Combination Therapy With Metoprolol and Nifedipine Versus Monotherapy in Patients With Stable Angina Pectoris

Results of the International Multicenter Angina Exercise (IMAGE) Study

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Objectives. **This study was designed to investigate whether combination therapy with metoprolol and nifedipine provides a greater anti-ischemic effect than does monotherapy in individual patients with stable angina pectoris.**

Background. **Combination therapy with a beta-adrenergic blocking agent (which reduces myocardial oxygen consumption) and a dihydropyridine calcium antagonist (which increases coronary blood flow) is a logical approach to the treatment of stable angina pectoris. However, it is not clear whether, in individual patients, this combined therapy is more effective than monotherapy.**

Methods. **Two hundred eighty patients with stable angina pectoris were enrolled in a double-blind trial in 25 European centers. Patients were randomized (week 0) to metoprolol (controlled release, 200 mg once daily) or nifedipine (Retard, 20 mg twice daily) for 6 weeks; placebo or the alternative drug was then added for a further 4 weeks. Exercise tests were performed at weeks 0, 6 and 10.**

Results. **At week 6, both metoprolol and nifedipine increased the mean exercise time to 1-mm ST segment depression in comparison with week 0 (both $p < 0.01$); metoprolol was more effective than nifedipine ($p < 0.05$). At week 10, the groups randomized to combination therapy had a further increase in time to 1-mm ST segment depression ($p < 0.05$ vs. placebo). Analysis of the results in individual patients revealed that 7 (11%) of 63 patients adding nifedipine to metoprolol and 17 (29%) of 59 patients ($p < 0.0001$) adding metoprolol to nifedipine showed an increase in exercise tolerance that was greater than the 90th percentile of the distribution of the changes observed in the corresponding monotherapy + placebo groups. However, among these patients, an additive effect was observed only in 1 (14%) of the 7 patients treated with metoprolol + nifedipine and in 4 (24%) of the 17 treated with nifedipine + metoprolol.**

Conclusions. **The mean additive anti-ischemic effect shown by combination therapy with metoprolol and nifedipine in patients with stable angina pectoris is not the result of an additive effect in individual patients. Rather, it may be attributed to the recruitment by the second drug of patients not responding to monotherapy.**

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Stable angina pectoris is characterized by transient ischemic episodes due to a discrepancy between myocardial oxygen supply and demand. Beta-adrenergic blocking agents, which reduce oxygen consumption, and dihydropyridine calcium antagonists, which act mainly by increasing coronary blood flow, may be considered two opposing pharmacologic approaches to prevent transient myocardial ischemia in this setting, and their antianginal efficacy has been shown in several controlled clinical trials. Because of their complementary mode of action, beta-blockers and dihydropyridine calcium antagonists are often used in combination to reduce anginal symptoms and increase exercise tolerance. However, it is not clear whether this combination therapy has more anti-ischemic effect than that of monotherapy with either agent. Among the studies comparing the antianginal effects of combined versus monotherapy, only a few (1–4) have been adequate in design, and none had enough power to clarify this issue, which remains a matter of debate (5–8). In some studies (1,4), indeed, combined treatment with metoprolol or propranolol and nifedipine has led to a significant increase in mean exercise tolerance in comparison with monotherapy. However, no study has reported

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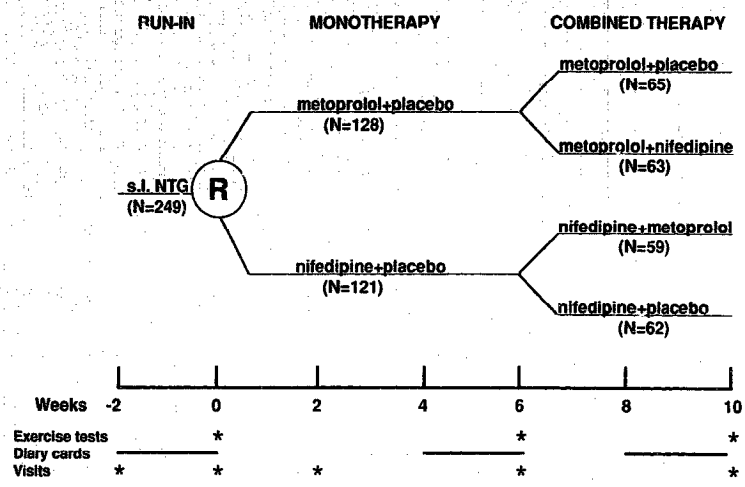

Figure 1. Study design. Numbers in parentheses indicate the number of patients included in the per-protocol analysis. s.l. NTG = sublingual nitroglycerin; R = randomization. *Time of exercise testing and hospital visits.

whether the additive effect observed in the combination group was due to a summation of the anti-ischemic effects of both drugs in individual patients or to an increase in exercise tolerance with the second drug in non-responders to monotherapy. The International Multicenter AnGina Exercise study (IMAGE) was designed to address this issue, which has clear clinical relevance because combined antianginal therapy is warranted only in those patients receiving a significant anti-ischemic effect from both drugs.

