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Effect of Mivazerol on Perioperative Cardiac Complications during Non-cardiac Surgery in Patients with Coronary Heart Disease

The European Mivazerol Trial (EMIT)

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Background: **Mivazerol[1] is a drug with α_2-agonist properties that reduces post-ganglionic noradrenaline availability and spinal efferent sympathetic output.**

Methods: **A double-blind randomized placebo-controlled trial was conducted in 61 European centers during a 2.5-yr period on 2,854 patients: 1,897 with coronary heart disease and 957 patients without overt coronary heart disease but classified as at high risk for it. The present analysis was restricted to those patients with previous known coronary heart disease of whom 48% had vascular surgery, 32% non-vascular thoracic or abdominal surgery, and 20% orthopedic surgery. Mivazerol or placebo were given intravenously from the induction of anesthesia for up to 72 h.**

Results: **In the 1,897 patients with established coronary heart disease, mivazerol did not reduce the primary endpoint—the combination of myocardial infarction or death—or all-cause deaths significantly. A preplanned subgroup analysis of 904 patients with known coronary heart disease undergoing vascular surgery showed that there were fewer primary endpoints in those receiving mivazerol (risk ratio [RR], 0.67; 95% CL, 0.45–0.98; $P = 0.037$) and fewer cardiac deaths (6 of 454 *vs.* 18 of 450: RR, 0.33; 95% confidence limits, 0.13–0.82; $P = 0.017$). The all-cause death rate was also decreased (RR, 0.41; 95% CL, 0.18–0.91; $P = 0.024$), although there was no significant reduction in myocardial infarction.**

Conclusion: **The α_2-adrenergic agonist, mivazerol, did not alter the rates of myocardial infarction or cardiac death in patients with known coronary heart disease undergoing non-cardiac surgery. However, it may have protected patients undergoing vascular surgery from further coronary events, and a specific study of such patients is now indicated (Key words: α_2-Adrenergic agonist; cardiac death; general and vascular surgery; myocardial infarction.)**

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THE sympathoadrenal system is activated during and after many anesthetic and surgical procedures.[1] There is myocardial, hemodynamic, and metabolic instability at this time. In patients with clinically manifested coronary heart disease (CHD) and in those classified as at risk for CHD, the incidence of myocardial ischemia or infarction, and of serious arrhythmias, heart failure, and cardiac death, is substantial. There is a range (8–19%) of risk of myocardial infarction (MI) or cardiac death depending on the severity of the preexisting CHD.[2] Patients undergoing vascular surgery have the highest risk.[3]

The hypothesis proposed is that interventions designed to moderate the catecholamine response to surgery and anesthesia might be expected to reduce the risk of myocardial complications in coronary patients. The use of a drug with α_2-agonist properties, which reduces

post–ganglionic noradrenaline output, might have such benefit.[4,5] Mivazerol hydrochloride is an α_2-receptor agonist[6] and also modulates sympathetic efferent stimuli from the spinal cord.[7,8] It reduces basal plasma noradrenaline concentrations in unstressed rats, dogs, and humans. It has antiischemic effects in rats and dogs;[9] in dogs with experimental coronary occlusion, ST-segment elevation and myocardial lactate production were reduced. In a small blinded controlled trial of mivazerol in patients undergoing treadmill exercise, dose-related antiischemic effects have been recorded.[10]

A previous clinical trial[11] in 300 patients with CHD or at risk for CHD showed that the use of mivazerol decreased tachycardia, hypertension, and myocardial ischemia after surgery. This trial also established the safety of mivazerol given intravenously as a bolus of 4 μg/kg and then at 1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$. These findings indicated the need for a larger trial.

The European Mivazerol Trial (EMIT) was designed to determine the efficacy and safety of intravenous mivazerol in patients with CHD and in patients assessed as at risk for CHD undergoing non-cardiac surgery.

Methods

Design of the Trial

Patients with known CHD and those at high risk for CHD were eligible for the trial. All were scheduled to have non-cardiac surgery estimated to last for at least 1 h and to have post-surgical hospitalization of at least 4 days.

Patients with CHD were defined by at least one of the following.

