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Medical Treatment to Reduce Total Ischemic Burden: Total Ischemic Burden Bisoprolol Study (TIBBS), a Multicenter Trial Comparing Bisoprolol and Nifedipine

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Objectives. **We compared the effects of bisoprolol on transient myocardial ischemia with those of nifedipine in patients with chronic stable angina.**

Background. **Both beta-adrenergic blocking agents and calcium antagonists reduce transient ischemic episodes, but comparisons of these agents have been made in only a few larger studies.**

Methods. **The Total Ischemic Burden Bisoprolol Study (TIBBS) was a randomized double-blind controlled study with two parallel groups; 330 patients from 30 centers in seven European countries with stable angina pectoris, a positive exercise test and more than two transient ischemic episodes during 48 h of Holter monitoring (central evaluation) were included. Of these patients 161 were randomized to receive bisoprolol and 169 to receive nifedipine slow release. There were two treatment phases of 4 weeks each, with 48-h Holter monitoring after each phase. During phase 1, patients received either 10 mg of bisoprolol daily or 2 × 20 mg of nifedipine slow release. During phase 2, they received either 20 mg of bisoprolol daily or 2 × 40 mg of nifedipine slow release.**

Results. **In phase 1 of the trial, 4 weeks of bisoprolol therapy (10 mg daily) reduced the mean [±SD] number of transient ischemic episodes from 8.1 ± 0.6 to 3.2 ± 0.4/48 h. Nifedipine (2 × 20 mg) reduced transient ischemic episodes from 8.3 ± 0.5 to 5.9 ± 0.4/48 h. Total duration of ischemia was reduced from 99.3 ± 10.1 to 31.9 ± 5.5 min/48 h with bisoprolol and from 101 ± 9.1 to 72.6 ± 8.1 min/48 h with nifedipine. Reductions were statistically significant for both drugs; the difference between bisoprolol and nifedipine was also significant ($p < 0.0001$). Bisoprolol reduced the heart rate at onset of episodes by 13.7 ± 1.4 beats/min from a baseline value of 99.5 ± 1.2 beats/min ($p < 0.001$). Heart rate was unchanged with nifedipine. Bisoprolol had significantly higher responder rates than nifedipine. Doubling of the dose in phase 2 of the trial had small additive effects. Only bisoprolol showed a marked circadian effect by reducing the morning peak of transient ischemic episodes (by 68% at peak time, 8:00 to 8:59 AM).**

Conclusions. **Both bisoprolol and nifedipine reduced the number and duration of transient ischemic episodes in patients with chronic stable angina. Bisoprolol was significantly more effective than nifedipine in both doses tested and reduced the morning peak of ischemic activity.**

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Transient, predominantly silent, myocardial ischemia may deserve treatment because of its prognostic implications (1–9). Beta-adrenergic blocking agents and calcium antagonists are prime candidates in the optimal treatment of transient ischemia by improving the load conditions or the oxygen supply of the heart, or both (10). Several smaller studies (11–14) have addressed the efficacy of beta-blockers or calcium antagonists on transient ischemia. The purpose of the Total Ischemic Burden Bisoprolol Study (TIBBS) was to study the effect of bisoprolol, a cardioselective, 24-h active beta-blocker (15), on the number and duration of transient ischemic episodes compared with nifedipine, a calcium antagonist previously shown to be effective in transient ischemia (16,17).

Methods

Study design. TIBBS was a randomized multicenter double-blind controlled study with two parallel groups. A placebo prephase of 10 days was followed by two treatment phases of 4 weeks each. Treatment during phase 1 was either with 10 mg of bisoprolol daily or 20 mg of nifedipine slow release twice a day. Treatment during phase 2 was double the dose of phase 1 for each group, that is, 20 mg of bisoprolol daily or 40 mg of nifedipine slow release twice a day.

