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EFFECT OF ATENOLOL ON MORTALITY AND CARDIOVASCULAR MORBIDITY AFTER NONCARDIAC SURGERY

DENNIS T. MANGANO, PH.D., M.D., ELIZABETH L. LAYUG, M.D., ARTHUR WALLACE, PH.D., M.D., AND IDA TATEO, M.S., FOR THE MULTICENTER STUDY OF PERIOPERATIVE ISCHEMIA RESEARCH GROUP*

ABSTRACT

Background Perioperative myocardial ischemia is the single most important potentially reversible risk factor for mortality and cardiovascular complications after noncardiac surgery. Although more than 1 million patients have such complications annually, there is no effective preventive therapy.

Methods We performed a randomized, double-blind, placebo-controlled trial to compare the effect of atenolol with that of a placebo on overall survival and cardiovascular morbidity in patients with or at risk for coronary artery disease who were undergoing noncardiac surgery. Atenolol was given intravenously before and immediately after surgery and orally thereafter for the duration of hospitalization. Patients were followed over the subsequent two years.

Results A total of 200 patients were enrolled. Ninety-nine were assigned to the atenolol group, and 101 to the placebo group. One hundred ninety-four patients survived to be discharged from the hospital, and 192 of these were followed for two years. Overall mortality after discharge from the hospital was significantly lower among the atenolol-treated patients than among those who were given placebo over the six months following hospital discharge (0 vs. 8 percent, $P<0.001$), over the first year (3 percent vs. 14 percent, $P=0.005$), and over two years (10 percent vs. 21 percent, $P=0.019$). The principal effect was a reduction in deaths from cardiac causes during the first six to eight months. Combined cardiovascular outcomes were similarly reduced among the atenolol-treated patients; event-free survival throughout the two-year study period was 68 percent in the placebo group and 83 percent in the atenolol group ($P=0.008$).

Conclusions In patients who have or are at risk for coronary artery disease who must undergo noncardiac surgery, treatment with atenolol during hospitalization can reduce mortality and the incidence of cardiovascular complications for as long as two years after surgery. (N Engl J Med 1996;335:1713-20.)

MORTALITY and morbidity due to cardiovascular disease are prevalent and costly for the 30 million patients who undergo noncardiac surgery annually in the United States, affecting more than 1 million of them.[1,2] In the subgroup of 3 million patients who require noncardiac surgery who have or are at risk for coronary artery disease, the most significant risk factors for mortality and cardiovascular morbidity are myocardial ischemia and nonfatal myocardial infarction during the first week after surgery; these factors increase the risk of serious cardiovascular outcomes by a factor of 2 to 20 over the two years after surgery.[3-5] Postoperative ischemic events appear to be related to the persistently exaggerated sympathetic response that is associated with substantial increases in the heart rate throughout the hospitalization.[6-10] Several small clinical trials have investigated the effect of the preoperative or intraoperative use of nitrates,[11,12] beta-blockers,[13-15] calcium-channel blockers,[16,17] or α_2-agonists[18,19] on hemodynamics and measures of myocardial ischemia. Although several of the preliminary findings were encouraging, previous trials have not investigated the effects of such therapies when administered over the entire postoperative hospital stay. Even more important, the effects of such intensive therapy on long-term mortality (i.e., mortality after discharge from the hospital) and the incidence of cardiovascular events remained to be determined.

We hypothesized that in patients who had or were

From the San Francisco Veterans Affairs Medical Center and University of California, San Francisco (D.T.M., A.W.), and the Ischemia Research and Education Foundation, San Francisco (E.L.L., I.T.). Address reprint requests to Dr. Mangano at the San Francisco Veterans Affairs Medical Center, 4150 Clement St., 129, San Francisco, CA 94121.

*Members of the Multicenter Study of Perioperative Ischemia Research Group are listed in the Appendix.

at risk for coronary artery disease, the intensive administration of beta-blockers before and after surgery, continuing throughout the period of hospitalization, would decrease mortality and the incidence of serious cardiovascular events during the two years after surgery.

METHODS

Study Population

Eligible patients were those with or at risk for coronary artery disease who were scheduled for elective noncardiac surgery requiring general anesthesia at the San Francisco Veterans Affairs Medical Center. The presence of coronary artery disease was indicated by a previous myocardial infarction, typical angina, or atypical angina with a positive stress test; a patient was considered at risk for coronary artery disease when he or she had at least two of the following cardiac risk factors: age ≥65 years, hypertension, current smoking, a serum cholesterol concentration ≥240 mg per deciliter (6.2 mmol per liter), and diabetes mellitus.[3,4] No more than 1 patient per day was enrolled, and of the 204 patients who agreed to participate in the study, 200 were enrolled and underwent randomization (1 withdrew and 3 did not have surgery); 99 were assigned to the atenolol group and 101 to the placebo group.