- The presence of typical angina pectoris (Canadian Heart Classification)
- History of MI or Q-wave electrocardiographic (ECG) evidence of MI older than 14 days
- Angiographically proven coronary artery stenosis > 70% in at least one major vessel or > 50% stenosis of the left main coronary artery
- Positive exercise ECG or silent ischemia diagnosed by Holter ambulatory recording
- Positive stress echocardiography
- Thallium or technetium defects
- Dipyrimadole thallium defect
- Patients with previous coronary artery bypass surgery (CABG) or percutaneous coronary angioplasty (PTCA), provided they fulfilled one of the above criteria

Patients at risk for CHD were defined by the presence of three or more of the following.

- Age > 65 yr
- Hypertension treated with any drug
- Cigarette smokers (1 or more packs per day for 2 of the past 3 yr)
- Hypercholesterolemia > 6 mM or managed with drugs
- Diabetes mellitus managed with drugs
- History of peripheral atherosclerotic vascular disease

Criteria for exclusion from randomization included the following.

- Unstable angina
- MI in the past 14 days
- Uninterpretable ECG Q-waves
- Cardiogenic shock
- Prescribed alpha-methyl dopa, clonidine, or any α_2 agonist
- Severe hepatic disorders (*e.g.*, elevation of hepatic enzymes more than twice the normal upper value or prolongation of prothrombin time in the absence of anticoagulants or hypoalbuminemia 10% or more below the normal range for age and sex)
- Renal insufficiency (*e.g.*, serum creatinine 10% above the upper limit of normal for age and sex)
- Emergency surgery
- Pregnant or nursing women or women aged less than 45 yr without adequate contraception

Patients undergoing any of three groups of surgery—vascular reconstructive surgery, major thoracic or abdominal surgery, and orthopedic surgery—were included. A preliminary survey in the participating European hospitals indicated that approximately 50% of patients admitted for major surgery needed vascular surgery, whereas thoracoabdominal surgery and orthopedic surgery represented 25–35% and 15–30%, respectively. The proportions of patients in each surgery group enrolled into the trial accorded with usual hospital practice. After the approval of ethics committees, the aim of the trial was to recruit patients, who signed an informed consent form, from 61 major hospitals in Europe (see appendix 2). Patient enrollment began in June 1994 and ended in February 1997.

Randomization was generated by a computerized algorithm and stratified by institution but not by surgical group. Within each surgical group, randomization was homogenous between placebo and mivazerol. Patients were randomized immediately before the drug or pla-

cebo infusion, and the results were analyzed on an intention-to-treat basis, *i.e.*, all randomized patients were counted with respect to any event up to discharge (mean 14 days) or 30 days if still in hospital. Treatments were assigned in sealed envelopes. There was less than 5% of cross-over in treatments, which could only occur when the investigator mixed up the treatment vials. In all centers, the principal investigator did not change during the trial.

Procedures

An intravenous infusion was started 20 min before the induction of anesthesia and continued for 72 h postoperatively. The placebo was 0.9% saline solution, and the active drug was mivazerol hydrochloride {3-[(1H-imidazol-4-yl) methyl]-2-hydroxybenzamide hydrochloride}, made and supplied by UCB Pharma Sector. Mivazerol, 4.0 μg/kg, was given during the first 10 min followed by a constant rate infusion of 1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$. The aim was to reach a target plasma concentration of 2.0 ng/ml. The use of nitrates was permitted only for management of ischemia. The use of any α_2 agonist was not allowed.

Blood for troponin-T, measured by an enzyme-linked immunosorbent assay (ELISA) method (Boehringer Mannheim, Germany), was taken at the same time each morning on postoperative days 1, 3, 5, 7, 12, 17, 22, 27 and at discharge. Blood mivazerol levels were measured by high-pressure liquid chromatography (HPLC) on postoperative days 1, 2, and 3. These were assessed centrally (Central Laboratory "Clide," Namur, Belgium) as were hematologic assessments (erythrocyte count, hemoglobin, hematocrit, leukocyte count and differential, and platelet counts) and other biochemical measurements (albumin, total protein, prothrombin time, serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], γGT, alkaline phosphatase, creatinine, potassium, sodium, and glucose).

The preoperative screening ECG was reviewed by a cardiologist from each hospital. ECGs were recorded, according to American Heart Association guidelines, daily on postoperative days 1–7 and 12, 17, 22, 27 and at discharge and whenever signs or symptoms indicated the need. They were analyzed centrally by a laboratory for ECG analysis (Premier Research Worldwide, Peterborough, England), and the results were only available at the end of the trial. Chest radiographs, cardiac enzymes, and other procedures were done when deemed necessary.