Sample size determination. We aimed for a power of 90% for detection of a difference between the groups of at least 0.45 SD (alpha 5% two-tailed). This means that a difference of three episodes/48 h should be detectable. Therefore, the sample size determination was 100 patients/treatment group who should be evaluable with respect to number and duration of transient ischemic episodes.

Patient selection. In 30 European centers (see Appendix for participating institutions and personnel), ambulatory patients were recruited for the placebo prephase if they fulfilled the following inclusion criteria: history of typical stable angina pectoris and positive exercise tolerance test with ST segment

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depression using a modified Bruce protocol on a treadmill or incremental work load of 25 W every 2 min on a bicycle. For women, the presence of coronary artery disease had to be further documented by a definite history of myocardial infarction, positive findings on the coronary angiogram with >70% stenosis in a major vessel or positive findings on exercise thallium scintigraphy. For men these additional diagnostic criteria were desirable but not mandatory. During the placebo prephase, the patients underwent 48-h ambulatory monitoring and were enrolled for randomized active treatment when they had at least two episodes of transient myocardial ischemia.

Patients were excluded if they met one or more of the following exclusion criteria: unstable angina pectoris, myocardial infarction within the past 3 months, bradycardia with <50 beats/min during the daytime, significant first-degree atrioventricular (AV) block (PQ > 0.24 s), second- or third-degree AV block, hypotension with systolic blood pressure <100 mm Hg or suspected poor compliance.

The following drugs were not given during the study: long-acting nitrates, beta-blockers (except the study medication), afterload-reducing agents, including calcium channel blockers and angiotensin-converting enzyme inhibitors (except the study medication), alpha$_1$-adrenoceptor blockers and beta$_2$-stimulants, tricyclic antidepressants or drugs known to influence ST segments (such as digitalis and antiarrhythmic agents).

Study protocol. If a patient met the inclusion criteria, he or she entered the 10-day placebo prephase and performed the qualifying exercise tolerance test on day −10. At the same time a physical examination and chemical laboratory tests were performed. From day −6 to day −4, the 48-h ambulatory electrocardiographic (ECG) monitoring was done. Express delivery of the tapes to the central laboratory, immediate evaluation and communication of the results by telephone or fax ensured the inclusion of suitable patients into the randomized treatment phases by day 0. At the end of treatment phase 1 after 4 weeks and at the end of treatment phase 2 after 8 weeks, 48-h Holter recordings were repeated, together with a check on anginal attacks, adverse events and a tablet count.

Ambulatory ECG monitoring. Two consecutive 24-h recordings were performed during the placebo prephase and at the end of each treatment phase using Oxford Medilog MR45 recorders and leads CM$_5$ and modified aVF. This is a combination device incorporating conventional recording of the ECG as well as microprocessor-controlled on-line processing of the data for arrhythmia and ST segment analysis (18). Accurate identification of QRS trigger, beat configuration and noise rejection is performed during the recording. On noise-free beats belonging to a normal beat family, the recorder performs a series of ST segment level and slope measurements directly from the patient leads, thus avoiding compromise of measurement accuracy by frequency response limitation or phase distortion common on tape-recorded ECGs. Verification of the data is possible by referring to the original, analog ECG. To ensure consistent evaluation, all tapes were read centrally and in a blinded manner in a core laboratory in London (J.A.D.) (see Appendix) using an Oxford Medilog Excel Analysis System. Each report was overread and reviewed (J.A.D.).

The criteria for an ischemic episode were ≥1 mm of horizontal or downsloping ST segment depression lasting ≥1 min and separated from another episode by ≥1 min. The maximal depth of the ST segment depression during each episode was noted to allow the calculation of an index of ST segment depression (mm) times duration (min) as the "total ischemic burden." Time and heart rate at the beginning of an episode of ischemia were documented.

Tape results were accepted for further analysis only if ≥75% of the recorded 48 h were of technically acceptable quality.