Administration of the Study Drugs

Patients were randomly assigned to receive either atenolol or placebo before the induction of anesthesia, immediately after surgery, and daily throughout their hospital stay (up to seven days). All clinical and study personnel were blinded to the study-group assignments throughout all phases of this trial. Intravenous and oral preparations of the active drug (atenolol) and placebo were prepared by the hospital pharmacy according to a computer-generated, randomized list that was retained only by the pharmacy and that remained confidential until formal unblinding after the data base was closed. The intravenous preparation consisted of two 10-ml syringes, each containing 5 mg of atenolol or placebo; the oral preparation consisted of two 50-mg tablets of atenolol or two placebo tablets. Approximately one hour before surgery, patients entered the preoperative area, their blood pressure was recorded with an automated cuff, and a five-lead continuous electrocardiogram was recorded. Thirty minutes before entry into the operating room, the intravenous administration of the study drug began.

Administration of the study drug at each time point required that the heart rate be ≥55 beats per minute, that the systolic blood pressure be ≥100 mm Hg, and that there be no evidence of congestive heart failure, third-degree heart block, or bronchospasm (as defined in the first International Study of Infarct Survival[20]). If these criteria were met, the first syringe of the study drug was infused over a period of five minutes, the patient was observed for an additional five minutes, and if the criteria continued to be met, the second syringe was infused over a period of five minutes. Immediately after surgery, the study drug was again given, in the same way.

Starting on the morning of the first postoperative day, and each day thereafter until the patient was discharged from the hospital (up to a maximum of seven days), patients received the study drug in the manner described for intravenous infusion (every 12 hours) or once a day orally (if possible), at which time, if the above criteria were met, atenolol (50 or 100 mg) or placebo was given daily. If the heart rate was above 65 beats per minute and the systolic blood pressure was 100 mm Hg or higher, two tablets of atenolol (total dose, 100 mg) or two tablets of placebo were given orally; if the heart rate was 55 or higher but no higher than 65 and the systolic blood pressure was 100 mm Hg or higher, one tablet of atenolol or one tablet of placebo was administered; if the heart rate was below 55 or the systolic blood pressure was below 100 mm Hg, no atenolol (or placebo) was given. No treating clinician was allowed to observe administration of the study drug either before or after surgery.

Clinical Care

All patients underwent general anesthesia with endotracheal intubation; preoperative medications were continued until the time of surgery, with beta-blockers replaced by the study drug on the morning of surgery. There were no other protocol-based restrictions of anesthetic or surgical technique, and clinical decisions were not controlled by the study protocol. Perioperative information, which was recorded and analyzed for possible confounding effects, included the type and duration of surgery, the anesthetic techniques used, details of fluid and blood loss and replacement, cardiovascular medications, hemodynamic variables, electrocardiographic data, and adverse events.

Follow-up and Outcome Measures

Of the 200 patients enrolled, 194 were discharged after surgery and 6 died during hospitalization. Three deaths were secondary to myocardial infarction (two in the placebo group and one in the atenolol group). Three deaths had noncardiac causes; two were secondary to metastatic cancer (both in the atenolol group), and one was caused by pulmonary failure after an infusion of 23 liters of crystalloid, colloid, and blood over a period of 24 hours for fluid loss (in the atenolol group). Among the 194 patients discharged, outcome data were collected for 192 (99 percent); 1 was lost to follow-up and 1 was not followed because surgery was not performed after he received the study drug. Six months, one year, and two years after surgery, study physicians conducted scheduled evaluations that were independent of the patients' usual clinical care.

Death was considered due to cardiac causes if the patient died of a myocardial infarction, dysrhythmia, or congestive heart failure caused primarily by a cardiac condition. The diagnosis of myocardial infarction required at least one of the following: development of new Q waves (as defined by Minnesota Code 1-1-1 or 1-2-7); new persistent ST-segment or T-wave changes (Minnesota Code 4-1, 4-2, 5-1, or 5-2)[3] associated at the time of hospitalization with an elevation of total creatine kinase and creatine kinase MB isoenzyme values; evidence at autopsy of acute myocardial infarction; or documentation of myocardial infarction in the hospital records.[3] Unstable angina was defined as severe precordial chest pain that lasted at least 30 minutes, was unresponsive to standard therapeutic maneuvers, and was associated with transient ST-segment or T-wave changes without the development of Q waves or diagnostic enzyme abnormalities. The diagnosis of congestive heart failure was made when a patient had symptoms or signs of pulmonary congestion (shortness of breath and rales), signs of new left or right ventricular failure (cardiomegaly, an S_3 sound, jugular venous distention, and peripheral edema), abnormal results on chest radiography (vascular redistribution, interstitial edema, and alveolar edema), and a change in medication involving at least the institution of treatment with diuretic agents.[3]

The outcome measures were prescribed by the study protocol. The primary outcome was mortality from all causes during the two years after discharge from the hospital. The secondary outcome variable combined myocardial infarction, unstable angina or congestive heart failure requiring hospital admission and clinical diagnosis and treatment, myocardial revascularization (coronary-artery bypass graft surgery or percutaneous transluminal coronary angioplasty), and death. Autopsy data, if available for patients who died during the two-year period, were reviewed at the central laboratory (at the Ischemia Research and Education Foundation) by a pathologist who was blinded to the patients' treatment assignments.