Endpoints

Endpoints were assessed independently by each of the five members of the Cardiac Endpoint Review Committee. They were blind to the treatment code. Decisions were reached by a majority (three of five). The Clinical Safety Monitoring Committee and the Statistical Monitoring Committee reported to a Steering Committee, which met on three occasions during the 2.5 yr of the trial. (For membership of the committees, see appendix 1).

The primary endpoint was the incidence of acute MI or death during the intra- and postoperative hospitalization period (up to 30 days after surgery). The definition of MI was a new Q-wave infarct (Minnesota Code 1.1–1.3) accompanied by either elevation of troponin-T $\geq$ 1 μg/l (or creatine kinase or creatine kinase MB in the case of unavailability—fewer than 1% of cases— of troponin-T) or a clinical syndrome consistent with MI. A new non-Q wave MI was diagnosed only if there was elevation of Troponin-T $\geq$ 1 μg/l and new ST-T wave changes consistent with non-Q wave infarction or a clinical syndrome consistent with MI. Troponin-T was measured at predefined times, according to the protocol, but when there was some clinical problem the investigators were free to choose whatever enzyme was most readily available to make an immediate diagnosis.

The cause of death was ascertained in all cases and classified as cardiac or non-cardiac by the Endpoint Review Committee. Cardiac deaths were defined as resulting from a primary identifiable cardiac cause or as sudden death (unknown cause). All other deaths were considered to be non-cardiac, even if cardiac causes were suspected but not sufficiently documented.

Secondary endpoints relate to the period of 30 days (follow-up visit). These included heart failure, life-threatening arrhythmias, and unstable angina: the criteria were precisely defined in the initial protocol.

Bradycardia was defined as a heart rate $<$ 40 beats/min. Tachycardia was defined as an increase of 20% or more above the baseline rate or $>$ 100 beats/min. Hypotension was defined as a decrease in systolic blood pressure of 20% or more below the baseline figure. Hypertension was defined as an increase in systolic blood pressure of 20% or more above the baseline figure. These guidelines were given to each investigator, and it was left to the caring physician to judge whether an adverse event occurred.

Statistical Analysis

Sample Size. The power calculations were based on an expected average incidence rate of myocardial infarc-

tion or death of 12%. On the basis of three interim analyses, a sample size of 2,700 was chosen to give an α value of 0.04 and a β value of 0.25, or 75% power with the aim to reduce the incidence of the primary endpoint (MI or death) by 33%. The final observed rate in the placebo group was 10.6%.

There were 2,854 patients enrolled: 1,897 (66.5%) had previous CHD and 957 (33.5%) were classified as at risk for CHD. After monitoring blinded data from 1,304 patients, it became apparent that the event rates in those classified as at risk for CHD were lower than expected and much lower ($\cong$4%) than those with manifested CHD. The protocol was amended in February 1996, and the decision was taken to restrict the assessment of the primary endpoint, and directly related events, to the patients with previous known CHD. To achieve the same power within the CHD patients, an increase in the sample size to 2,700 was necessary. Enrollment continued unmodified. Patients (957) initially classified as at risk for CHD were included only in assessment of secondary endpoints, the results of which are not presented here.

Analysis of the results of the primary endpoint, and related endpoints, was preplanned for each surgical group. Of the 1,897 patients with known previous CHD, 904 (48%) had vascular surgery, 607 (32%) had thoracoabdominal surgery, and 386 (20%) had orthopedic surgery.

Continuous monitoring of blinded data demonstrated that the incidence rate of the primary endpoint was substantially lower in patients with CHD undergoing thoracoabdominal or orthopedic surgery than the rate among vascular surgery patients.

All withdrawals and protocol violators were fully documented.

Statistical Methods. Differences in rates of outcome between treatment groups were tested by the log rank statistic, stratified by grouped centers according to country (Belgium, France, Germany, other) and the three types of surgery, whichever was appropriate. Tests of heterogeneity in the primary outcome between different strata were tested by the Cox proportional hazards model likelihood ratio test, where interaction terms were defined by treatment group $\times$ strata indicators.

Kaplan-Meier life-tables were used to compare time until the primary endpoint (MI or death), cardiac deaths, and MI by treatment group and for different types of surgery.

Differences between proportions were tested by chi-square tests with Yates correction or Fisher exact test in the case of small numbers.

