Comparison of Propranolol, Diltiazem, and Nifedipine in the Treatment of Ambulatory Ischemia in Patients With Stable Angina

Differential Effects on Ambulatory Ischemia, Exercise Performance, and Anginal Symptoms

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Episodes of transient myocardial ischemia during ambulatory activities are common in patients with stable coronary artery disease and who are often asymptomatic. Selection of therapy for episodes of asymptomatic ischemia is limited by a lack of direct comparative studies. To determine the most effective monotherapy for patients with stable angina and a high frequency of asymptomatic ischemic episodes, propranolol-LA (mean daily dose, 293 mg), diltiazem-SR (mean daily dose, 350 mg), nifedipine (mean daily dose, 79 mg) were each compared with placebo, each for 2 weeks, in a randomized, double-blinded, crossover trial. Entry criteria were a positive exercise treadmill test during placebo therapy characterized by 1.0 mm or more ST segment depression and angina pectoris, and six or more episodes of transient ST segment depression of 1.0 mm or more on a 48-hour ambulatory electrocardiogram. One hundred ninety-four patients were screened, 63 were eligible and received randomized therapy, of which 56 patients completed at least two of the four treatment periods and were included in an intent-to-treat analysis. Fifty patients completed all four treatment phases and were included in the protocol-completed analysis. Anti-ischemia efficacy was assessed by 48-hour ambulatory electrocardiographic monitoring, exercise treadmill tests, and anginal diaries. Ninety-four percent of all episodes of ambulatory ischemia were asymptomatic. Compared with placebo, only propranolol was associated with a marked reduction in all manifestations of asymptomatic ischemia during ambulatory electrocardiographic monitoring (2.3 versus 1.0 episodes/24 hr; mean duration of ischemia per 24 hours, 43.6 versus 5.7 minutes; both p<0.0001). Diltiazem's reduction of the frequency of episodes compared with placebo (2.3 versus 1.9 episodes/24 hr) was associated with a trend (p=0.08) in the protocol-completed analysis and with a significant reduction in the intent-to-treat analysis (p=0.03). Nifedipine had no significant effect on any measured variable of ambulatory ischemia. The dosages of medication used may have been excessive for some patients, and a more beneficial effect may have been evident at a lower dose. In contrast to the marked effects of the active agents on ambulatory asymptomatic ischemia, the effects on exercise performance and angina pectoris were slight. The active agents modestly improved treadmill exercise duration time until 1 mm ST segment depression (3%), and only propranolol and diltiazem had significant effects. Only diltiazem significantly prolonged the total exercise time. Anginal frequency was significantly decreased by both propranolol and diltiazem. We conclude that propranolol is effective for treating episodes of asymptomatic ischemia in patients with stable angina and that the magnitude of improvement in ambulatory asymptomatic ischemia is far greater than the improvement in exercise performance and angina symptoms. (Circulation 1990;82:1962–1972)
The phenomenon of transient myocardial ischemia occurring during routine ambulatory activities in patients with stable coronary artery disease has attracted a great deal of clinical and investigative interest. These episodes of ischemia, which can be detected by ambulatory electrocardiographic (ECG) monitoring, are common in patients with stable coronary artery disease, often occur in the absence of symptoms (i.e., asymptomatic or silent ischemia), and have been associated with an increased risk of death or adverse cardiac events compared with patients without such episodes. The mechanisms responsible for such ischemic episodes are unclear but may include transient increases in myocardial oxygen demand, reductions in coronary blood supply due to transient coronary vasoconstriction, or some combination of these two mechanisms.

Although a variety of anti-ischemic medications have been studied as treatment for episodes of ambulatory asymptomatic ischemia, the number of patients studied in controlled trials is small, and definitive comparisons are lacking. Prominent among the agents studied are the β-adrenergic receptor blocker propranolol and the calcium channel antagonists diltiazem and nifedipine. In addition, the relative efficacy of anti-ischemic agents for the treatment of asymptomatic ischemic compared with their efficacy for the treatment of angina and exercise performance is unknown. The purposes of this study were 1) to determine the most efficacious single-agent therapy for reducing the frequency and duration of episodes of asymptomatic ischemia in patients with stable exertional angina, 2) to explore the role of heart rate in the pathophysiology of such episodes, and 3) to compare the relative efficacy of the active agents on the different manifestations of ischemia.

