differences between conventional therapy and nifedipine when results were compared for subgroups of patients who did and those who did not receive β-blockers before randomization. In the subgroup of 67 patients who were receiving prior β-blockade (average dose of propranolol, 115.1 ± 13.0 mg/day), which was continued as baseline therapy, an increase in β-blockade and/or addition of nitrates failed to control pain as rapidly as did treatment with nifedipine (figure 2; p = .026). The opposite result was observed in the subgroup of 59 patients who had not received β-blockers before randomization; in these patients subsequent treatment with β-blocker and/or nitrate therapy led to more rapid control of pain than did initiation of nifedipine treatment (figure 3; p < .001).

These differences in therapeutic response in the presence or absence of prerandomization propranolol were not reflected in other less sensitive indexes of anginal control. Thus, although prior treatment with propranolol was noted to influence the speed with which patients became pain free during levels 1 to 3 of therapy with nifedipine or conventional therapy when the method of life table analysis was used, no difference was noted in the percentage of patients who obtained relief of chest pain, a less sensitive end point. In addition, there was no difference between conventional therapy and nifedipine with regard to the reduction in attacks of angina per 24 hr, the reduction in nitroglycerin use, or the percentage of patients requiring morphine in either subgroup of patients receiving different prerandomization therapy.

For the study population as a whole there were no significant differences in time to relief of pain during levels 1 to 3 for the two treatment groups in subgroups with (n = 36) or without (n = 90) new ST segment elevation and in subgroups with (n = 80) or without (n = 46) angina at rest. Results in separate clinical units were consistent with the results for the entire study population.

**Heart rate responses.** There were no significant differences between treatment groups in mean heart rate at the time of randomization in either group A or in group B. In group A the administration of propranolol produced the expected slowing, while nifedipine therapy led to a significant increase in heart rate. The average of the highest heart rates observed during level 1 of therapy with propranolol and nitrates fell by 3.7 ± 1.6 beats/min to 76.0 ± 1.7 (p = .025), while therapy with nifedipine led to an increase of 5.1 ± 1.6 beats/min.

### TABLE 6

<table>
<thead>
<tr>
<th>Results of initial conventional or nifedipine therapy</th>
<th>Initial conventional therapy (no. of patients)</th>
<th>Initial nifedipine therapy (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients starting therapy</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Pain relief with initial therapy (levels 1–3)</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Premature termination during levels 1–3 without pain relief</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Number of patients entering level 4</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Pain relief with added therapy (levels 4–6)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Premature termination at levels 4–6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>No pain relief despite all six levels of therapy</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Myocardial infarction within 2 weeks</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Mortality within 2 weeks</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

*For at least 48 hr.
TABLE 7
Control of anginal attacks

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine</th>
<th></th>
<th>Propranolol and/or nitrates</th>
<th></th>
</tr>
</thead>
</table>
|                     | Day 0      | Day 1               | Day 2                       | Day 0–day 2         | p value \^  
| Anginal attacks per 24 hr (n) | 3.3 ± 0.3  | 1.0 ± 0.2           | 0.4 ± 0.1                   | -2.8 ± 0.3          | 3.0 ± 0.4  
| (56)                | (56)       | (56)                | (56)                        | (56)                | (56)       |
| Nitroglycerin tablets used per 24 hr (n) | 2.7 ± 0.4  | 1.4 ± 0.3           | 0.7 ± 0.2                   | -2.1 ± 0.4          | 2.5 ± 0.5   
| (57)                | (57)       | (57)                | (57)                        | (57)                | (57)       |
| % Patients requiring morphine | 21         | 11                  | (13/63)                     | (7/63)              | 13         
|                     |            |                     |                             |                     | 8          |

\^ For day 0 through day 2 reduction in nifedipine group vs day 0 through day 2 reduction in the group that received propranolol and/or nitrate therapy.

min to a rate of 83.4 ± 2.2 beats/min (p = .003). In group B nitrates did not significantly change the highest heart rate (an increase of 2.9 ± 2.4 beats/min to 79.7 ± 5.0), but nifedipine led to a significant (p = .026) increase (6.1 ± 2.5 beats/min increase to 77.8 ± 5.0 beats/min; figure 4).