Three formal interim looks at the data were planned according to the O'Brien and Fleming method.[12] It was agreed that, when the trial was completed and if not stopped prematurely, it would be declared positive when the adjusted final P value was 0.041 for the primary hypothesis. All patients included in the study were considered for intention-to-treat analysis.

Results

The results presented relate to the 1,897 patients with known previous CHD. The low incidence of events in the additional 957 patients classified at risk for CHD meant that the overall design of the trial lacked statistical power to demonstrate any differences between the total trial population of 2,854 mivazerol and placebo-treated patients (See Statistical Analysis—Sample Size section).

Center variability was assessed by 12 predefined strata (the combination of four countries—Belgium, France, Germany, and Other—and three surgical groups). Although there was a non-significant degree of heterogeneity between countries, adjustment for these 12 strata by statistical modeling did not change any of the trial endpoint findings.

For all randomized patients, there were no missing data for the primary endpoint. For the secondary endpoints, 7% of the intention-to-treat patients had missing data: this occurred when the patient was not monitored after 30 days (the follow-up visit). Protocol deviations occurred in both treatment groups mostly as a result of early discharge from hospital. These were mostly missing ECGs (mivazerol group, 42%; placebo group, 38%), missing troponin measurements (mivazerol group, 21%; placebo group, 19.5%), and incomplete infusion periods (See below).

Preoperative

The baseline characteristics of the 1,897 CHD patients are shown in table 1 according to the surgery undertaken. In both the mivazerol- and placebo-treated groups, 27% of those with MI had Q-wave infarcts. Compared with those operated on for thoracoabdominal or orthopedic conditions, patients undergoing vascular surgery were younger ($P < 0.0001$), more likely to be smokers, less likely to have angina pectoris or heart failure, less likely to be taking nitrates or β-blocking drugs and more likely to be taking Ca^{2+}-antagonists or aspirin. There were no other differences in baseline drug-taking between the surgery groups. There were more women in the orthopedic surgery group.

Table 1. Baseline Characteristics of CHD Patients

	Type of surgery							
	Vascular (%)		Thoracic/Abdominal (%)		Orthopedic (%)		ALL (%)	
	Placebo	Mivazerol	Placebo	Mivazerol	Placebo	Mivazerol	Placebo	Mivazerol
Males	86.4	81.7	76.9	76	46.9	46.6	75.2	72.8
Age (yr)								
<65	32.7	38.3	31.2	28.2	17.9	20.5	29.1	31.5
65–75	50.4	44.9	44.1	51.6	47.4	47.9	47.8	47.7
>75	16.9	16.7	24.7	20.2	34.7	31.6	23.1	20.8
Cigarette smoking	42.2	46.3	23.7	23.4	12.2	14.2	30.2	32.8
Angina pectoris	35.1	33.9	48.5	43.3	50.5	54.7	42.5	41.1
Diabetes mellitus	21.8	22.5	21	22.8	25	25.9	22.2	23.4
Hypertension	63.3	63.2	59	59.6	68.4	65.5	63	61.9
Hypercholesterolemia	49.6	47.8	41	36.2	41.8	37.9	45.3	41.2
Heart failure	16.9	14.3	22	22.8	24	27.9	20	19.8
Nitrates	39.6	36.1	50.5	49.7	49	54.7	45	44.2
β-blockers	26.9	32.6	32.2	38.1	31.1	35.8	29.4	35
Ca^{2+} blockers	53.1	49.1	42.4	39.7	44.9	43.7	48	45
ACE inhibitors	26.9	27.5	27.8	26.3	22.4	25.8	26.2	26.8
Aspirin	42.7	45.6	39.3	36.9	36.7	32.1	40.4	40.1

CHD = coronary heart disease; ALL = all types of surgery; ACE = angiotensin-converting enzyme.

The principal surgical procedures in the vascular group were aortic anastomoses (57%) and femoral–popliteal anastomoses (37%). The operations in the thoracoabdominal group were colon, 19%; prostate, 12%; lung, 9%; stomach, 8%; rectum, 8%; and kidney, 7%. Many procedures were for cancer treatment. Hip and knee prostheses represented 79% of the orthopedic surgical procedures.

Intraoperative

General anesthesia was used in 76% of mivazerol-treated patients and in 77% of those given the placebo infusion; in the remainder, anesthesia was administered *via* either epidural or spinal. There was no statistically detectable interaction between treatments and the type of anesthesia.