**Methods**

**Study Design**

A double-blinded, randomized, placebo-controlled, multicenter trial design was used, with a four-period crossover arranged in Latin squares. Patients were eligible for inclusion if they satisfied all of the following criteria: 1) had coronary artery disease documented by at least one of the following: coronary angiogram indicating one or more major coronary arteries or their primary branches with a 50% or more reduction in luminal diameter, previously documented myocardial infarction, or a reversible perfusion defect during stress-redistribution thallium-201 scintigraphy; 2) had a stable pattern of angina (i.e., no major change in the frequency, severity, or ease of provocation of angina) for at least 2 months before screening; 3) had a “positive” exercise treadmill test defined as 1.0 mm or more of horizontal or downsloping ST segment depression accompanied by angina; 4) had the ability to complete stage 1 of the Bruce protocol and a positive ischemic response occurring at stage 3 or less; 5) six or more episodes of reversible ST segment depression of 1.0 mm or more lasting 1.0 minute or more in duration on a 48-hour screening ambulatory ECG (or Holter), at least two of which were asymptomatic.

Patients were excluded if they had any of the following: 1) myocardial infarction or cardiac surgery within 3 months of the screening visit or a history of unstable angina within 2 months of the screening visit; 2) congestive heart failure of New York Heart Association class III or greater; 3) ST segment deviation of 1 mm or more at rest or in response to hyperventilation or positional changes on the baseline ambulatory ECG; 4) the presence of left ventricular hypertrophy, conduction defects, or any other condition that may interfere with the accurate interpretation of the ST segment deviation; 5) atrial arrhythmias, sinus bradycardia, or bundle branch block; 6) atrioventricular nodal block, sick sinus syndrome, ventricular preexitation, or presence of an electronic pacemaker; 7) presence of marked coronary artery vasospasm (Prinzmetal’s angina); 8) uncontrolled hypertension (≥180/105 mm Hg) or hypotension (supine systolic blood pressure <100 mm Hg); 9) significant major systemic disease; 10) concomitant therapy with digitalis or other agents known to affect ST segment morphology at rest or during exercise; 11) significant contraindications to β-blocker therapy; and 12) females of childbearing potential.

Patients considered to be potential study candidates were withdrawn from all anti-ischemic medications except nitroglycerin sublingually p.r.n. before the first screening visit. They were then given placebo in a single-blinded fashion for 1–2 weeks, after which they underwent a screening exercise treadmill. If ischemic ST segment depression and angina developed, a 48-hour screening ambulatory ECG was obtained, and the recording was sent to the ambulatory ECG core Laboratory. If six or more episodes of reversible ST segment depression of 1.0 mm or more were observed, at least two of which were asymptomatic, the patients entered the first of four double-blinded treatment phases, each of which lasted 2 weeks.

During the first week of each double-blinded phase, each patient received, according to a balanced randomization scheme, either propranolol-LA, diltiazem-SR, nifedipine, or placebo. The dose was gradually increased during a 3-day period to the...
highest dose tolerated without the development of disturbing side effects. The mean daily dose of study medication used was propranolol-LA 293 mg in two divided doses, diltiazem-SR 350 mg in two divided doses, and nifedipine 79 mg in three divided doses. For each drug regimen, the maximum tolerated dose was continued until the end of each study phase, at which time an exercise treadmill test was performed, followed by a 48-hour ambulatory ECG. An anginal diary was maintained by the patient throughout the treatment period, and the frequencies of angina and nitroglycerin consumption were reviewed at the end of each treatment period. After each treatment phase, the next randomly assigned treatment schedule was initiated. The total study duration per patient was 9–10 weeks.

**Ambulatory ECG Monitoring**

Ambulatory ECG recordings were performed using CardioData AM Cassette Recorders (Marlboro, Mass.). Electrodes were applied to record a modified V\textsubscript{2} and a modified aVF lead. After the leads were connected to the patient but before the ambulatory recording session was begun, a cable from the recorder was inserted into a standard ECG machine. Recordings were made during hyperventilation and in the left- and right-lateral decubitus, standing, supine, and sitting positions to ensure that artifactual ST segment deviation did not occur. The recordings were analyzed with a CardioData Mk 4 playback system with modified software.\textsuperscript{14,15} The technician and the physician reviewer were unaware of medication assignment or treatment order. An ischemic episode was defined as transient ischemic ST segment depression 1.0 mm or greater lasting at least 1 minute. The onset of the episode was defined as the time at which the ST segment became depressed by at least 0.5 mm, and the offset was defined as the time after the peak depression 1.0 mm or greater at which the ST segment returned toward the baseline and became depressed less than 0.5 mm. After an episode of ST segment depression, the baseline had to remain stable and without deviation for at least 5 minutes before new ST segment depression could qualify as a discrete additional episode. The variables evaluated included the number of episodes of ischemic ST segment depression, and the average and total duration of ischemia in minutes. Values were corrected for a 24-hour period. Other variables analyzed were the maximum ST segment depression during the episode; the product of the maximum depth of ST segment depression and duration of the episode (the “ST product”); the heart rate 5 minutes before an episode, at the onset of the episode, and the peak heart rate during the episode. Episodes of ischemia identified by the ambulatory ECG were correlated with symptoms identified in the patient's diary to determine whether the ischemic events were silent or associated with angina.