For groups A and B combined, the contrast between the tendency of conventional therapy to decrease heart rate and the tendency of nifedipine to increase it was greatly accentuated in patients who had not received prior propranolol therapy (figure 5). In the subgroup of patients who had not received prior propranolol therapy, heart rate was not significantly changed in the group treated with propranolol and/or nitrates (decrease of 3.1 ± 2.2 beats/min), but was significantly increased in the group treated with nifedipine (by 9.3 ± 1.9 beats/min; p < .001). No significant changes were noted in either the propranolol or the nitrate group (decrease of 0.9 ± 1.7 beats/min) or in the nifedipine group (increase of 2.4 ± 1.8 beats/min) among patients who had received prior treatment with propranolol.

Conventional therapy and nifedipine produced similar decreases in arterial pressure in groups A and B. In group A the mean decrease in systolic arterial pressure from that at the time of randomization to the highest value recorded during level 1 of therapy was -6.1 ± 2.5 mm Hg for propranolol and nitrates vs -11.8 ± 3.5 mm Hg for nifedipine (NS for propranolol and nitrates vs nifedipine). Similar decreases in arterial pressure were noted in group B ( -11.1 ± 6.8 mm Hg for nitrates vs -7.9 ± 4.4 mm Hg for nifedipine), but

![FIGURE 2](image2.png)

**FIGURE 2.** The probability of being pain free for at least 48 hr in the subgroup of patients receiving propranolol before randomization (n = 67). In this subgroup nifedipine (---) was more effective in producing pain relief than were additional propranolol and/or nitrates (p = .026).

![FIGURE 3](image3.png)

**FIGURE 3.** The probability of being pain free for at least 48 hr in the subgroup of patients not receiving propranolol before randomization (n = 59). In this subgroup initiation of propranolol and/or nitrate therapy (-----) was more effective in producing pain relief than was initiation of nifedipine (---) (p < .001).
in 14 days of randomization between those randomized to initial conventional or nifedipine therapy (nine of 63 patients [14%] for conventional therapy vs nine of 63 patients [14%] for nifedipine). (These patients do not include the four identified by the core laboratory as having experienced a myocardial infarction before randomization.) MB-CK infarct size index was similar (5.8 ± 1.8 vs 7.6 ± 2.2 MB-CK–geq/m² for conventional and nifedipine therapy, respectively, NS). In addition, no significant differences were noted in the loss of R wave voltage in these patients with infarction.

Mortality. In the 14 days after randomization, there were no deaths among those patients randomized to conventional therapy and four deaths among those initially randomized to nifedipine (NS, p = .13). Three of the four deaths occurred after level 3 had been passed, i.e., after propranolol and/or nitrate therapy had been added. In one of these patients, symptoms of infarction began during initial nifedipine therapy, but the patient died while receiving maintenance nitrate and propranolol 6 days after nifedipine had been discontinued. All four deaths resulted from a myocardial infarction that occurred after randomization and led to cardiogenic shock; three of these four patients had a history of a myocardial infarction before randomization.

From 2 weeks to 6 months after randomization, there were two deaths in the conventional therapy group and one in the nifedipine group, resulting in a 6 month mortality of two of 63 (3%) in the group receiving conventional therapy vs five of 63 (8%) in the group initially randomized to nifedipine (NS). Three of the five patients in the nifedipine group actually received propranolol and/or nitrates before their deaths.

Results of coronary arteriography. Although coronary arteriography was not required by the protocol, 53 (42%) of the patients underwent this procedure in the interval from 3 months before to 3 months after randomization. Significant coronary stenosis was defined as ≥70% narrowing of the luminal diameter. Ten of the patients had no coronary stenosis, 14 had obstruction in one vessel, 10 in two vessels and 19 in three vessels. Seven patients had concomitant obstruction of the left main coronary artery. Within this subset of 53 patients in which coronary arterial anatomy was defined, there was no differential response to conventional or nifedipine therapy on the basis of the degree of coronary stenosis. Furthermore, those with more severe disease (three-vessel and left main disease) were not more likely to fail to respond to any level of medical therapy.
than those with less severe coronary atherosclerosis.