Statistical analysis. All data from the case report forms and the central Holter tape evaluation were continuously entered into a central data base. The randomization plan was not disclosed before all the data had been checked for plausibility and any necessary corrections had been carried out. The number and duration of ischemic episodes and the total ischemic burden as the difference from baseline were defined as primary target variables of efficacy. Results are presented as mean value ± SEM. Differences from baseline values were checked for significance considering the 95% confidence limits. If the confidence interval does not include zero, the mean baseline difference was regarded as significantly different from zero. The efficacy variables were compared between the two treatment groups by the Wilcoxon rank-sum test. Comparisons within each group between the 4- and 8-week measurements were performed by the Wilcoxon signed-rank test. Responder rates were analyzed using the Fisher exact test. Significance level was alpha 5%, two-tailed.

Results

Study patients. From April 1991 to February 1993, 631 patients fulfilled the inclusion criteria and had a positive result on the exercise ECG. Of these, 330 had two or more transient episodes of ischemia during 48-h ambulatory ECG monitoring and thus could be randomized to receive bisoprolol (161 patients) or nifedipine (169 patients). The baseline characteristics of the randomized patients are shown in Table 1. There were no significant differences in gender, age, smoking history or other baseline values.

Of the patients who started randomized treatment, there were 10 dropouts in the bisoprolol group and 17 in the nifedipine group, mostly because of adverse drug reactions (described later). Data had to be excluded from analysis because of ineligible tapes or protocol violations for 18 patients in the bisoprolol group and 17 in the nifedipine group. Thus, for phase 1 of the randomized treatments there were 133 patients with eligible tapes in the bisoprolol group and 135 in the nifedipine group. For phase 2 of the randomized treatment, weeks 5 to 8 on the double dose, there were 17 dropouts and 16 data exclusions in the bisoprolol group and 12 dropouts and 18 exclusions in the nifedipine group. Patients with eligible tapes for phase 2 included 118 with bisoprolol and 122 with

Table 1. Baseline Characteristics of Randomized Study Patients

	Bisoprolol (n = 161)	Nifedipine Slow Release (n = 169)	p Value
Male/female	134/27	146/23	0.45
Smoker and ex-smoker (%)	57.2	62.2	0.31
Age (yr)	57.6 (38–77)	57.3 (32–78)	0.75
History of angina (mo)	24.8 (1–256)	20.5 (2–195)	0.50
Positive history of myocardial infarction	44	53	0.47
Weight (kg)	77.2 ± 9.3	75.7 ± 9.8	0.16
SBP (mm Hg)	139.9 ± 16.2	140.0 ± 18.9	0.92
HR (beats/min)	74.2 ± 10.6	74.0 ± 10.3	0.85
ETT			
Maximal rate-pressure product (mm Hg × beats/min)	23,684 ± 5,320	24,147 ± 5,402	0.44
Maximal ST segment depression (mV)	0.22 ± 0.10	0.22 ± 0.09	0.80

Data presented are mean value ± SD, median value (range) or number of patients. ETT = exercise tolerance test; HR = heart rate; SBP = systolic blood pressure.

nifedipine (patients with protocol violations or ineligible tapes at the end of phase 1 entered phase 2 of the trial in the normal way). In the bisoprolol group there were 111 patients (nifedipine slow release, 112 patients) with eligible tapes in both phase 1 and phase 2 of the trial.

Treatment effects on ambulatory ischemia. Table 2 presents an overview of the results obtained with ambulatory ECG monitoring. Number and duration of the ischemic episodes as well as the total ischemic burden showed a marked and statistically significant reduction with both antianginal drugs in the low dosages (confidence intervals do not include zero). All reductions were significantly greater with bisoprolol than with nifedipine ($p < 0.0001$); the effects of bisoprolol were about twice those of nifedipine. Heart rate at onset of ischemic episodes was 99.5 ± 1.17 beats/min in the bisoprolol group and 101.2 ± 1.03 beats/min in the nifedipine group during the placebo prephase. At the end of the low-dose phase, 54 patients in the bisoprolol group and 20 in the nifedipine group had no ischemic episodes. These patients were not included in the analysis of treatment effects on heart rate at the onset of ischemic episodes. Bisoprolol treatment resulted in a significant reduction in heart rate of 13.7 ± 1.39 beats/min, whereas with nifedipine a small but not significant increase of 1.4 ± 1.08 beats/min was observed ($p = 0.0001$, bisoprolol vs. nifedipine).