**Exercise Treadmill Testing**

Exercise tests were symptom-limited maximal tests performed approximately 2 hours after the medication dose using the standard Bruce protocol. The original ECG tracings obtained during the exercise test were sent to the Exercise Treadmill Test Core Laboratory where they were interpreted by a physician unaware of medication assignment or treatment order.

**Statistical Analyses**

Analyses of variance\textsuperscript{16} and the Iman-Conover procedure,\textsuperscript{17} adapted to a four-period crossover design, were used for all statistical analyses. The former method was used when the residuals for the response variables were normally distributed; otherwise, rank transformations were used with the latter procedure. The dependent variable was the response variable. The independent variables included investigator, patient within investigator, period, and treatment.

Three factors were not included in the final analyses because the p value for each was greater than 0.05: treatment by investigator interaction, period within investigator, and carryover effects.

All statistical tests were two-sided with α=0.05. An overall test was performed first, and if significant, then Fisher's protected least-significant difference procedure\textsuperscript{18} was used for paired comparisons. All means presented are means adjusted by the full model. When the analysis used rank transformations, the adjusted means were found by transposing from mean rank to raw data and interpolated. The standard errors of rank-transformed means are not presented because their values are not meaningful.

**Results**

**Patient Population**

From a group of 194 screened patients from eight institutions, 63 eligible patients received randomized therapy. Of these, seven discontinued participation after completing less than two double-blinded treatment periods (one because of death; five because of the development of unstable angina or myocardial infarction, and one because of an orthopedic problem) and were, therefore, not available for any analysis of comparative efficacy. Of the six patients who developed a cardiac event, three were taking nifedipine at the time of their event, and each of the three remaining patients was on one of the other therapies: propranolol, diltiazem, or placebo. Fifty-six patients completed two or more double-blinded treatment periods and are included in the intent-to-treat analysis. Six of these patients did not correctly complete the four treatment periods for the following reasons: one discontinued participating because of worsening angina; one discontinued participation because of dizziness, and four completed the study but did not adhere to the protocol (one because of use of a concomitant proscribed medication and three because of lack of performance of the ambulatory ECG during a treatment phase). The protocol-
completed analysis includes all 50 patients who correctly completed all four treatment periods. As stipulated in the protocol before initiation of the study, the results from the protocol-completed analysis are presented first because that analysis provides the most meaningful comparison of the four periods. The results from the intent-to-treat analysis are presented second, whenever the latter analysis yielded different results.

In the 56 patients who completed two or more treatment periods, there were 42 male and 14 female patients, with a mean age of 60.1 ± 8.1 years (±SD). The mean duration of angina before randomization was 60 ± 58 months. Thirty-three patients (52%) had experienced a previous myocardial infarction, 21 (38%) had a previous revascularization procedure (coronary artery bypass surgery or percutaneous transluminal coronary angioplasty). Twenty-six patients (46%) had a history of systemic arterial hypertension, 38 (68%) had a history of cigarette smoking, and 14 (25%) had a history of diabetes mellitus. Previous antianginal therapy included a β-adrenergic blocking agent in 30 patients (54%), a calcium channel antagonist in 38 (68%), and a long-acting nitrate preparation in 40 (71%). Concomitant medication during the study included aspirin in 25 patients (45%), antihypertensive therapy in 15 (24%), and antiarrhythmic therapy in two (3%). Fifty-two patients (93%) were in Canadian class 1 or 2, whereas four (7%) were in class 3.

**Effect of Anti-Ischemia Medication on Heart Rate and Blood Pressure**

Propranolol and diltiazem significantly reduced the resting heart rate compared with placebo (p ≤ 0.001), although propranolol reduced the heart rate to a significantly greater degree than did diltiazem (p = 0.0001) (Table 1). Nifedipine significantly increased the heart rate compared with placebo as well as compared with propranolol and diltiazem (each p ≤ 0.0001). Compared with placebo, none of the medications significantly reduced the resting systolic blood pressure. The resting double product was significantly reduced by propranolol. The effect of the medications on the mean heart rate throughout the ambulatory ECG monitoring period is displayed in Figure 1.