Discussion

These findings indicate that ischemic pain in patients with unstable angina pectoris can be controlled as readily with nifedipine alone as with conventional medical therapy (β-blockade and nitrates). Among the patients in the entire study population there were no significant differences between these two forms of therapy with respect to several indexes of the efficacy of medical therapy (e.g., time to pain relief, percentage of patients achieving pain relief, reduction in the number of attacks of pain per day, reduction in the amount of nitroglycerin required or in the number of patients requiring morphine therapy). Pain relief was achieved by level 3 therapy in 73% (46 of 63) of the patients randomly assigned to conventional therapy and in 70% (44 of 63) of the patients in the nifedipine group. As is generally the case for routine initial management of unstable angina pectoris, the results of coronary angiography were not used to guide selection of therapy. It is possible that different results could be obtained in patients in whom therapy is altered specifically to conform with the presence or absence of severe obstructive coronary disease, but such information is often unavailable for patients presenting with unstable angina.

The size of the study population was large enough (126 patients) to provide adequate power for detection of a clinically significant difference between the two regimens if such a difference existed. Specifically, this study had a 90% chance of detecting a significant difference between the two groups if the true rate of pain relief were 73% in the control population and either lower than 45% or greater than 94% in the nifedipine-treated population (assuming a two-sided significance test with a p value of .05).

Several important features of this study deserve mention. First, it is one of a limited number of randomized, double-blind evaluations of medical therapy for unstable angina pectoris. The rationale for medical therapy of unstable angina is based on extrapolations from randomized studies of stable angina, although the pathogenetic mechanisms of dynamic obstruction and/or thrombosis may be more frequent in unstable angina. Second, the characteristics of the patients eligible to enroll in this study were rigorously defined. The lack of a universally accepted definition of unstable angina, as well as its variable natural history, have often produced confusion in comparison of results between randomized studies. Third, data are available for a subgroup of unstable angina patients with ST segment depression and transient T wave changes during attacks, i.e., the subgroup that is most commonly seen in clinical practice. The effects of calcium-channel blockers have been well studied in the subgroup of patients with frequent episodes of pain at rest associated with ST segment elevation,21-24 but only a small amount of information is available regarding the response to calcium-channel blockers in patients with unstable angina with ST segment depression. The results in this subgroup did not differ from those observed in the entire study population.

Although the most general analysis of the data showed equivalence between nifedipine and conventional therapy, significant differences emerged from analysis of the patient subgroups of those who had and had not received previous β-blocker therapy. The latter was continued after randomization as background therapy. By definition, this level of β-blockade had failed to control the unstable angina since patients still experienced episodes of pain that qualified them for the study. In such patients, initiation of nifedipine relieved pain more rapidly than did administration of additional propranolol and/or nitrates. In contrast, among patients not receiving a β-blocker before randomization, initial treatment with propranolol and/or nitrates was superior to nifedipine. The heart rate responses to therapy in those who did and did not receive prior β-blockade were compatible with a plausible mechanism for this differential effect. Nifedipine produced a greater increase in heart rate in patients who had not received prior propranolol than it did in patients already receiving β-blockade. Conversely, conventional therapy produced a greater slowing of heart rate in patients who had not previously received propranolol than in those who had. Thus, in the patients who had not received prior propranolol, the change in heart rate with nifedipine therapy was 12.4 beats/min higher than with conventional therapy (p < .001). In contrast, in those who had received prior propranolol therapy, the change in heart rate with nifedipine therapy was only 3.3 beats/min higher than in those who received conventional therapy. This greater increase in heart rate and the resultant increase in myocardial oxygen demand when nifedipine was given to patients who had not received a β-blocker would be expected to diminish its effectiveness.

Results in patients already receiving β-blockade are consistent with the finding of Gerstenbliuth et al.25 that addition of nifedipine is superior to addition of placebo for the control of unstable angina in patients already treated with propranolol. Our results, however, indicate a greater benefit of nifedipine because it was supe-
rior not only to placebo alone, but also to the addition of propranolol and/or nitrates in patients previously taking \(\beta\)-blockers. The findings of the present study do not support the concern that propranolol, because of a tendency to enhance spasm,\(^{14}\) is harmful to patients with unstable angina. Gerstenblith et al.\(^{28}\) speculated that the benefit of nifedipine observed in their study might have been even more marked if propranolol had not been administered concomitantly. However, in our study nifedipine seemed to be more effective when given against a background of \(\beta\)-blockade than when given in its absence.

Although the findings in the subgroups receiving and not receiving prior \(\beta\)-blockade are of interest, they must be interpreted with caution because this particular analysis was not planned before the start of the trial. In addition, other less sensitive end points of the trial, such as nitroglycerin use and number of anginal attacks per day, failed to show significant differences between these subgroups.