The additional effects of the double dose of bisoprolol and nifedipine are summarized in Table 3. These effects are small and significant only for bisoprolol, with a further reduction in the number of ischemic episodes and mean heart rate at the onset of ischemic episodes.

In Figure 1 the time course of the variables from baseline to high dose is presented for those patients with a valid 48-h Holter tape at baseline and at the end of the low and high dose treatment phases.

Treatment effects on angina pectoris. The effects of both treatments on the number of angina attacks per week are

Table 2. Effects of Low Doses in 133 Patients Taking Bisoprolol and 135 Patients Taking Nifedipine

	Baseline (mean ± SEM)	Low Dose (mean ± SEM)	Mean Change (mean [95% confidence limit])	Median Change	p Value (bisoprolol vs. nifedipine)
No. of episodes/48 h					
Bisoprolol	8.1 ± 0.56	3.2 ± 0.41	−4.9 (−5.8,−4.0)*	−4.0	0.0001
Nifedipine	8.3 ± 0.50	5.9 ± 0.43	−2.5 (−4.3,−1.5)*	−2.0	
Total duration of episodes (min/48 h)					
Bisoprolol	99.3 ± 10.13	31.9 ± 5.45	−67.4 (−84.0,−50.7)*	−39.0	0.0001
Nifedipine	101.0 ± 9.10	72.6 ± 8.05	−28.4 (−45.9,−10.9)*	−12.0	
Total ischemic burden (ST segment depression [mm] × episode duration [min])					
Bisoprolol	193.7 ± 27.14	58.9 ± 11.66	−134.8 (−178.7,−90.9)*	−46.0	0.0030
Nifedipine	194.7 ± 23.83	117.0 ± 16.72	−77.8 (−121.5,−34.0)*	−23.0	
Mean HR before ST segment depression (beats/min)					
Bisoprolol	99.5 ± 1.17	84.0 ± 1.54†	−13.7 (−16.5,−11.0)*†	−14.2	0.0001
Nifedipine	101.2 ± 1.03	102.7 ± 1.17†	+1.4 (−0.8, 3.5)†	+1.4	

*Significant reduction; confidence limits do not include zero. †79 patients in the bisoprolol group and 115 patients in the nifedipine group at the end of phase 1 (only patients with ischemic episodes). HR = heart rate.

Table 3. Additional Effects of Double Dose of Bisoprolol and Nifedipine

	No. of Pts	End Phase 1: Low Dose (mean ± SEM)	End Phase 2: High Dose (mean ± SEM)	Mean Change (mean [95% confidence limits])	Median Change	p Value (low dose vs. high dose)
No. of episodes/48 h						
Bisoprolol	111	3.3 ± 0.45	2.6 ± 0.42	−0.7 (−1.4, 0.0)	0.0	0.030
Nifedipine	112	6.1 ± 0.48	5.7 ± 0.56	−0.4 (−1.3, 0.4)	0.0	0.296
Total duration of episodes (min/48 h)						
Bisoprolol	111	32.3 ± 6.10	27.6 ± 6.21	−4.7 (−14.0, 4.7)	0.0	0.141
Nifedipine	112	75.5 ± 8.99	69.7 ± 9.42	−5.8 (−19.2, 7.6)	−5.0	0.140
Total ischemic burden (ST segment depression [mm] × episode duration [min])						
Bisoprolol	111	55.2 ± 12.34	51.5 ± 15.24	−3.6 (−23.5, 16.3)	0.0	0.284
Nifedipine	112	118.8 ± 17.51	104.9 ± 16.46	−13.9 (−39.2, 11.4)	−4.0	0.151
Mean HR before ST segment depression (beats/min)						
Bisoprolol		84.5 ± 1.68*	83.2 ± 1.73†	−3.0 (−6.0, −0.1)‡	−4.6	0.006
Nifedipine		102.0 ± 1.23*	102.5 ± 1.44†	+0.7 (−2.0, 3.5)‡	+0.3	0.460