Statistical Analysis

We designed the study to permit the assessment of both in-hospital events (such as hemodynamic changes, dysrhythmias, and

ischemia[21]) and adverse cardiovascular outcomes during the two years after discharge. Using the log-rank survival test for the estimation of the sample size (BMDP statistical software), we calculated that 198 patients would be necessary for the assessment of mortality and 158 for the assessment of the combined outcome variable; using the z statistic, we calculated that 170 patients would be required for the assessment of in-hospital events. The risk of death in different categories (death from all causes, from cardiac causes, and from noncardiac causes, all at six months, one year, and two years) was compared between the groups by Kaplan–Meier methods, as was event-free survival after discharge. Univariable predictors of two-year mortality were identified with Cox proportional-hazards regression techniques,[22] after we first verified that the assumption of the hazards model was valid.[23] Predictors with two-tailed P values below 0.10 were entered into the multivariable models, and a series of models was constructed by adding variables, as long as the resulting multivariable model had a lower P value (by chi-square analysis) than competing models. Analyses were performed with use of Statistical Analysis System software (SAS Institute, Cary, N.C.).

RESULTS

The 200 study patients were middle-aged or elderly persons who smoked and had a history of hypertension and chronic medical problems (Table 1). There were no significant differences between the groups, except that a higher proportion of the atenolol group was receiving treatment for hypertension.

TABLE 1. CHARACTERISTICS OF THE PATIENTS, ACCORDING TO STUDY GROUP.*

CHARACTERISTIC	ATENOLOL (N=99)	PLACEBO (N=101)	P VALUE
Definite coronary artery disease (%)	36	42	0.38
At risk for coronary artery disease (%)†	63	59	0.38
History of cardiac disease (%)			
Myocardial infarction	18	26	0.26
Coronary bypass surgery	11	17	0.31
Percutaneous transluminal coronary angioplasty	1	3	0.30
Typical angina	25	36	0.13
Dysrhythmia	13	13	1.00
Congestive heart failure	9	7	0.61
Cardiac risk factors (%)			
Current smoking	35	38	0.77
Hypertension	71	60	0.08
Cholesterol ≥240 mg/dl (6.2 mmol/liter)	10	6	0.31
Diabetes mellitus	28	35	0.36
Age ≥65 yr	65	75	0.22
Preoperative medications (%)			
Antiarrhythmic agents	0	3	0.25
Beta-blockers	18	8	0.02
Calcium-channel blockers	22	34	0.11
Diuretics	28	17	0.04
Antihypertensive agents	30	19	0.05
Digoxin	6	10	0.44
Nitrates	8	13	0.36
Age (yr)	68±8.6 (44–89)	67±10.2 (44–82)	0.11
Duration of anesthesia and surgery (hr)	6.2±2.7 (2.7–15.6)	5.7±2.4 (1.5–12.7)	0.18
Type of surgery (%)			
Major vascular	38	43	0.64
Intraabdominal	21	21	0.92
Orthopedic	12	15	0.57
Neurosurgical	10	8	0.59
Other‡	18	14	0.41

*Plus–minus values are means ±SD. Ranges are shown in parentheses.

†Patients considered at risk for coronary artery disease were those with two or more of the following: age ≥65 years, hypertension, current smoking, serum cholesterol concentration ≥240 mg per deciliter (6.2 mmol per liter), and diabetes mellitus.

‡Other surgery included intrathoracic procedures (in 1 patient in the atenolol group and 3 in the placebo group), other general or plastic surgery (in 15 in the atenolol group and 11 in the placebo group), and head and neck surgery (in 2 in the atenolol group).

Overall Mortality and Mortality from Cardiac Causes

Thirty patients (15.6 percent of the 192 who were followed after hospital discharge) died during the two-year follow-up period. Twenty-one of these deaths (12 of which were from cardiac causes) occurred in the placebo group, and 9 (4 of which were from cardiac causes) in the atenolol group; thus, overall mortality was 55 percent lower in the atenolol group ($P=0.019$), and mortality from cardiac causes was 65 percent lower ($P=0.033$). The principal effect of atenolol therapy was on cardiac outcomes occurring during the first six to eight months (1 death from noncardiac causes in the atenolol group vs. 10 in the placebo group, 7 of which were from cardiac causes; $P<0.001$); the length of time to the first death was 19 days in the placebo group and 237 days in the atenolol group. After eight months, there was no substantial difference between the groups; however, the early difference in survival between the groups was preserved at one year (3 deaths in the atenolol group vs. 14 in the placebo group, $P=0.005$) and at two years (9 vs. 21, $P=0.019$); the survival rate was significantly higher in the atenolol group at all times (Fig. 1).