Twenty-seven of the 36 patients who failed to respond to the therapy to which they were initially assigned were treated with the addition of the alternate therapy (levels 4 to 6). The addition of the alternate therapy was accompanied by the control of pain in 37\% (10/27) of the patients (five of 13 patients receiving additional propranolol and/or nitrate therapy, five of 14 receiving additional nifedipine). This finding, which is similar to that of other investigators for the addition of nifedipine,\(^{25-27}\) could be the result of the additional therapy but could also represent spontaneous cessation of unstable angina.\(^{12}\) The data indicate, however, that regardless of which therapy is administered first, the combination of nifedipine with propranolol and nitrates (in association with standard care) resulted in control of unstable angina for at least 48 hr in 100 of 126 (79\%) patients.

Although higher doses of nitrates have been proposed as therapy for unstable angina,\(^{34}\) the dosage used in this study (20 mg isosorbide dinitrate every 6 hr) was sufficient to produce headache in 30\% of the patients receiving the drug. Headache was severe enough to require discontinuation of nitrates in four patients; in contrast, the nifedipine dose (30 mg every 6 hr), which was as effective as the nitrate dose in controlling pain, produced headache in only 5\% of patients and in no instance was the headache severe enough to require discontinuation of therapy.

The incidence of myocardial infarction within 2 weeks of randomization, the second major end point of the study, was identical for patients initially randomized to conventional (14\%) and to nifedipine (14\%) therapies. This finding is similar to results obtained in other studies in which relatively strict criteria for the diagnosis of unstable angina were used.\(^{8, 10}\) Thus, the conditions of a substantial number of patients progressed to infarction despite intensive therapy. Emerging evidence that transmural myocardial infarction is usually associated with coronary thrombosis\(^{35}\) implies that the occurrence of infarction in patients with unstable angina in many cases is due to thrombosis. Furthermore, a recent study of 1266 men with unstable angina randomly assigned to aspirin or placebo therapy for 12 weeks demonstrated a 51\% reduction in the incidence of death or acute myocardial infarction.\(^{36}\) Thus, there appears to be a need for a general reappraisal of the value of antiplatelet agents, anticoagulants,\(^{13}\) and fibrinolytic\(^{37, 38}\) therapy for the prevention of infarction in patients with unstable angina.

Too few deaths occurred in the study to support any conclusions about the effect of nifedipine compared with conventional therapy on mortality in patients with unstable angina. Furthermore, interpretation of the four deaths that occurred in those who initially received nifedipine is complicated by the fact that two of the four occurred in patients receiving triple therapy (nifedipine, nitrates, and propranolol) and one occurred in a patient on nitrates and propranolol alone.

It is of interest that all of the deaths occurred as a result of a myocardial infarction leading to cardiogenic shock. Nifedipine might be expected to be of benefit in limiting infarct size in these patients, but a study of nifedipine therapy for threatened and acute myocardial infarction conducted in parallel with the present study did not show such a beneficial effect.\(^{39}\) The lack of benefit in the infarction study could have been due to a delay in initiation of therapy (mean interval from onset of pain to treatment, 4.6 \pm 0.1 hr), which would not occur in the unstable angina setting. However, the number of patients with infarction in the unstable angina study is far too small to detect a beneficial effect, if present. Hence, neither of the two studies offers direct evidence for or against the continuation of nifedipine therapy in patients with unstable angina whose conditions progress to myocardial infarction.

The findings of this randomized double-blind study support the use of nifedipine alone as an alternative to propranolol and/or nitrates for the initial medical therapy of unstable angina pectoris. In patients already receiving \(\beta\)-blockade, nifedipine appears to be superior to nitrates and additional propranolol. In patients not receiving prior \(\beta\)-blockade, propranolol and/or nitrates appear to be superior. Although these subgroup results are derived from a post hoc analysis of the data and are
not reflected in other measures of anginal control, they are supported by previous studies indicating that the combination of nifedipine and propranolol is well tolerated and effective for stable angina. Propranolol blunts the tachycardia that nifedipine may produce, while nifedipine is the least likely of the presently available calcium-channel blockers to increase the tendency of propranolol to produce atrioventricular block, excessive bradycardia, or left ventricular dysfunction. Thus, the demonstrated safety of the combination of nifedipine and β-blockade, the lack of an adverse effect on heart rate, and the apparent beneficial effect of the combination in controlling angina observed in this study support the value of combining nifedipine with β-blockade as therapy for unstable angina.

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