**Table 1. Effect of Anti-Ischemia Medication on Resting Heart Rate and Blood Pressure**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Diltiazem</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting HR (beats/min)</td>
<td>70.5 ± 0.9</td>
<td>55.2 ± 0.9*</td>
<td>66.5 ± 0.9*</td>
<td>77.4 ± 0.9*</td>
</tr>
<tr>
<td>Resting systolic BP (mm Hg)</td>
<td>130.9 ± 1.7</td>
<td>125.2 ± 1.8</td>
<td>129.6 ± 1.8</td>
<td>127.7 ± 1.8</td>
</tr>
<tr>
<td>Resting diastolic BP (mm Hg)</td>
<td>79.3 ± 0.9</td>
<td>74.7 ± 0.9*</td>
<td>75.6 ± 0.9†</td>
<td>75.8 ± 0.9†</td>
</tr>
<tr>
<td>Resting double product (× 103)</td>
<td>10.5 ± 0.2</td>
<td>9.5 ± 0.2†</td>
<td>9.9 ± 0.2</td>
<td>9.8 ± 0.2‡</td>
</tr>
</tbody>
</table>

Data are mean ± SEM, adjusted by the statistical model. n = 50 patients. HR, heart rate; BP, blood pressure.

*p < 0.001 compared with placebo; †p < 0.01 compared with placebo; ‡p < 0.05 compared with placebo.

**Effect of Anti-Ischemia Medication on Episodes of Ambulatory Ischemia**

Ninety-four percent of all episodes of ambulatory ischemia were asymptomatic during the double-blinded treatment phases; the symptomatic episodes (6% of total number of episodes) were combined with the asymptomatic episodes for subsequent analyses. Propranolol therapy was associated with a significant reduction in all manifestations of ischemia during ambulatory monitoring compared with placebo (Table 2 and Figure 2). Compared with placebo, propranolol resulted in a 57% reduction in the frequency of episodes of ST segment depression, a 58% reduction in the mean duration of each episode, an 87% reduction in the total duration of ST segment depression per day, a 39% reduction in the mean maximum ST segment depression per episode, a 68% reduction in the mean ST product per episode, and an 88% reduction in the cumulative ST product per 24 hours (all p < 0.0001). Propranolol was also significantly more effective than either diltiazem or nifedipine for each of these outcomes (all p < 0.001).
The reduction in the frequency of episodes observed during diltiazem therapy compared with placebo (i.e., 17%) was associated with a trend ($p=0.08$) in the protocol-completed analysis; in the intent-to-treat analysis, the reduction was slightly more marked (28%) and was significant ($p=0.03$). Diltiazem had no effect on the mean duration of ischemia per episode, cumulative duration of ischemia per 24 hours, maximum ST segment depression per episode, mean ST product per episode, or cumulative ST product per 24 hours in either the protocol-completed or intent-to-treat analysis.

Nifedipine had no significant effect on any measured variable of ambulatory ischemia. The anti-ischemia results were similar when individual patient responses to the different therapies were considered. For example, among the protocol-completed patients, 15 patients (30%) had no ischemia on propranolol therapy, whereas only seven patients (14%) had no ischemia on placebo therapy. A similar number of patients (11 patients or 22%) had no ischemia on either the diltiazem or nifedipine regimen.

**Effect of Anti-Ischemia Medications on the Relation Between Heart Rate Patterns and Episodes of Ambulatory Ischemia**

Heart rate activity associated with episodes of ischemia. The mean heart rate at the onset of ischemic ST segment depression during ambulatory ECG monitoring was lower on propranolol and diltiazem than on placebo therapy (each $p<0.01$), whereas the mean heart rate at onset on nifedipine was similar to that on placebo (Table 2). The mean heart rate 5 minutes before the onset, at the onset, and the maximal heart rate during each episode were all significantly lower on propranolol and diltiazem than placebo.

### Table 2. Effect of Anti-Ischemia Medication on Episodes of Ischemia During Ambulatory Electrocardiographic Monitoring