Methods

Patient selection. For this multicenter trial, 290 patients with chronic stable angina pectoris were enrolled in 25 European centers. To qualify for the study, the patients had to report typical anginal symptoms that had been stable for ≥6 months and show a positive response to exercise stress testing, with ≥3 min of exercise tolerance. The exclusion criteria included age >75 years, recent (<6 months) myocardial infarction, heart failure and angina of such severity that even temporary withdrawal of antianginal therapy was not feasible. Patients with serious concomitant diseases, including obstructive lung disease and insulin-dependent diabetes mellitus, or with hemoglobin levels <11 g/dl or systolic blood pressure <100 mm Hg, were also excluded. Only patients with sinus rhythm who had an analyzable ST segment on electrocardiography were included.

Study protocol (Fig. 1). After the patients gave informed consent, all previous cardiovascular medications were gradually discontinued over a 2-week placebo run-in period during which only sublingual nitroglycerin was allowed (for interruption of anginal attacks). At the end of this period (week 0), a baseline symptom-limited exercise test was performed and the patients were randomly allocated to double-blind treatment for 6 weeks with either metoprolol (controlled release, 200 mg once daily) or nifedipine (Retard, 20 mg tablets twice daily) according to a parallel group design. After this period, the metoprolol-treated patients were further randomized to the addition of placebo or nifedipine for a further 4 weeks, and the nifedipine-treated patients were assigned to the addition of placebo or metoprolol. Both randomizations were decided at week 0. The study was conducted in blinded fashion with use of the double-dummy technique (i.e., throughout the study, including the run-in period, patients took 3 tablets/day of either metoprolol at 8:00 A.M, nifedipine at 8:00 AM and at 8:00 PM or the corresponding placebos). At the end of both the monotherapy and combined therapy periods (week 6 and week 10), exercise tests were repeated according to the same protocol 1 to 4 h after morning drug intake. To standardize data collection and exercise testing, a member of the steering committee visited all participating centers during the planning phase of the study. The study was conducted in accordance with the Declarations of Helsinki and Tokyo, and the protocol was approved by the Ethics Committee of each participating center.

Diary cards. Throughout the study, the patients recorded the occurrence of anginal attacks on diary cards that were collected at the end of the run-in period and after 6 and 10 weeks of double-blind treatment. The mean weekly number of anginal attacks was calculated for each patient for the run-in period and the final 2 weeks of both the monotherapy and combined therapy periods. Compliance with the therapeutic regimen was evaluated at each visit by counting the number of returned tablets. Good compliance was defined as 80% to 120% of scheduled tablet consumption.

Exercise test. Bicycle exercise tests were performed at an initial work load of 30 W, which was subsequently increased by 10 W every minute. A standard 12-lead electrocardiogram (ECG) and blood pressure levels were recorded immediately before the start of the test, and at 1-min intervals during exercise and for at least the 1st 10 min of the recovery phase. The exercise test was stopped at the occurrence of moderate to

severe angina, dyspnea, exhaustion or ST segment depression >3 mm. Horizontal or downsloping ST segment depression >0.1 mV for 0.08 s after the J point, with or without chest pain, was considered to demonstrate a positive exercise test result. The time to 1-mm ST segment depression was used to define patients' ischemic threshold. For the subsequent exercise tests performed during treatment, total exercise time was used as an ersatz end-point in patients who did not show >1-mm ST segment depression (9).

Statistical analysis. Statistical analysis was performed on the data of the 249 patients completing the study (per protocol analysis). The absolute difference in time to 1-mm ST segment depression from week 6 to week 10 was the main efficacy variable. The group data are reported as mean values with 95% confidence intervals. To analyze the effect of combined therapy in individual patients, the 90th percentile of the distribution of the changes in time to 1-mm ST segment depression from week 6 to week 10 observed in the pooled placebo groups was arbitrarily considered the upper limit of spontaneous variability in our study patients. This limit was found to be 144 s and corresponded to a 33% increase in time to 1-mm ST segment depression over the mean values observed at week 6. Patients in the combination groups whose change in time to 1-mm ST segment depression from week 6 to week 10 was >144 s were considered to have had a true pharmacologic effect during the combination phase of the study. The proportions of such patients were compared between combination groups by using the chi-square test. In these patients, the presence of an additive anti-ischemic effect of combined therapy was investigated by analyzing the changes in time to 1-mm ST segment depression from week 0 to week 6 (monotherapy phase). An additive anti-ischemic effect was considered to have occurred in patients whose change in time to 1-mm ST segment depression during monotherapy exceeded the 50th percentile of the distribution of the changes observed in the respective monotherapy group.