The average durations of the anesthesia and operation were longer in those undergoing vascular surgery (5 h) compared with thoracoabdominal (4 h) and orthopedic surgery (3 h; $P < 0.001$). There was no difference in the usage of drugs during the infusion periods (table 2), except for atropine (table 3).

The infusion was started 20 min before the induction of anesthesia and continued into the postoperative recovery phase. The aim was to maintain the infusion throughout the operation and for 72 h after leaving the operating room. The mean duration of the infusion was 68.45 h for the mivazerol group and 69.10 h for the placebo group. The half-life of mivazerol is 3–4 h, and so it can be presumed that some effect continued for the full 72 h. In 10.5% (150) of mivazerol group patients and 9.4% (134) of placebo group patients, the infusion had to

Table 2. Drugs Used Postoperatively during Infusion

	Type of Surgery					
	Vascular		Thoracic/Abdominal		Orthopedic	
	Placebo n = 450 (%)	Mivazerol n = 454 (%)	Placebo n = 295 (%)	Mivazerol n = 312 (%)	Placebo n = 196 (%)	Mivazerol n = 190 (%)
Nitrates	25	22	24	27	33	33
β-blockers	40	32	41	38	54	56
Ca^{2+} blockers	57	48	46	31	41	42
ACE inhibitors	18	14	14	12	19	20
Administered catecholamines	26	26	23	24	8	12

Table 3. Use of Atropine in CHD Patients

Type of Surgery	During Infusion [No. (%)] Placebo	Mivazerol	*P*	After Infusion [No. (%)] Placebo	Mivazerol	*P*
Vascular	16 (3.6)	45 (9.9)	< 0.001	11 (2.4)	15 (3.3)	NS
Thoracic-abdominal (607)	13 (4.4)	17 (5.4)	NS	9 (3.1)	11 (3.5)	NS
Orthopedic (386)	7 (3.6)	19 (10.0)	0.02	4 (2.0)	4 (2.1)	NS
Total (1,897)	36 (3.8)	81 (8.5)	< 0.001	24 (2.6)	30 (3.1)	NS

CHD = coronary heart disease; NS = not significant.

Number of patients on placebo: 941; number of patients on mivazerol: 946.

be stopped prematurely: of these, 62% were because of adverse events, such as hypotension, brady- or tachycardia, cardiac arrest, or organ failure; and 19% (of the 62%) had to be withdrawn from the trial. Interruption of the infusion because of such an event was equally distributed between the two treatment groups.

Postoperative

1,897 Patients with Coronary Heart Disease. Overall, there was a 10.4% decrease in the primary endpoint (MI or death) and a 37% reduction in all-cause deaths in the mivazerol group compared with placebo group, but neither decrease was statistically significant. However, there were fewer cardiac deaths (25 of 941, placebo group; 13 of 956, mivazerol group; $P = 0.037$).

During the infusion period, there were 11 cases of cardiac arrest–asystole (one fatal) in the mivazerol group and 10 (six fatal) in the placebo group: only 2 of these occurred during surgery (one in each treatment group). After the infusion period, an additional 13 patients had cardiac arrest–asystole: 7 on mivazerol (four deaths) and 6 on placebo (four deaths).

Table 4. Outcome during Hospitalization

	Placebo [No. (%)]	Mivazerol [No. (%)]	Risk Ratios	95% CL	*P*
Primary endpoint of myocardial infarction and/or death					
All surgeries (941/946)	100 (10.6)	91 (9.5)	0.89	0.67–1.18	NS
Vascular (450/454)	64 (14.2)	44 (9.7)	0.67	0.45–0.98	0.039
Thoracic-abdominal (295/312)	26 (8.8)	31 (9.9)	1.15	0.68–1.93	NS
Orthopedic (196/190)	10 (5.1)	16 (8.4)	1.64	0.75–3.62	NS
All cause deaths					
All surgeries (941/946)	34 (3.6)	22 (2.3)	0.61	0.35–1.03	NS
Vascular (450/454)	20 (4.4)	8 (1.8)	0.37	0.16–0.82	0.014
Thoracic-abdominal (295/312)	13 (4.4)	11 (3.5)	0.79	0.35–1.76	NS
Orthopedic (196/190)	1 (0.5)	3 (1.6)	Small no. of events		NS
Cardiac deaths					
All surgeries (941/946)	25 (2.7)	13 (1.4)	0.50	0.25–0.96	0.037
Vascular (450/454)	18 (4.0)	6 (1.3)	0.32	0.12–0.76	0.009
Thoracic-abdominal (295/312)	6 (2.0)	5 (1.6)	0.81	0.23–2.68	NS*
Orthopedic (196/190)	1 (0.5)	2 (1.1)	Small no. of events		NS
Myocardial infarction					
All surgeries (941/946)	79 (8.4)	78 (8.2)	0.94	0.69–1.28	NS
Vascular (450/454)	53 (11.8)	42 (9.3)	0.73	0.48–1.10	NS
Thoracic-abdominal (295/312)	17 (5.8)	23 (7.4)	1.46	0.69–2.34	NS
Orthopedic (196/190)	9 (4.6)	13 (6.8)	Small no. of events		NS
Myocardial infarction and/or cardiac death					
All surgeries (941/946)	94 (10.0)	83 (8.8)	0.84	0.63–1.13	NS
Vascular (450/454)	63 (14.0)	43 (9.5)	0.63	0.43–0.93	0.02
Thoracic-abdominal (295/312)	27 (9.2)	25 (8.0)	1.13	0.63–2.04	NS
Orthopedic (196/190)	10 (5.1)	15 (7.9)	1.52	0.69–3.50	NS