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Diltiazem</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of episodes of ST depression/24 hr*</td>
<td>2.3</td>
<td>1.0‡</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Mean duration/episode (min)*</td>
<td>13.9</td>
<td>5.9‡</td>
<td>12.3</td>
<td>15.0</td>
</tr>
<tr>
<td>Cumulative duration/24 hr (min)*</td>
<td>43.6</td>
<td>5.7‡</td>
<td>26.6</td>
<td>41.2</td>
</tr>
<tr>
<td>Mean maximum ST depression/episode (mm)*</td>
<td>−1.8</td>
<td>−1.1‡</td>
<td>−1.4</td>
<td>−1.6</td>
</tr>
<tr>
<td>Mean ST product/episode (mm · min)*</td>
<td>21.5</td>
<td>6.9‡</td>
<td>16.0</td>
<td>22.4</td>
</tr>
<tr>
<td>Cumulative ST product/24 hr (mm · min)*</td>
<td>57.1</td>
<td>6.8‡</td>
<td>32.6</td>
<td>51.5</td>
</tr>
<tr>
<td>Mean HR 5 minutes before episode (beats/min)†</td>
<td>82.0±1.5</td>
<td>65.9±1.7‡</td>
<td>78.5±1.6§</td>
<td>83.9±1.6</td>
</tr>
<tr>
<td>Mean HR at onset of ST depression (beats/min)†</td>
<td>94.8±2.0</td>
<td>78.2±1.7‡</td>
<td>89.6±2.0§</td>
<td>96.2±1.9</td>
</tr>
<tr>
<td>Difference in HR from 5 minutes before episode to onset of episode (beats/min)†</td>
<td>12.9±1.4</td>
<td>12.3±1.4</td>
<td>11.2±1.5</td>
<td>12.0±1.4</td>
</tr>
<tr>
<td>Mean maximum HR during episode (beats/min)†</td>
<td>106.3±2.3</td>
<td>82.2±1.8‡</td>
<td>97.9±2.3§</td>
<td>106.5±2.3</td>
</tr>
</tbody>
</table>

*Mean, adjusted by the statistical model and transformed from ranks back to original units. Standard errors are not presented because their values after rank transformation are not meaningful.
†Mean±SEM, adjusted by the statistical model.
HR, heart rate.
‡$p<0.0001$ compared with placebo; §$p<0.01$ compared with placebo.
on placebo (each $p<0.01$). The respective values on propranolol were significantly lower than those on diltiazem ($p=0.0001$). However, on each therapy, the increase in heart rate from 5 minutes before the episode to the onset of the episode was similar to that on placebo.

Relation between heart rate patterns throughout the day and frequency of episodes of ambulatory ischemia. On placebo, there was a marked increase in the mean heart rate in the morning hours with a gradual decrease in heart rate in the evening (Figure 3). The frequency distribution of episodes of asymptomatic ischemia closely paralleled the heart rate activity throughout the day. On propranolol, the heart rate was reduced throughout the day and was associated with a parallel reduction in episodes of ischemia. On diltiazem, there was a morning increase in heart rate, but there was no apparent increase in the frequency of ischemic episodes. Episodes of ischemia were more frequent in the late afternoon and early evening. During nifedipine treatment, both the heart rate pattern and the frequency distribution of ischemic episodes were very similar to what occurred during placebo.

To investigate the relation between changes in heart rate and the occurrence of episodes of ischemia, we created a variable “heart rate delta” that was defined as the difference between the mean heart rate per hour and the maximum heart rate per hour obtained during the ambulatory ECG recording for each patient during each treatment phase. The heart rate delta for each hour was correlated with the number of ischemic episodes occurring during each hour. The hypothesis was that if episodes of ambulatory ischemia were primarily due to an increase in heart rate (which may reflect an increased myocardial oxygen demand), then there should be a close correlation between these heart rate deltas per hour and episodes of ischemia per hour. Although there was a significant linear correlation between the two variables during each of the treatment periods ($p\leq0.01$), the Pearson correlation coefficient was low ($r$ values ranging from 0.146 to 0.197).

Effect of Anti-Ischemia Medication on Exercise Test Performance

Only diltiazem was associated with significant prolongation of symptom-limited total exercise time compared with placebo. Compared with placebo, both diltiazem and propranolol increased the exercise time to onset of 1 mm ST segment depression slightly ($p=0.01$ for diltiazem and $p=0.0005$ for propranolol) and exhibited a trend toward increasing the exercise time to angina (overall $p=0.06$). The improvement in exercise performance was slight and never more than 8% (Table 3). The submaximal double product (at 3 minutes of exercise) and maximum double product attained were significantly lower during propranolol therapy compared with all other medications (each $p=0.0001$) and was lower during diltiazem therapy compared with placebo ($p=0.002$). The maximum ST segment depression during the exercise test was significantly less for all three active agents compared with placebo. Although most patients terminated exercise because of fatigue and shortness of breath, many patients stopped exercise because of progressive angina.
Effect of Anti-Ischemia Medication on Angina Frequency and Nitroglycerin Consumption

Propranolol and diltiazem significantly reduced the number of angina episodes per week compared with placebo: from 2.3 episodes on placebo to 1.3 episodes on propranolol (p = 0.001), to 1.3 on diltiazem (p = 0.001), and to 2.0 on nifedipine (p = NS). Propranolol reduced the need for nitroglycerin consumption per week compared with placebo: from 1.3 tablets on placebo to 0.7 tablets on propranolol (p < 0.01), to 1.0 tablets on diltiazem (p = NS), and to 1.2 tablets on nifedipine (p = NS).