Combined Cardiac Outcomes

Atenolol-treated patients who survived to hospital discharge had a significant decrease in the rate of cardiac events, as compared with the rate in the placebo group, within six months after surgery (there were no such events in the atenolol group, as compared with 12 in the placebo group; $P<0.001$), a decrease of 67 percent from the rate in the placebo group within one year (7 events vs. 22 events, $P=0.003$), and a decrease of 48 percent in the two years after surgery (16 events vs. 32 events, $P=0.008$). The principal effect of atenolol treatment was evident over the first 6 to 8 months after surgery; the time to the first adverse event in each group was 6 days for the placebo group, as compared with 158 days for the atenolol group. Thereafter, there was no substantial difference between the groups; however, the early difference in event-free survival was preserved over the two years after surgery (Fig. 2).

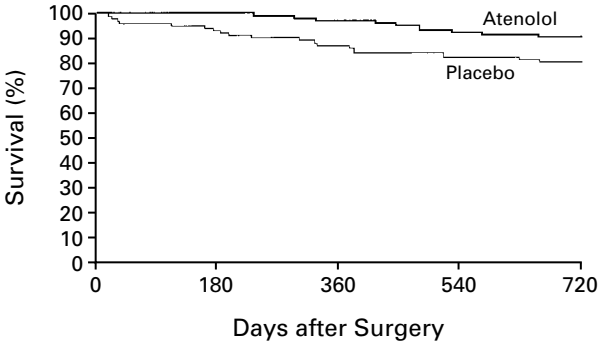

Figure 1. Overall Survival in the Two Years after Noncardiac Surgery among 192 Patients in the Atenolol and Placebo Groups Who Survived to Hospital Discharge.

The rate of survival at 6 months (180 days) was 100 percent in the atenolol group and 92 percent in the placebo group ($P<0.001$); at 1 year (360 days), the rates were 97 percent and 86 percent, respectively ($P=0.005$); and at 2 years (720 days), 90 percent and 79 percent ($P=0.019$).

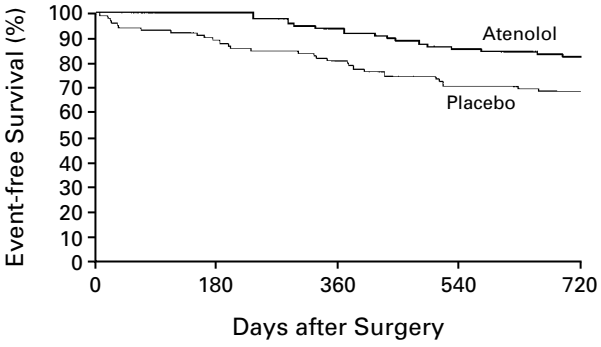

Figure 2. Event-free Survival in the Two Years after Noncardiac Surgery among 192 Patients in the Atenolol and Placebo Groups Who Survived to Hospital Discharge.

The outcome measure combined the following events: myocardial infarction, unstable angina, the need for coronary-artery bypass surgery, and congestive heart failure. The rate of event-free survival at 6 months (180 days) was 100 percent in the atenolol group and 88 percent in the placebo group ($P<0.001$); at 1 year (360 days), the rates were 92 percent and 78 percent, respectively ($P=0.003$); and at 2 years (720 days), 83 percent and 68 percent ($P=0.008$).

Table 2. Predictors of Death among Patients Undergoing Noncardiac Surgery.*

Predictor	Hazard Ratio (95% CI)	P Value
Univariable models		
Atenolol	0.4 (0.2–0.9)	0.03
Diabetes mellitus	3.1 (1.4–6.8)	0.01
Oral hypoglycemic treatment	2.6 (1.1–6.2)	0.03
Insulin treatment	2.6 (1.0–6.9)	0.05
Ischemia on Holter monitoring on postoperative days 0–2	2.3 (1.0–5.3)	0.04
Multivariable models		
Diabetes mellitus	2.8 (1.4–6.2)	0.01
Atenolol	0.5 (0.2–1.1)	0.06

*The patients included in these models were the 192 of the original randomized group of 200 who survived to hospital discharge and were followed for two years after discharge; 30 of these 192 patients (15.6 percent) died during the two years of follow-up. CI denotes confidence interval.