CL = confidence limits; NS = not significant.

* Unstable estimates.

Table 5. Adverse Events for All Randomized Patients (CHD and "At-risk" Patients)

	Placebo, n = 1,423 (%)	Mivazerol, n = 1,431 (%)	*P*
Hypertension	39	33	NS
Hypotension	32	41	NS
Tachycardia	32	28	NS
Bradycardia	5	14	0.039
Fever	22	23	NS
Nausea	13	13	NS
Vomiting	11	12	NS
Anemia	10	11	NS
Serious adverse effects during infusion period and for next 20 h (no. of cases)			
Bradycardia	7	17	0.039
Fatal (cardiac death)	3	1	NS
Asystole	10	11	NS
Fatal (cardiac death)	6	1	NS
			NS
Hypotension	21	24	

NS = not significant.

There were no significant differences in the incidence of MI and cardiac death, or cardiac death or MI alone, in the thoracoabdominal or orthopedic groups either alone or combined (table 4).

Mivazerol did not reduce the incidence of MI among patients with CHD undergoing all types of surgery, but there was reduction in the median area under the Troponin-T curve (10.6 μg/l) compared with the placebo group (18.4 μg/l).

Although bradycardia was recorded more in the mivazerol-treated patients, there was no difference according to the type of surgery. Atropine, or related compounds, were used significantly more often during the infusion periods of mivazerol (table 3). There was no significant difference during the infusion periods in the use of adrenergic or dopaminergic agents between the mivazerol-treated (22.5%) and placebo groups (21.4%).

There was no protocolized postoperative regimen because there were 61 centers involved, and part of the purpose of EMIT was to measure the effect of mivazerol within the standard practice of the participating institutions. Data concerning safety of mivazerol were collected for both populations, those "at risk" and the CHD group, which form the basis of this report (table 5). These give a more global picture than either alone. There were no significant differences in the incidence of adverse reactions, such as hyper- or hypotension, tachycardia, fever, nausea and vomiting, and anemia. There were no significant differences between the placebo- and mivazerol-treated groups of patients undergoing vascular surgery regarding SGOT, SGPT, γ-GT, bilirubin, or plasma creatinine levels.

The results were not influenced by the concurrent use of β-blockers (table 6). Table 6 shows the percent of patients with an MI or cardiac death who were on or not on β-blockers. The principal indication for the preoperative use of β-blockers was hypertension. There was no statistical difference in the overall use of hypertensive drugs between the two treatment groups.

A test of heterogeneity within the CHD population revealed that the incidence of the primary outcome differed between the three surgery types ($P = 0.064$), with a positive result in patients needing vascular surgery and none in those receiving other forms of surgery. The results in the subgroup undergoing vascular surgery will therefore be considered separately.

Subgroup of 904 Patients Having Vascular Surgery. There was a significant reduction in overall death or MI in the preplanned subgroup undergoing vascular surgery in the risk ratio (RR, 0.67; CL, 0.45–0.98) in those receiving mivazerol ($P = 0.037$; table 4). All-cause deaths were 20 of 450 in the placebo group and 8 of 454 in the mivazerol group ($P = 0.024$), and for cardiac deaths 18 of 450 *versus* 6 of 454 ($p = 0.009$). Additionally, there was a non-significant trend (−21%) in MI in the mivazerol-treated group. These positive results were confined to patients undergoing aortic surgery ($P = 0.043$), and there was no statistically significant benefit in patients having infrainguinal reconstructive surgery.