Number of patients (Pts) differs because heart rate (HR) at onset of ischemic episode is only applicable in those patients with episodes. *Bisoprolol (n = 69); nifedipine (n = 98). †Bisoprolol (n = 53); nifedipine (n = 95). ‡Bisoprolol (n = 44); nifedipine (n = 85).

shown in Table 4. Patients were asked for their frequency of angina during the preceding week both at the start and end of the placebo phase and at the end of the low and high dose treatment phases. From 5.4 ± 0.56 and 5.7 ± 0.59 attacks/week, the number of anginal attacks was reduced to 2.8 ± 0.47 and 4.4 ± 0.61 in the bisoprolol and nifedipine groups, respectively. For patients receiving the high dose, the weekly attacks were reduced from a baseline value of 5.8 ± 0.71 to 2.3 ± 0.41 with bisoprolol and from 5.7 ± 0.65 to 3.2 ± 0.48 with nifedipine. Both drugs effectively reduced the frequency of angina pectoris. However, in individual patients the correlation of the number of anginal attacks per week and the number of ischemic episodes per 48 h was weak (for baseline and differences with treatments, r = 0.210 to 0.251).

The time course of the number of weekly anginal attacks recorded at each visit is shown in Figure 2 for those patients who were eligible for both treatment phases.

Effects on circadian variation of ischemia. Figure 3 shows the effects of bisoprolol and nifedipine on the circadian variation of transient ischemic episodes. During phase 1 of the study, the pronounced morning peak of episode frequency was markedly reduced with 10 mg of bisoprolol. With nifedipine slow release (2 × 20 mg), the circadian profile was unchanged but showed a clear overall reduction in the number of episodes. The second peak of transient ischemic episodes during the late afternoon hours was more reduced with nifedipine than the morning peak.

Responder rates. During both phases of the trial, the percent of patients who responded to treatment with a reduction in episodes of transient ischemia was evaluated. Table 5 shows the responder rates during phase 1 of the trial. For various definitions of response (between 25% and 100% reduction in the number of episodes), there was always a higher responder rate for bisoprolol than for nifedipine. The difference was significant with the Fisher exact test and was similar for duration of episodes and total ischemic burden in a similar manner. During phase 2 of the trial there was some further increase in responder rates. The differences between bisoprolol and nifedipine remained significant: 52.5% of patients achieved 100% reduction of transient ischemic episodes with bisoprolol versus only 15.6% of those with nifedipine.

Adverse drug effects. One patient had an acute myocardial infarction after randomization to nifedipine but before administration of the first medication. During the study, 27 patients taking bisoprolol and 29 taking nifedipine slow release had to be withdrawn from treatment: adverse events in 20 patients taking bisoprolol, 14 nifedipine; treatment failure in 6 patients taking bisoprolol, 10 nifedipine; other problems in 1 patient taking bisoprolol, 5 nifedipine. In most patients the adverse event recorded was of cardiovascular origin. Lack of effect on angina pectoris, occurrence of tachycardia and edema during nifedipine treatment and dyspnea and bradycardia with bisoprolol therapy were the main problems observed.