Results

Patient characteristics and outcome. Of the 290 enrolled patients, 10 were not randomized (6 who were unwilling to participate because of increased angina during the run-in phase, 2 who did not satisfy inclusion criteria and 2 who were excluded for unknown reasons). Two hundred eighty patients entered the double-blind phase; 249 completed the study, whereas 31 dropped out. Compliance was considered good in 95% of the patients and did not differ among treatment groups. Table 1 shows the baseline characteristics of the patients completing the study, classified by randomization group. Thirty-five percent of the patients were in New York Heart Association functional class II, 58% in class III and 7% in class IV, with an equal distribution among the randomization groups.

Effect of treatment on angina frequency (Table 2). Complete diary card data were obtained from 240 of the 249 patients completing the study. In comparison with week 0, there was a similar significant reduction in angina frequency with both metoprolol and nifedipine at the end of the monotherapy period. During the combination part of the study, a further significant reduction ($p < 0.05$) in angina frequency was observed in the group adding metoprolol to nifedipine, whereas no significant changes were observed for the other groups. However, at week 10, angina frequency did not differ among groups.

Effect of treatment on exercise tolerance. At the end of the run-in period, the patients showed a wide range of exercise tolerance at 1-mm ST segment depression (Fig. 2). In comparison with baseline, both metoprolol and nifedipine increased the mean exercise time to 1-mm ST segment depression at week 6 (both $p < 0.01$); improvement was significantly greater in the patients receiving metoprolol ($p < 0.05$) (Table 3). At week 10, there was no further change in exercise tolerance in either group in which placebo was added to the original monotherapy, but the combination of the two active drugs led to a considerable increase in mean exercise tolerance ($p < 0.05$ vs. placebo). During combination therapy, the mean effects of metoprolol added to nifedipine (64 s, $p < 0.05$ vs. week 6) and of nifedipine added to metoprolol (35 s, $p = 0.07$ vs. week 6) were of approximately the same magnitude as those observed with the two drugs during monotherapy (73 and 43 s, respectively) (Table 3).

Seven patients (11%) in the metoprolol + nifedipine group and 17 (29%) in the nifedipine + metoprolol group ($p <$

Table 1. Demographic and Baseline Exercise Test Characteristics of All Patients Included in Per-Protocol Analysis

	Metoprolol + Placebo (n = 65)	Metoprolol + Nifedipine (n = 63)	Nifedipine + Placebo (n = 62)	Nifedipine + Metoprolol (n = 59)
Age (yr)	59 ± 8	59 ± 8	60 ± 8	59 ± 9
Gender (M/F)	56/9	53/10	51/11	45/14
Hypertension	12	7	8	6
Diabetes	3	2	3	4
Smokers	41	38	37	34
Previous myocardial infarction	4	4	8	7
Previous antianginal medications	38	39	38	34
Anginal episodes/wk (no. of episodes)	5.7 ± 7	5.2 ± 5	5.4 ± 6	7.1 ± 9
Time to 1-mm ST depression (s)	358 ± 168	386 ± 162	382 ± 148	371 ± 144
Total exercise time (s)	489 ± 175	520 ± 185	522 ± 155	496 ± 155

Unless otherwise indicated, values are expressed as mean value ± SD or number of patients. F = female; M = male.

Table 2. Effect of Treatment on Weekly Number of Anginal Attacks

	Metoprolol (n = 122)		Nifedipine (n = 118)	
Week 6				
Mean Δ	−1.95		−1.57	
95% CI	−1.25 to −2.64		−0.69 to −2.45	
	Metoprolol + Placebo (n = 61)	Metoprolol + Nifedipine (n = 61)	Nifedipine + Placebo (n = 61)	Nifedipine + Metoprolol (n = 57)
Week 6				
Mean Δ	−1.93	−1.97	−1.77	−1.36
95% CI	−0.78 to −3.07	−1.16 to −2.79	−0.57 to −2.96	−0.04 to −2.69
Week 10				
Mean Δ	−2.01	−2.06	−2.32	−2.71
95% CI	−0.82 to −3.19	−1.11 to −3.02	−0.70 to −3.93	−1.93 to −3.80

Data are expressed as mean change from number of attacks at baseline (Mean Δ) and 95% confidence interval (CI). Values at week 6 are reported according to monotherapy groups (above) and combination groups (below). Baseline values are reported in Table 1.