Side Effects and Complications

Premature crossover to the next therapy occurred 10 times among the 50 protocol-completed patients because of intolerable side effects: two while on placebo, two while on propranolol, one while on diltiazem, and five while on nifedipine. The most frequent side effects on each of the therapies and their respective incidences were weakness (10%) while on propranolol, peripheral edema (5%) while on diltiazem, angina (15%) while on nifedipine, and angina (9%) while on placebo.

Discussion

Although there is evidence in patients with stable coronary artery disease that episodes of asymptomatic ischemia during ambulatory ECG monitoring are common and are associated with an adverse outcome compared with evidence in similar patients who do not have such episodes,2-12 it is not clear how best to treat such episodes. Furthermore, it is unknown whether treatment directed at improving anginal symptoms and exercise performance is equally effective in treating episodes of asymptomatic ischemia. Our results clearly indicate that in patients with stable exertional angina and asymptomatic ischemia, propranolol was highly effective in reducing the frequency and severity of asymptomatic ischemic episodes. Diltiazem produced a mild, but significant, reduction in the frequency of silent ischemic episodes in the intent-to-treat analysis, but statistical significance was not achieved in the protocol-completed analysis. Nifedipine had no significant effect on any manifestation of asymptomatic ischemia.

There was a striking discrepancy between the marked effects of propranolol on asymptomatic ischemia and its modest effects on exercise test performance. Although each of the three agents appeared to prolong the exercise time until the onset of angina and 1 mm ST segment depression, the improvement was very small, and statistical significance was achieved only for the improvement in time to ischemic ST segment depression observed with propranolol and diltiazem. Only diltiazem significantly prolonged the total exercise time and then only by 8%. Propranolol and diltiazem were both associated with a highly significant reduction in the number of angina episodes per week (43% for each), and propranolol alone was associated with a reduction in weekly nitroglycerin consumption for pain relief.

Pathophysiological Mechanisms Leading to Episodes of Asymptomatic Ischemia

There has been controversy on whether episodes of ischemia during daily life in patients with stable coronary disease are due to increases in myocardial oxygen demand, to a primary decrease in myocardial blood supply, or to both. The importance of episodic coronary vasoconstriction is suggested by the observations that episodes of ischemia during ambulatory ECG monitoring generally occur without a preceding rise in heart rate or occur with a heart rate rise that is less than that occurring during a supervised exercise test14-17,19,20 and that episodes of asymptomatic ischemia often occur after mental stress21-23 or ciga-
smoke24,25 without a major increase in double product.

Other investigators, in contrast, have demonstrated that most episodes of asymptomatic ischemia are indeed preceded by an increase in heart rate26–28 and that the frequency distribution of episodes parallels the increases in heart rate and blood pressure throughout the day.8,20,28–30 It is likely that in many cases both increases in myocardial oxygen demand and reductions in myocardial oxygen supply contribute to the pathophysiology of ischemia during ambulatory activities because coronary tone may be highest in the morning31 and because increased heart rate in the morning is significantly more likely to result in ischemia compared with a similar rise in heart rate in the evening.20

Our results support the concept that increases in heart rate and, therefore, presumably in myocardial oxygen consumption, frequently contribute to the development of episodes of asymptomatic ischemia because the distribution of episode frequency throughout a 24-hour period appears to parallel closely the distribution of mean heart rate and because more than half of the episodes were preceded by an increase in heart rate of 10 beats/min or more during the 5 minutes before the onset of ischemia. Furthermore, the similar increase in heart rate before ischemic episodes in all four treatment arms underscores the presence of a common mechanism. However, it is clear that this mechanism is not solely responsible for these episodes and that the differential efficacy among the three active agents is not due entirely to their respective effect on heart rate.

It, therefore, seems that although increases in heart rate are associated with episodes of ischemia, episodic decreases in coronary blood supply may contribute to the ischemic process as well. It must be noted, however, that ambulatory blood pressure was not measured in these patients during Holter monitoring, and it is possible that some ischemic episodes were provoked by transient increases in blood pressure unaccompanied by a substantial increase in heart rate. If heightened systemic or coronary vasoconstriction were central to the process of those episodes of asymptomatic ischemia not mediated by an increase in heart rate, however, it is not clear why the calcium channel antagonists were not more efficacious.

Effect of Single-Agent Therapy on Episodes of Ambulatory Ischemia

Propranolol. Although the β-adrenergic blockers have been found to be effective in reducing episodes of ischemia during ambulatory activities,27,30,32–37 they have not been directly compared with the calcium channel antagonists diltiazem and nifedipine, which have very different effects on the heart rate.