Discussion

Prevalence of transient ischemia. Of 627 study patients who had a positive result on the exercise ECG, 330 had two or more transient ischemic episodes on 48-h ambulatory monitoring, thus demonstrating the excellence of the exercise ECG in screening patients for studies of transient ischemia. However, in our study, the exercise ECG was obtained in different centers throughout Europe after either a treadmill or a bicycle exercise protocol. Thus, comparison of a large number of exercise ECG results would have methodologic differences, and, therefore, centralized blinded evaluation of ambulatory

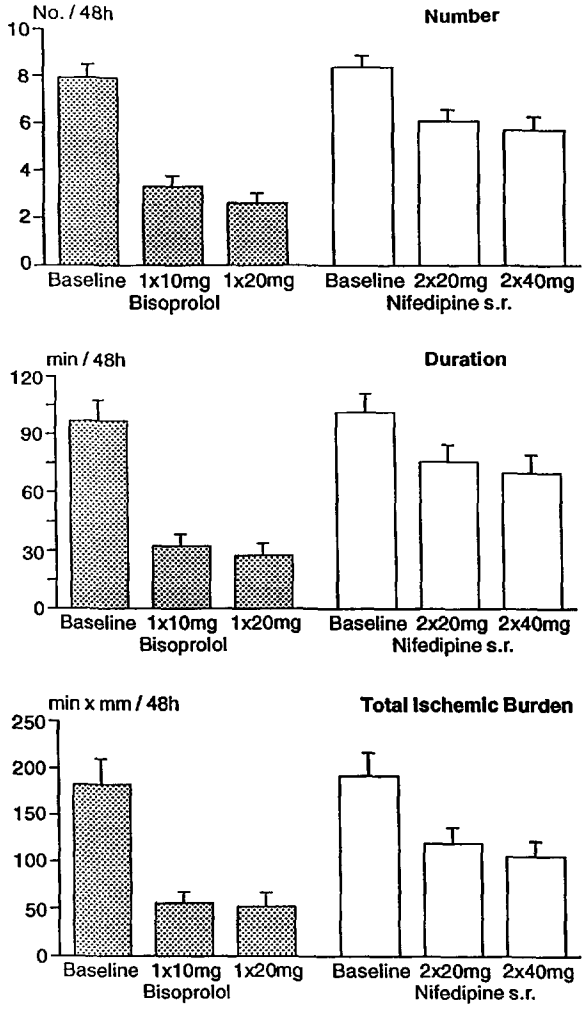

Figure 1. Effects of bisoprolol and nifedipine slow release (s.r.) on different measures of transient ischemic episodes (patients evaluable for phases 1 and 2: bisoprolol, n = 111; nifedipine, n = 112). Number, duration and total ischemic burden (mean ± SEM) are reduced significantly with both drugs. The difference in reduction between bisoprolol and nifedipine is also significant (at least p = 0.01) for all variables compared. The doubling of the dose in phase 2 of the trial showed only a small incremental effect.

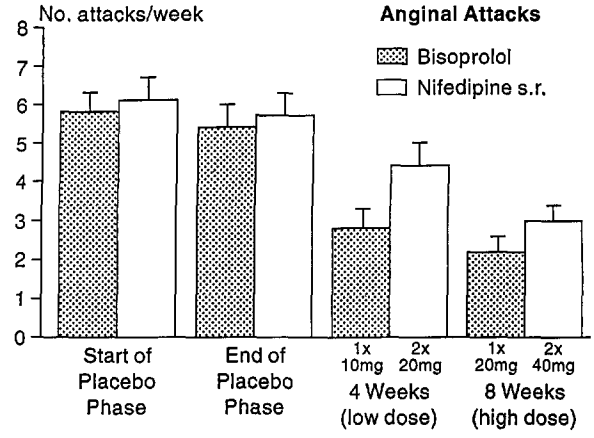

Figure 2. Number of anginal attacks per week (mean ± SEM) as recorded during the control visits of the patients (patients evaluable for phases 1 and 2). s.r. = slow release.