Other Indicators of Treatment Effect

During treatment, the average heart rate was significantly lower in the atenolol group (75 beats per minute, vs. 87 in the placebo group; $P<0.001$), as was the maximal heart rate (113 vs. 130 beats per minute, $P<0.001$). Multivariable correlates associated with survival at two years (shown in Table 2) were a history of diabetes mellitus and atenolol therapy, with atenolol improving two-year survival in patients with diabetes by approximately 75 percent (hazard ratio for death, 0.25; $P=0.03$). Similarly, in atenolol-treated patients, the presence of diabetes was not associated with a significantly increased risk of death (hazard ratio, 1.2; $P=0.76$), whereas in patients given placebo, the presence of diabetes was associated with a quadrupling of the risk (hazard ratio, 4.0; $P=0.003$). No other perioperative variables were associated with outcome. Several medications were used more frequently in one group than in another (Table 3), but there was no independent association between the use of these medications and outcome, as shown by the estimated odds ratios and the corresponding P values (Table 3).

During the two years after discharge from the hospital, there was no difference between the groups in the use of any cardiovascular medication (Table 3); therefore, the use of such medications did not confound the observed effect of atenolol on two-year mortality. These data also indicate that cardiovascular medications administered before admission to the hospital were still given at hospital discharge in most patients, but not all, and that after discharge the patients in the placebo group continued to use cardiovascular medications at least as often as the patients in the atenolol group.

Tolerance and Adverse Reactions

More than 85 percent of the patients tolerated the intravenous administration of atenolol before and immediately after surgery and its oral administration during the postoperative period; more than 60 percent were able to receive the full daily dose of atenolol (10 mg intravenously or 100 mg orally) (Table 4). In approximately 10 percent of the patients, the intravenous administration of atenolol before or after surgery was associated with a decrease of 20 percent or more in the systolic blood pressure or heart rate (Table 4); however, no patient had a systolic blood pressure below 90 mm Hg or a heart rate below 40 beats per minute, and none required therapy.

TABLE 3. USE OF CARDIOVASCULAR MEDICATIONS BEFORE AND AFTER SURGERY, ACCORDING TO STUDY GROUP.*

STUDY PERIOD	NO. WITH DATA		BETA-BLOCKERS			CALCIUM-CHANNEL BLOCKERS			NITRATES			ACE INHIBITORS		
	ATENOLOL	PLACEBO	ATENOLOL	PLACEBO	P VALUE	ATENOLOL	PLACEBO	P VALUE	ATENOLOL	PLACEBO	P VALUE	ATENOLOL	PLACEBO	P VALUE
			% of patients			% of patients			% of patients			% of patients		
Before admission	99	101	19.4	8.2	0.02†	23.7	34.7	0.11‡	8.6	13.3	0.36	23.7	8.2	0.003§
At hospital discharge¶	95	99	14.0	7.1	0.12‖	19.4	27.6	0.18**	7.5	15.3	0.09††	20.4	6.1	0.003‡‡
At 6 mo	93	91	13.8	8.3	0.27	19.0	29.9	0.10§§	16.1	22.4	0.30	15.2	18.4	0.58
At 12 mo	90	85	16.7	13.7	0.61	23.8	30.3	0.36	19.1	26.7	0.25	23.8	23.6	0.98
At 24 mo	84	78	15.5	13.9	0.79	18.8	25.4	0.36	14.1	18.2	0.51	18.1	21.5	0.61

*Chi-square statistics were used to compare the two groups. ACE denotes angiotensin-converting enzyme.

†Odds ratio for mortality at two years associated with beta-blocker use before admission = 0.80 (P=0.73).

‡Odds ratio for mortality at two years associated with use of calcium-channel blockers before admission = 1.06 (P=0.90).

§Odds ratio for mortality at two years associated with ACE-inhibitor use before admission = 1.45 (P=0.50).

¶One patient of the 95 in the atenolol group was not included in these calculations because surgery was delayed for several days after the study drug was given.

‖Odds ratio for mortality at two years associated with beta-blocker use at discharge = 0.61 (P=0.52).

**Odds ratio for mortality at two years associated with use of calcium-channel blockers at discharge = 0.85 (P=0.74).

††Odds ratio for mortality at two years associated with nitrate use at discharge = 1.32 (P=0.64).

‡‡Odds ratio for mortality at two years associated with ACE-inhibitor use at discharge = 1.17 (P=0.79).

§§Odds ratio for mortality at two years associated with use of calcium-channel blockers for six months = 1.05 (P=0.92).

The oral administration of atenolol was not associated with an increased incidence of hypotension, bradycardia, or other events.