0.0001) showed an increase in time to 1-mm ST segment depression from week 6 to week 10 that was greater than the 90th percentile of the distribution of the changes observed in the corresponding monotherapy + placebo groups. The great majority of these patients had responded poorly to monotherapy. In fact, of the 24 patients showing a true pharmacologic effect during the combination phase of the study, only 1 (14%) of 7 in the group adding nifedipine to metoprolol and 4 (24%) of 17 in the group adding metoprolol to nifedipine, showed changes in time to 1-mm ST segment depression during monotherapy of above the 50th percentile of the distribution of the changes observed in the corresponding monotherapy group, thus demonstrating the additive antiischemic effect of metoprolol and nifedipine.

Safety. The safety data base of the IMAGE study refers to 2,692 patient-weeks—1,133 with metoprolol, 1,055 with nifedipine and 504 with combination treatment. Table 4 shows the reasons for patient dropout classified according to the categories of cardiovascular events, side effects and non–drug-related causes. There were 14 cardiovascular events including 1 sudden death, 3 acute myocardial infarctions, 8 cases of unstable angina, 1 of syncope and 1 of stroke. The incidence of these events did not differ among treatment groups. Ten patients (3.5% of the total study group) dropped out of the study because of drug-related side effects that were among those expected from metoprolol and nifedipine. No patient withdrew because of side effects during combination therapy.

Discussion

Rationale for and clinical efficacy of combination therapy with metoprolol and nifedipine in stable angina pectoris. Patients with stable angina pectoris experience episodes of myocardial ischemia due to a transient discrepancy between myocardial oxygen demand and supply. In the present study, we considered metoprolol and nifedipine to be the prototypes of two opposing, and possibly complementary, approaches aimed at preventing an imbalance between oxygen supply and demand. In fact, the main mechanism of action of metoprolol is to reduce myocardial oxygen consumption through its effect on heart rate and contractility, whereas nifedipine predominantly increases coronary blood flow by inhibiting vasomotor tone at the site of eccentric stenoses and at the level of the precapillary sphincters (10). Several placebo-controlled trials (11,12) have shown that both metoprolol and nifedipine are effective antianginal agents. The present study in a large group of patients with stable angina pectoris confirms that both drugs increase exercise tolerance and reduce angina frequency, metoprolol significantly more effectively than nifedipine.

Because the two agents act predominantly on different determinants of the supply/demand ratio, their combination has been considered a logical second step in patients who remain symptomatic or continue to show a positive exercise test response despite treatment with a single agent. This approach has been favored by the results of clinical trials (1,4,6) showing that the combination of a beta-blocker and nifedipine increases exercise tolerance over that achieved with monotherapy. Similarly, the present study shows that, on average, when the two drugs are used in combination, the

Figure 2. Patient distribution according to the time to 1-mm ST segment depression during the exercise test performed at the end of the run-in period.

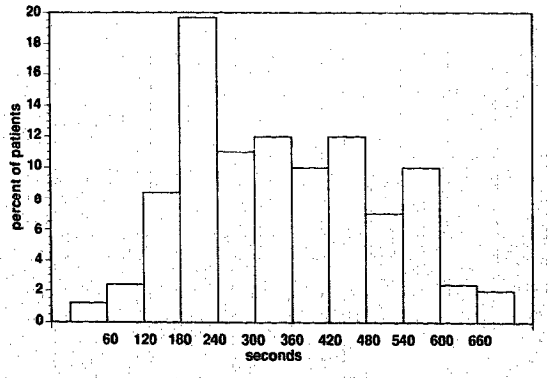

Table 3. Effect of Treatment on Time to 1-mm ST Segment Depression

	Metoprolol (n = 128)		Nifedipine (n = 121)	
Week 6				
Mean increase	70		43	
95% CI	47–92		16–69	
	Metoprolol + Placebo (n = 65)	Metoprolol + Nifedipine (n = 63)	Nifedipine + Placebo (n = 62)	Nifedipine + Metoprolol (n = 59)
Week 6				
Mean increase	66	73	43	43
95% CI	34–98	40–107	6–79	5–80
Week 10				
Mean increase	49	108	37	107
95% CI	17–80	71–145	1–72	64–151

Data are expressed as mean increase (in seconds) from baseline time to 1-mm ST segment depression. Values at week 6 are reported according to monotherapy (above) and combination groups (below). Baseline values are reported in Table 1.

prolongation of mean exercise tolerance is the sum of that obtained with metoprolol and nifedipine during monotherapy.