Even among the β-blockers, the specific importance of heart rate reduction in the treatment in ischemic episodes is underscored by a study38 demonstrating that pindolol, a β-blocker with intrinsic sympathomimetic activity and lack of heart rate reduction, was not as effective as atenolol in reducing the frequency, duration, and magnitude of episodes of ambulatory ischemia.38

Diltiazem. In contrast to our results, Frishman et al39 recently reported that diltiazem (mean daily dose, 351 mg) led to a marked reduction in the number of episodes of ST segment depression recorded during ambulatory activities (from 8.1 episodes on placebo to 3.9 episodes/day on diltiazem, p<0.03). However, their patients had many more episodes of angina per week and of ambulatory ischemia per day during the placebo phase (11.7 and 8.1 episodes, respectively) compared with our patients (2.3 and 2.3 episodes, respectively), and the difference in magnitude of therapeutic efficacy may reflect differences in patient populations. These investigators also observed that diltiazem was more effective than nifedipine (mean daily dose, 91 mg) in reducing episodes of ambulatory ischemia, and they speculated that this difference in efficacy was due to the fact that diltiazem, but not nifedipine, reduced the heart rate throughout the day. Our study importantly extends this concept and demonstrates that an even greater magnitude of heart rate reduction, as seen with propranolol compared with diltiazem, is associated with an even greater therapeutic efficacy.

Nifedipine. Early studies demonstrated a substantial reduction in episodes of ambulatory ischemia in patients treated with nifedipine,32,40 but more recent studies have not reported a benefit.39,41,42 In each of the studies in which nifedipine has not been efficacious, the mean daily, or mean hourly heart rate has either been unchanged or has actually increased significantly compared with that on placebo. It is likely that the reflex tachycardia and consequent increased myocardial oxygen demand outweighed the beneficial effects of preventing vasoconstriction. It is possible that the daily dose of nifedipine used in this study (mean, 79 mg) was relatively excessive for these patients; if lower doses had been used, the reflex tachycardia might have been avoided, and nifedipine might have been more effective.

Of note, although the mean number of daily episodes of ischemia while on nifedipine appears similar to the mean number of episodes on diltiazem, only the improvement on diltiazem was significant in the intent-to-treat analysis (Table 2, Figure 2). This apparent discrepancy occurred because the statistical analysis is based on a model using rank-transformed data. The statistical model indicated that the effect of nifedipine was not significant, although when the ranked data were transformed back to original units, the mean number of daily episodes appeared to be different on nifedipine compared with placebo. Thus, episodes of ischemia were reduced from 2.3 episodes/day on placebo to 2.0 episodes/day on nifedipine (p=0.15 in the protocol-corrected analysis and p=0.16 in the intention-to-treat analysis).

Effect of Single-Agent Therapy on Exercise Test Performance

It is not clear why exercise performance was not further improved by the active agents in our patients.
Propranolol and diltiazem exerted negligible effects on exercise end points, a finding that contrasts with most available data. Although previous studies have shown somewhat variable results, they generally have demonstrated a significant and substantial increase in exercise time to these end points for each of these active agents at comparable doses used.\(^{34,39,41-53}\) The lack of a consistent increase in total exercise time on active anti-ischemic medication has also been observed by others,\(^{54}\) however, and may be because most patients in this study were limited by fatigue or shortness of breath and not by angina. It is also possible, alternatively, that the patient population that we studied is different from the populations studied by others. The more typical patients with a positive exercise test may now be referred for a revascularization procedure, leaving a somewhat atypical sample of coronary patients available for study participation.

The magnitude of improvement in exercise time to the development of ST segment depression and angina on propranolol was far less than the magnitude of reduction in double product at submaximal or maximal exercise (Table 3). Although unlikely, propranolol might have lowered the ischemic threshold so that ischemia was more readily provoked during exercise on propranolol than it was on placebo. This concept is supported by the fact that the mean heart rate at the onset of ST segment depression during ambulatory monitoring was significantly lower on propranolol than on placebo (Table 2).