DISCUSSION

The results of this trial demonstrate that, in patients who have or are at risk for coronary artery disease and who are undergoing noncardiac surgery, mortality and cardiovascular events after discharge from the hospital can be substantially reduced by the administration of atenolol throughout hospitalization for surgery. The length of time to the first adverse event, survival, and event-free survival were all significantly improved with atenolol, particularly during the first six to eight months after surgery, and the effects on survival persisted for at least two years. Among the atenolol-treated patients who survived to discharge from the hospital, survival was 90 percent two years after surgery, as compared with 79 percent in the placebo group, and event-free survival was 83 percent, as compared with 68 percent. Moreover, perioperative beta-blockade appeared to be well tolerated by these patients, despite the high prevalence of cardiac and pulmonary disease.

What is the rationale for using perioperative beta-blockade for the prevention of long-term adverse outcomes? Studies conducted over the past decade have established the association between postoperative myocardial ischemia and adverse outcomes after discharge, with the odds of such outcomes 28 times higher in patients with postoperative ischemia, as compared with those without ischemia, by six months after surgery, 20 times higher at one year, and 14 times higher at two years.[3-5,24-26] In addition, studies have demonstrated an association between postoperative ischemia and an elevated heart rate and have suggested that mitigation of this heart-rate response may reduce the incidence or severity of ischemia (or both).[6-10,21] Thus, we concluded that intensive perioperative beta-blockade, if it could attenuate the heart-rate response and limit the development of ischemia, might substantially reduce longer-term cardiac complications.

The large treatment effect that we observed — namely, an absolute increase of 15 percentage points in event-free survival after hospital discharge (from 68 percent to 83 percent) in the atenolol group as compared with the placebo group — was unexpected. Several smaller trials, however, have reported sizable effects of beta-blockers on perioperative ischemia,[13-15,21] and observational studies have demonstrated an 18 percent difference in event-free survival at two years between patients who had postoperative ischemia and those who did not.[4] Furthermore, we found that the principal effect of beta-blockade was evident within the first six to eight months after surgery; this finding is consistent with the temporal profile of the association between

TABLE 4. DAILY DOSE AND SIDE EFFECTS OF ATENOLOL.*

VARIABLE	DAY OF SURGERY				DAYS 1–7†	
	BEFORE SURGERY		AFTER SURGERY			
	Atenolol	*Placebo*	*Atenolol*	*Placebo*	*Atenolol*	*Placebo*
	percentage of patients					
Dosage‡						
Full dose	69	79	74	88	63	82
Half dose	19	10	10	6	30	18
Not treated	11	12	15	7	6	1
Side effects						
Hypotension						
Systolic BP <90 mm Hg	0	0	0	0	14	12
>20% decrease in systolic BP	4	0	2	0	—	—
Treated	0	0	0	0	0	0
Bradycardia§						
Heart rate <40 bpm	0	0	0	0	6	5
>20% decrease in heart rate	9	0	4	0	—	—
Treated	0	0	0	0	0	0
Bradycardia and hypotension						
Systolic BP <90 mm Hg and heart rate <40 bpm	0	0	0	0	0	0
>20% decrease in heart rate and systolic BP	2	0	1	0	—	—
Treated	0	0	0	0	0	0
Congestive heart failure	0	0	0	0	2	5
Bronchospasm¶	3	0	0	0	0	0

*There were 99 patients in the atenolol group and 101 in the placebo group. BP denotes blood pressure, and bpm beats per minute.

†Effects include hypotension, bradycardia, congestive heart failure, or bronchospasm at any time on days 1 through 7, as reported by the clinical staff.

‡The full dose was 10 mg for intravenous administration, and 100 mg for oral administration. A half-dose was 5 mg intravenously and 50 mg orally. Patients not treated received no study drug because the criteria for administration were not met.

§Two patients in the atenolol group whose condition was stable after intravenous drug administration received treatment after intubation for bradycardia 30 to 75 minutes after the intravenous administration of atenolol.

¶Two patients had bronchospasm after intubation, 1 to 3 hours after intravenous atenolol administration; one patient had bronchospasm after extubation, 8.5 hours after intravenous atenolol administration.

perioperative myocardial ischemia and outcomes at six months (short-term results) and one year (intermediate results).[4] Although our trial was small, the observed rates of events in the placebo group were similar to those reported in observational studies of similar patients. In addition, as in nonsurgical patients,[27-31] beta-blockade also had effects on nonfatal cardiac outcomes, such as myocardial infarction, congestive heart failure, and unstable angina requiring revascularization.

The treatment effect in this trial cannot be attributed to important differences between the two study groups at base line; in fact, a larger proportion of the atenolol-treated patients had cardiovascular disease before surgery, and this group had a greater number of risk factors known to affect the incidence of cardiovascular complications after surgery.[3,32-34] Our results also cannot be explained by differences in surgical technique, details of the hospital stay, or the use of cardiovascular medications (specifically, beta-blockers, calcium-channel blockers, nitrates, angiotensin-converting–enzyme inhibitors, or aspirin) before or after surgery or at the time of discharge. Most variables were distributed evenly in the two groups, and the variables that may not have been similar in the two groups, such as treatment for heart failure or diabetes, were shown not to affect the results of the trial.