In the vascular surgery subgroup, the benefit of mivazerol occurred mostly within the first 4 days after the

Table 6. Usage of β-Blockers: Distribution of MI or Cardiac Death in Patients Receiving β-blockers

	Vascular Surgery		Thoracic-abdominal Surgery		Orthopedic	
	Placebo	Mivazerol	Placebo	Mivazerol	Placebo	Mivazerol
No. of patients	450	454	295	312	196	190
% not receiving β-blockers	14.3	9.5	6	8.3	5.9	8.2
% on receiving β-blockers	13.2	9.5	9.5	7.6	3.3	7.4

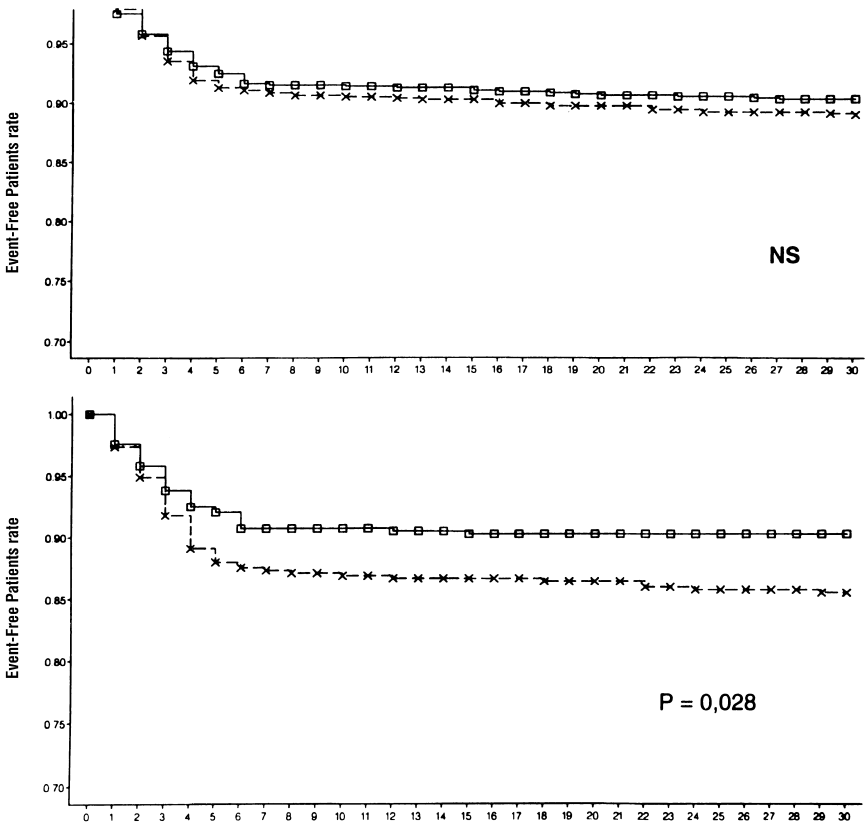

Fig. 1. The survival (Kaplan-Meier) curves for the primary endpoint during the fixed period of 30 days from the induction of anesthesia and surgery. After postoperative day 6, there were four additional events: one in the mivazerol-treated group and three in the placebo group. (*Top*) Myocardial infarction (MI) or death for all surgery groups. (*Bottom*) MI or death for patients undergoing vascular surgery.

induction of anesthesia (fig. 1). During this period, there were 10 cardiac deaths (and two non-cardiac deaths) in the placebo group and 5 (and one non-cardiac) in the mivazerol group. Of the 10 placebo group cardiac deaths, 3 patients died from acute myocardial infarction, 4 from acute pulmonary edema or failure, 2 from arrhythmias, and 1 suddenly. In the mivazerol group, four patients died from acute myocardial infarction and one from arrhythmia. During postoperative days 6–30, there were with fewer deaths from cardiac failure (eight *vs.* two deaths) in the mivazerol-treated patients.

There was no significant difference in heart failure or arrhythmias in patients treated with mivazerol compared with placebo (24 *vs.* 35 for heart failure and 12 *vs.* 12 for arrhythmias).