**Effect of Single-Agent Therapy on Angina and Nitroglycerin Consumption**

Propranolol and diltiazem reduced the weekly frequency of angina attacks, and propranolol also reduced weekly the need for nitroglycerin consumption. However, the mean weekly anginal frequency and nitroglycerin consumption observed during placebo treatment in our study (2.3 episodes and 1.3 tablets, respectively) are much lower than the frequency of these occurrences in previous studies during the placebo phase (5–22 episodes and 9–13 tablets, respectively),\(^{32,39,42,47,49–53,55,56}\) and the lack of a more striking outcome in our patients may primarily reflect a loss of power due to a lower event rate on placebo. Our patients had similar characteristics of coronary disease as patient populations in similar studies, that is, a history of angina and a positive exercise test, as well as documented evidence of coronary disease (by angiography, previous myocardial infarction, or reversible perfusion defect by exercise thallium scintigraphy). No special selection criteria were used to identify candidates for this study except for the presence of frequent episodes of asymptomatic ischemia. We previously reported that there were no clinical or exercise test variables in this study population that could predict which patients with stable angina would also have frequent episodes of asymptomatic ischemia; such patients could only be identified by Holter monitoring.\(^{57}\) Although un-likely, the number of symptomatic episodes of ischemia could have been underestimated because of inaccurate angina diaries. We believe that the patients in this study are representative of patients with stable angina who are now treated medically in the United States. These patients were selected from eight different medical centers across the country, and the patient characteristics and the treatment responses were similar in each institution. In this era of revascularization procedures, the more symptomatically limited patients may be referred for such invasive procedures, and the patients with episodic ischemia now on medical therapy may be those who are less symptomatic than heretofore or have already been revascularized.

The fact that seven (11%) of the 63 randomized patients with stable and minimally symptomatic angina discontinued participation prematurely because of death, myocardial infarction, or unstable or worsening angina underscores the reported association of the presence of ambulatory ischemic episodes and adverse coronary events.\(^{9–12}\) Also of note, four of the seven cardiac events occurred while the patients were on nifedipine, suggesting that the short-acting formulation of nifedipine may not be an effective anti-ischemia agent when used alone.

**Clinical Implications**

The results observed in this study are important for two major reasons. The first is that there is an apparent relation between increases in the ambient heart rate during ambulatory activities and the development of episodes of ischemia, the overwhelming majority of which are symptomatically silent. The second is that agents that reduce the heart rate maximally are the most effective in treating asymptomatic ischemia. It is worth noting that agents that significantly reduce heart rate and β-adrenergic activity seem to confer widespread protection against cardiovascular events.\(^{58–60}\) Heightened β-adrenergic activity in patients with stable coronary disease may be a critical common denominator underlying the development of both reversible and irreversible cardiac events.

The second important outcome from our study is the appreciation that ambulatory ECG monitoring for the detection of episodes of ambulatory ischemia may be a much more useful tool than angina diaries and exercise performance to evaluate the presence of ischemia in patients with stable exertional angina and the response to anti-ischemia medications. For patients with coronary disease who are now not referred for revascularization procedures but are treated medically and who have stable and relatively infrequent episodes of angina but frequent episodes of asymptomatic ischemia, a β-adrenergic blocker without intrinsic sympathomimetic activity is most effective to control most manifestations of ischemia.
Appendix

Angina and Silent Ischemia Study (ASIS) Participating Institutions and Personnel

Clinical centers. Brigham and Women’s Hospital, Boston: Satinder Bhatia, MD, Principal Investigator; John D. Parker, MD, Principal Investigator; Dorothy G. Curtis, RN, Research Nurse Coordinator; Donna M. Maciak, RN, Research Nurse. University of Virginia, Charlottesville: Robert Gibson, MD, Principal Investigator; Lorene Shaw, RN, Research Nurse. University of South Florida, Tampa: Stephen P. Glasser, MD, Principal Investigator; Teresa Wizda West, RN, Research Nurse. Sacred Heart and Deaconess Hospital, Spokane, Washington: Marcus A. DeWood, MD, Principal Investigator; Marian Fisher, RN, Research Nurse. University of Texas, San Antonio: Michael H. Crawford, MD, Principal Investigator; Judy Vittitoe, RN, Research Nurse. University of Connecticut, Farmington: David Hager, MD, Principal Investigator; Frank Messineo, MD, Principal Investigator; Ellen McCabe, RN, Research Nurse. Hospital of the Good Samaritan, Los Angeles: Thomas L. Shook, MD, Principal Investigator; Sandra Allen, MSN, Research Nurse.

Clinical coordinating center. Harvard Medical School, Boston: Peter H. Stone, MD, Principal Investigator; Eugene Braunwald, MD, Principal Investigator; Dorothy G. Curtis, RN, Research Nurse Coordinator; Donna M. Maciak, RN, Research Nurse.

Ambulatory ECG (Holter) core laboratory. Harvard Medical School, Boston: Thomas L. Shook, MD, Principal Investigator; Khether Raby, MD, Principal Investigator; Peter H. Stone, MD, Principal Investigator; Gail MacCallum, BS, Holter Analyst.

Exercise test core laboratory. Brigham and Women’s Hospital, Boston: Peter H. Stone, MD, Principal Investigator.

Marion Merrell Dow Inc. Phillip M. Young, PharmD, Senior Clinical Research Scientist; Robert Hoop, MPH, Biostatistician; Esam Sadarous RPh, Clinical Research Associate; Barbara Geiger, RN, Clinical Research Associate.

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