The large sample size of the IMAGE study also allowed us to investigate whether this additive effect could be demonstrated at an individual level. Surprisingly, the proportion of patients with increased exercise tolerance after both monotherapy and combination therapy was small. Most of the additional effect observed in the groups receiving combination therapy was the result of an increase in exercise tolerance in patients who had not had such an increase during monotherapy; this recruitment effect was particularly evident in patients adding metoprolol to nifedipine. A partial explanation for the lack of additive effect in individual patients may be that both metoprolol and nifedipine have, in addition to their main antianginal mechanisms, other effects that may favorably affect the oxygen supply/demand ratio (8). A beta$_1$-selective blocker such as metoprolol may also improve coronary blood flow by prolonging coronary diastolic filling time and by redistributing flow to the ischemic subendocardial regions; nifedipine may also reduce left ventricular afterload, thus decreasing oxygen consumption. Finally, both agents can improve ventricular relaxation, which may further enhance subendocardial blood flow. Hence, metoprolol and nifedipine appear to reduce myocardial ischemia by a variety of similar mechanisms that may not be additive in individual patients.

In the present study, we considered the effect of metoprolol and nifedipine on exercise tolerance to be the most reliable measure of drug efficacy; we did not investigate the effect of combination therapy on anginal symptoms in individual patients. In some way, the mean effect on anginal symptoms mimicked the mean effect on exercise tolerance, because only the group adding metoprolol to nifedipine had a significant reduction in angina frequency. However, in contrast to the exercise test data, no differences in angina frequency between combination and monotherapy were observed at the end of the study. This discrepancy between the effects of drugs on ECG ischemia and on symptoms has been shown in other studies (13,14) and in the IMAGE study (15). In addition, the standardized therapy with metoprolol and nifedipine used in the IMAGE study reduced angina frequency from a mean of 5 to 7 attacks/week at the end of the run-in period to an average of 3 to 4 attacks/week at the end of the study; thus, most patients continued to have a disturbing frequency of anginal attacks after therapy.

Table 4. Reasons for Withdrawal From Study

	Cardiovascular Events	Side Effects	Non-Drug Related
Metoprolol	Sudden death (1) Myocardial infarction (1) Unstable angina (3) Stroke (1) Syncope (1)	Itching (1) Depression (1) Dizziness (1)	Pharyngitis (1) Poor compliance (1)
Nifedipine	Myocardial infarction (1) Unstable angina (2)	Palpitation (3) Gastric pain (1) Headache (1) Dizziness (1) Ankle edema (1)	Elective coronary surgery (1) Leg pain (1)
Combined therapy	Myocardial infarction (1) Unstable angina (3)		Noncardiac surgery (2) Poor compliance (1)

Numbers in parentheses indicate the number of patients with the condition. For each patient, only the main reason for withdrawal is listed.

A logical alternative to combined therapy would be to select the most effective drug for each individual patient and to titrate the dosage until exercise-induced ischemia disappears, the patient becomes asymptomatic during daily life or the maximal tolerated dosage is reached. Unfortunately, it is not easy to predict the best pharmacologic approach for an individual patient as a previous report of the IMAGE study (16) showed that the characteristics of anginal symptoms and the results of exercise testing do not predict a preferential effect of metoprolol or nifedipine (except in patients with very low exercise tolerance, who seem to benefit more from the beta-blocker).

Safety of nifedipine, metoprolol and their combination in stable angina pectoris. The safety data base of the IMAGE study is reassuring in view of the recent reports of the possible proischemic effect of dihydropyridine calcium antagonists (17–19). In fact, during a period of more than 1,000 patient-weeks of treatment with 20 mg twice daily of monotherapy with nifedipine in the classical Retard formulation, no excess of proischemic complications was observed in comparison with those reported with metoprolol. This positive result may be attributed to the relatively low dosage of nifedipine and to the fact that the Retard formulation seems to elicit little, if any, reflex tachycardia. The combination of metoprolol and nifedipine was also well tolerated. Because the IMAGE study encompassed a broad spectrum of patients with stable angina pectoris ranging from functional class II to IV and from a very low to good exercise tolerance, our tolerability data may represent a good example of what is likely to happen in the general population of patients with stable angina.

Clinical implications. The results of the present study show that group data may be misleading when considering the possible additive effect of two drugs used in combination in patients with angina pectoris. The effect of monotherapy should be carefully and objectively evaluated in individual patients before stepping up to a second drug and, in the case of ineffectiveness of the first agent, clinicians should first consider the choice of an alternative drug instead of combined therapy.

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