ECG tapes was performed for objective documentation and comparison of anti-ischemic effects. The multicenter design of our study also allowed the inclusion of a sufficient number of patients to overcome methodologic problems with the variability of myocardial ischemia (19–21). The inclusion in our study of >50% of screened patients is a remarkably higher rate than that for other published studies. Fox et al. (22) reported transient ischemia in 16% of 409 patients screened for inclusion in the Regionally Organized Cardiac Key European Trial (ROCKET) study, and Parmley et al. (23) included 207 of 1,174 patients screened by 48-h ambulatory ECG monitoring for inclusion in a study on the effects of nifedipine gastrointestinal therapeutic system (GITS). One reason may have been the higher prevalence of more severely diseased patients in the centers in Sweden, Poland and East Germany.

Beta-blockade versus calcium antagonism. In our study the effects of the beta-blocker bisoprolol were greatly superior to those of the calcium antagonist nifedipine. Although both drugs showed significant treatment effects on both angina pectoris and transient ischemic episodes, the effects of bisoprolol were more marked at the dose levels tested. There is

Table 4. Treatment Effect on Angina Pectoris

	Baseline		Treatment		After Treatment	
	No. of Anginal Attacks/Week	Mean ± SEM	No. of Anginal Attacks/Week	Mean ± SEM	(no. of anginal attacks/wk)	Mean Change (mean [95% confidence limits])
Start of placebo						
Bisoprolol	159	5.9 ± 0.52				
Nifedipine	163	6.0 ± 0.51				
Low dose						
Bisoprolol	143	5.4 ± 0.56	136	2.8 ± 0.47	136	−2.6 (−1.5, −3.7)*
Nifedipine	147	5.7 ± 0.59	140	4.4 ± 0.61	140	−1.2 (0.1, −2.5)
High dose						
Bisoprolol	125	5.8 ± 0.71	120	2.3 ± 0.41	120	−3.0 (−2.3, −3.8)*
Nifedipine	129	5.7 ± 0.65	125	3.2 ± 0.48	125	−2.3 (−1.1, −3.6)*

*Significant reduction; confidence limits do not include zero.

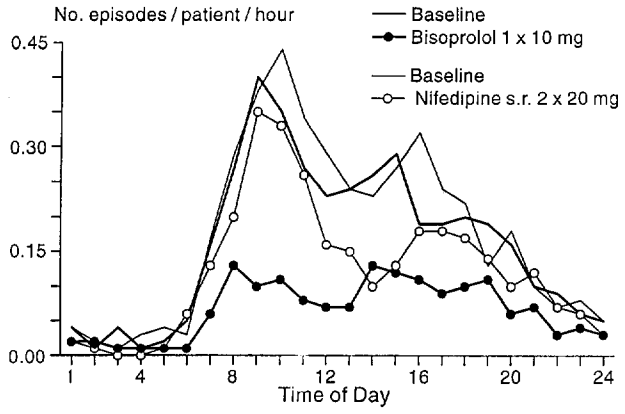

Figure 3. Effect of bisoprolol and nifedipine on the circadian distribution of transient ischemic episodes (sum of episodes/h on two consecutive days as mean value/patient; patients evaluable for phases 1 and 2: bisoprolol, n = 111, nifedipine, n = 112). From comparable baseline curves, bisoprolol effectively reduces the morning and afternoon peaks of transient ischemic episodes, whereas nifedipine reduces the overall number of episodes but leaves the circadian distribution unchanged. s.r. = slow release.

ongoing discussion about the importance of increased demand versus reduced supply in the pathophysiology of ambulatory myocardial ischemia (24). The results obtained in our large patient groups would certainly favor a primary role for increased demand as the trigger for ambulatory myocardial ischemia. Increases in heart rate have often been shown to be the main determinants of ambulatory silent ischemia (25–30), but there may be a subset of patients who respond differently (31), in particular to such triggers as mental stress (32–34).

Furthermore the threshold at which ischemia occurs may vary (21). In our study bisoprolol not only reduced markedly the number and duration of transient ischemic episodes, but also reduced the heart rate at which ischemic episodes occurred.