For the patients having vascular surgery, the mean length of stay in the intensive care units was not different (77 h for mivazerol *vs.* 84 h for placebo; P = NS).

In summary, in this subgroup of patients having vascular surgery, there were fewer cardiac events and deaths between 0 and 30 days in those given mivazerol ($P = 0.028$; fig. 1).

Discussion

The intravenous infusion of mivazerol from induction of anesthesia and for 72 h after surgery did not reduce the incidence of myocardial infarction or death in coronary patients undergoing three types of non-cardiac surgery. However, in a preplanned subgroup of 904 patients undergoing reparative vascular surgery, there was a significant reduction of cardiac deaths during the operative and immediate recovery periods. The fact that patients undergoing vascular surgery had a different response to an equal number of patients having non-vascular thoracoabdominal and orthopedic surgery requires comment.

Patients with known CHD who need major vascular surgery are more at risk for MI and cardiac death during and after non-cardiac surgery than similar patients having other forms of surgery.[3] The extent of this increased risk has been reemphasized recently by a review of the Coronary Artery Surgery Study (CASS) database, which provided comparison of the incidence of postoperative myocardial infarction or death in CHD patients having

major vascular surgery (≅11%) with those having thoracic (≅8%) or abdominal (≅4%) or orthopedic (<1%) surgeries.[13] Many of the risk factors contributing to peripheral vascular disease are similar to those for CHD. Also, major arterial surgery is often associated with substantial fluctuations in intravascular fluid volumes, cardiac filling pressure, and systolic blood pressure.[14] The increased risk for patients undergoing vascular surgery is recognized in the ACC/AHA Task Force report for perioperative cardiovascular evaluation for non-cardiac surgery.[15]

The period when patients are regaining consciousness, recovering from the anesthetic, and becoming aware of postoperative pain is particularly stressful.[1] It is then that catecholamine surges can occur, causing increased myocardial oxygen consumption and metabolic instability, and then that modulation of catecholamine response would be expected to be beneficial. Mivazerol, which has α_2-adrenergic agonist properties[6] and modulates spinal efferent impulses,[7] might be expected to have achieved this by reducing sympathetic activity and postganglionic noradrenaline availability, particularly because in the EMIT, mivazerol was infused from the moment of induction of anesthesia through the surgery and during the postoperative recovery stage. Considering that myocardial ischemia and postoperative elevation of heart rate are adverse prognostic factors for cardiac morbidity and mortality, a decrease in the incidence and severity of major cardiac events beyond the strict mivazerol infusion period is to be expected.

Until now, the management of perioperative cardiac complications has been empirical.[16] α_2-Agonists, such as clonidine[17] and dexmedetomine,[18] have been used during major surgery for their anesthetic-sparing and hemodynamic-stabilizing effects but may cause hypotension and bradycardia. The significant increase in the use of atropine during the infusion of mivazerol in the EMIT reflects its known bradycardiac action,[8–10] but there was no difference in the use of adrenergic or dopaminergic compounds during the infusion periods, suggesting that mivazerol did not produce any important hypotensive effect.

Small trials using nitrates[19] and Ca^{2+} antagonists[20] have been reported but without any clear benefit for perioperative cardiac complications. β-blockade may be beneficial,[21,22] although it may be associated with an early increase in plasma catecholamines, hypotension, and decreased myocardial contractility. Recently, β-blockade has been recommended for use during noncardiac surgery on the basis of a double-blind randomized trial of 200 patients with CHD, or at risk for CHD.[23] That trial showed that there were significantly fewer cardiac deaths (0 atenolol:7 placebo) during the 6 months after hospital discharge, but it was not powered to show an effect on perioperative mortality and morbidity. Furthermore, the late benefit did not appear to relate directly to any protection during the immediate postoperative period. These results need confirmation because they may have been influenced by drugs used during later weeks.

Overall, the results of EMIT are negative, but the significant beneficial trend in patients with CHD undergoing vascular surgery, derived from a preplanned subgroup analysis based on tests of heterogeneity, is encouraging and reinforces the results of an earlier small trial,[11] which showed that mivazerol reduced tachycardia and myocardial ischemia during anesthesia. Of course, this trial describes the effects of only one-dose concentration of mivazerol; in the future, others might need to be tested. Now a specifically designed second trial is needed to confirm whether treatment with an α_2 agonist, such as mivazerol, is truly beneficial in CHD patients undergoing vascular surgery.

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