Assessing the effect of the long-term use of cardiovascular medications over the two years of the study is critical to the analysis of the results of this trial, because one interpretation might be that the patients treated with atenolol received more intensive cardiovascular therapy than the patients given placebo, thereby confounding our findings. However, this did not occur. First, the use of beta-blockers, calcium-channel blockers, nitrates, angiotensin-converting–enzyme inhibitors, and aspirin did not differ significantly between groups 6, 12, or 24 months after surgery (Table 4). Nor was the use of any of these medications associated with any study outcome be-

fore or after surgery or at discharge. This finding is not surprising, given the results of our previous two-year observational study of 474 patients with similar risk profiles, in which no association was demonstrated between the routine use of cardiovascular medications and long-term outcome.[3-5] Finally, as Table 4 suggests, the patients in the placebo group continued to use these cardiovascular medications at least as often as the patients in the atenolol group during the two years after hospital discharge. These results confirm that the observed effect of atenolol on mortality was not confounded by the use of these medications during the two years after discharge.

Clinical Implications

In patients at risk for coronary artery disease who are about to undergo major surgery, the standard practice is to control the heart rate before surgery, to continue beta-blocking medication up to the time of surgery, and to modulate the heart-rate response during surgery by means of anesthetic techniques. After surgery, however, the heart rate is not well controlled and rises above preoperative levels by 30 percent or more throughout the extended postoperative period.[4,9,10,24,26] Furthermore, even brief periods of tachycardia during the postoperative period may precipitate ischemia in this group of patients, who also are subject to alterations in perfusion, oxygenation, and coagulation as well as other types of stress imposed by the exaggerated sympathetic and inflammatory responses to surgery.

Despite the recognition of the general problem of perioperative infarction, as well as the potentially deleterious effect of an unchecked postoperative sympathetic response, and despite their awareness of the efficacy of beta-blockade in ambulatory patients with coronary artery disease, clinicians have been reluctant to prescribe beta-blockers after surgery, even for patients who were maintained on beta-blockers before their admission for surgery. Such reluctance appears to be based on several areas of concern, including safety (the fear of precipitating postoperative heart failure, hypotension, and bronchospasm), the efficacy of these drugs (which is unproved for surgical patients), and cost. Our study addressed the first two of these issues, and our findings demonstrate the efficacy and safety of perioperative beta-blockade, even for patients with a history of heart failure and pulmonary disease. Regarding cost, we chose to evaluate a therapy that is available in generic-drug form. By conservative estimates, our study population represents approximately 10 percent of the 30 million patients who undergo noncardiac surgery each year (or 3 million patients). Even assuming that atenolol has an effect only one fifth as strong as the 11 percent absolute reduction (from 21 percent to 10 percent) in overall long-term mortality found in our trial (or approximately a 2 percent absolute reduction), then intensive perioperative beta-blockade might give 60,000 U.S. patients each year at least an additional two years of life, or save 120,000 life-years (3 million surgical patients $\times$ 2 percent reduction in mortality $\times$ 2 additional years per patient) at a cost of less than $100 per patient (a conservative estimate for one week of atenolol therapy). For the 3 million patients at risk, the overall cost, based on the conservative assumption, would equal $2,500 per life-year saved.

The results of this trial thus indicate that in patients who have or are at risk for coronary artery disease and who must undergo major noncardiac surgery, mortality and the incidence of cardiovascular events after hospital discharge can be reduced by the use of beta-adrenergic blockade throughout the hospital stay. Intensive perioperative beta-blockade appears to be safe and well tolerated, and given the availability of a generic beta-blocking agent, the estimated savings in lives more than outweighs the cost of therapy.

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APPENDIX

The Multicenter Study of Perioperative Ischemia Research Group is a consortium of investigators from approximately 150 medical centers worldwide; its focus is the problems of perioperative myocardial infarction, stroke, and renal dysfunction (as well as other organ dysfunction) and the implications of such diseases for health economics. The Ischemia Research and Education Foundation is a nonprofit foundation that supports multicenter research in these areas and is closely affiliated with the study investigators and their institutions. The coordinating analysis group consisted of the following: *director* — D.T. Mangano; *data collection* — E. Layug, J. Li, C. Dietzel, S. Kaileh, and D.T. Mangano; *data analysis* — I. Tateo, E. Layug, A. Wallace, and D.T. Mangano; *editorial administrative assistants* — D. Beatty, B. Xavier, M. Riddle, and W. von Ehrenburg; and *consultants* — S. Zhou, A. Herskowitz, W. Browner, M. Hollenberg, and K. Ziola.