We compared the effects of bisoprolol with those of the widely used calcium antagonist nifedipine in the available formulation at the start of the study. It is conceivable that nifedipine in a newer formulation, the gastrointestinal therapeutic system (GITS) used in the study by Parmley et al. (23), might have produced more favorable results. A reduction in the episodes of transient ischemia has been shown for diltiazem (35), a calcium antagonist that reduces heart rate, and for amlodipine (36), a calcium antagonist with a long half-life. However, in both studies the reduction in episodes was ~50% of the baseline value, which is less than the 60%–70% achieved with bisoprolol in our study. A detrimental effect of nifedipine may be induced in some patients with collateral flow, as Egstrup and Andersen (37) have shown. In their patient group with good collateral flow, nifedipine administration was followed by an increase in total and silent ischemia. Smaller studies (38–40) have shown conflicting results with nifedipine and other calcium antagonists compared with, or in addition to, beta-blockers. In a recent study (41) comparing diltiazem and atenolol in patients with variable-threshold angina, there was a greater reduction of ischemic episodes with diltiazem than with atenolol.

Open question: prognosis. Because angina pectoris is not treated only for pain relief but also in the hope that effective treatment of angina will reduce dangerous sequelae, such as myocardial infarction and sudden death, transient, predominantly silent ischemia is also treated on the basis of prognosis. However, the medical treatment of silent ischemia is not uniformly accepted (42–46). The solution of this problem must await larger studies that show that treatment of silent ischemia can in fact improve the prognostic outcome of patients. Initial results point in that direction: Lim et al. (47) showed that in patients with painless ischemia that was abolished by medical treatment, the prognosis was significantly better than in those with painless ischemia, as detected with radionuclide ventriculography, that persisted despite treatment. Raby et al. (48) showed a higher event rate in patients with transient ST segment depression on ambulatory ECG monitoring that persisted during medical therapy. Suppression of silent ischemia by beta-blockade may not be all that is needed to improve prognosis because it has been shown (49) that the morning increase in platelet aggregability remains unchanged in patients with coronary artery disease in whom the morning peak of transient ischemic episodes was reduced.

Conclusions. This large multicenter study included selected patients with stable angina pectoris, a positive result on the exercise ECG and evidence of transient ischemia on ambulatory ECG monitoring. Bisoprolol in a single daily dose was an effective antianginal and anti-ischemic treatment. In the reduction of the number and duration of ischemic episodes

Table 5. Responder Rates

Reduction in No. of Episodes	Low Dose			High Dose		
	Bisoprolol (1 × 10 mg) (n = 133)	Nifedipine (2 × 20 mg s.r.) (n = 135)	p Value (bisoprolol vs. nifedipine)	Bisoprolol (1 × 20 mg) (n = 118)	Nifedipine (2 × 40 mg s.r.) (n = 122)	p Value (bisoprolol vs. nifedipine)
≥25%	114 (85.7%)	80 (59.3%)	>0.0001	105 (89.0%)	76 (62.3%)	<0.0001
≥50%	98 (73.7%)	57 (42.4%)	>0.0001	95 (80.5%)	60 (49.2%)	<0.0001
≥75%	75 (56.4%)	31 (23.0%)	<0.0001	80 (67.8%)	40 (32.8%)	<0.0001
100%	54 (40.6%)	20 (14.8%)	<0.0001	62 (52.5%)	19 (15.6%)	<0.0001

Data presented are number (%) of responders. s.r. = slow release.

and total ischemic burden, bisoprolol proved superior to nifedipine, which also showed significant treatment effects. Bisoprolol was also superior to nifedipine with regard to responder rates and effect on angina and on the circadian variation of ischemic episodes. Thus, in a large group of patients with stable coronary artery disease, the main determinant of transient myocardial ischemia seems to be increased oxygen demand, which can be reduced by reducing heart rate with a beta-blocker. The question of whether the observed marked treatment effects on transient myocardial ischemia translate into an improved prognosis for the patients must await the results of larger prospective studies.

Appendix

Participating Institutions and Personnel for the Total Ischemic Burden Bisoprolol Study

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