REFERENCES

1. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990;72:153-84.
2. Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. N Engl J Med 1995;333:1750-6.
3. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990;323:1781-8.
4. Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM. Long-term cardiac prognosis following noncardiac surgery. JAMA 1992;268:233-9.
5. Browner WS, Li J, Mangano DT. In-hospital and long-term mortality in male veterans following noncardiac surgery. JAMA 1992;268:228-32.
6. Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 1983;59:499-505.
7. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia predicts infarction and death during 2 year follow-up of unstable angina. J Am Coll Cardiol 1987;10:756-60.
8. Siliciano D, Mangano DT. Postoperative myocardial ischemia: mechanisms and therapies. In: Estafanous FG, ed. Opioids in anesthesia II. Boston: Butterworth–Heinemann, 1991:164-77.
9. Mangano DT, Hollenberg M, Fegert G, et al. Perioperative myocardial ischemia in patients undergoing noncardiac surgery. I. Incidence and severity during the 4 day perioperative period. J Am Coll Cardiol 1991;17:843-50.
10. Mangano DT, Wong MG, London MJ, Tubau JF, Rapp JA, Study of Perioperative Ischemia (SPI) Research Group. Perioperative myocardial is-

chemia in patients undergoing noncardiac surgery. II. Incidence and severity during the 1st week after surgery. J Am Coll Cardiol 1991;17:851-7.
11. Coriat P, Daloz M, Bousseau D, Fusciardi J, Echter E, Viars P. Prevention of intraoperative myocardial ischemia during noncardiac surgery with intravenous nitroglycerin. Anesthesiology 1984;61:193-6.
12. Gallagher JD, Moore RA, Jose AB, Botros SB, Clark DL. Prophylactic nitroglycerin infusions during coronary artery bypass surgery. Anesthesiology 1986;64:785-9.
13. Stone JG, Foëx P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. Anesthesiology 1988;68:495-500.
14. Magnusson J, Thulin T, Werner O, Jarhult J, Thomson D. Haemodynamic effects of pretreatment with metoprolol in hypertensive patients undergoing surgery. Br J Anaesth 1986;58:251-60.
15. Cucchiara RF, Benefiel DJ, Matteo RS, DeWood M, Albin MS. Evaluation of esmolol in controlling increases in heart rate and blood pressure during endotracheal intubation in patients undergoing carotid endarterectomy. Anesthesiology 1986;65:528-31.
16. Chung F, Houston PL, Cheng DC, et al. Calcium channel blockade does not offer adequate protection from perioperative myocardial ischemia. Anesthesiology 1988;69:343-7.
17. Merin RG. Calcium channel blocking drugs and anesthetics: is the drug interaction beneficial or detrimental? Anesthesiology 1987;66:111-3.
18. Ghignone M, Calvillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. Anesthesiology 1987;67:3-10.
19. Talke P, Li J, Jain U, et al. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. Anesthesiology 1995;82:620-33.
20. ISIS-I (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-I. Lancet 1986;2:57-66.
21. Wallace A, Layug E, Browner W, et al. Randomized, double blinded, placebo controlled trial of atenolol for the prevention of perioperative myocardial ischemia in high risk patients scheduled for non cardiac surgery. Anesthesiology 1994;81:Suppl:A99. abstract.
22. Modelling survival data. In: Collett D. Modelling survival data in medical research. London: Chapman & Hall, 1994:53-106.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
24. Raby KE, Goldman L, Creager MA, et al. Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. N Engl J Med 1989;321:1296-300.
25. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 1985;62:107-14.
26. Eisenberg MJ, London MJ, Leung JM, et al. Monitoring for myocardial ischemia during noncardiac surgery: a technology assessment of transesophageal echocardiography and 12-lead electrocardiography. JAMA 1992;268:210-6.
27. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335-71.
28. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction: patients and methods. Am J Cardiol 1985;56:3G-9G.
29. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life: the Atenolol Silent Ischemia Study (ASIST). Circulation 1994;90:762-8.
30. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992;327:248-54.
31. May GS, Eberlein KA, Furberg CD, Passamani ER, DeMets DL. Secondary prevention after myocardial infarction: a review of long-term trials. Prog Cardiovasc Dis 1982;24:331-52.
32. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977;297:845-50.
33. Detsky AS, Abrams HB, Forbath N, Scott JG, Hilliard JR. Cardiac assessment for patients undergoing noncardiac surgery: a multifactorial clinical risk index. Arch Intern Med 1986;146:2131-4.
34. Hollenberg M, Mangano DT, Browner WS, London MJ, Tubau JF, Tateo IM. Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. JAMA 1992;268:205-9.