■ CLINICAL INVESTIGATIONS

Anesthesiology
1998; 88:7-17

Prophylactic Atenolol Reduces Postoperative Myocardial Ischemia

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Background: **Perioperative myocardial ischemia occurs in 20–40% of patients at risk for cardiac complications and is associated with a ninefold increase in risk for perioperative cardiac death, myocardial infarction, or unstable angina, and a twofold long-term risk. Perioperative atenolol administration reduces the risk of death for as long as 2 yr after surgery. This randomized, placebo-controlled, double-blinded trial tested the hypothesis that perioperative atenolol administration reduces the incidence and severity of perioperative myocardial ischemia, potentially explaining the observed reduction in the risk for death.**

Methods: **Two-hundred patients with, or at risk for, coronary artery disease were randomized to two study groups (atenolol and placebo). Monitoring included a preoperative history and physical examination and daily assessment of any adverse events. Twelve-lead electrocardiography (ECG), three-lead Holter ECG, and creatinine phosphokinase with myocardial banding (CPK with MB) data were collected 24 h before until 7 days after surgery. Atenolol (0, 5, or 10 mg) or placebo was administered intravenously before induction of anesthesia and every 12 h after operation until the patient could take oral medications. Atenolol (0, 50, or 100 mg) was administered orally once a day as specified by blood pressure and heart rate.**

Results: **During the postoperative period, the incidence of myocardial ischemia was significantly reduced in the atenolol group: days 0–2 (atenolol, 17 of 99 patients; placebo, 34 of 101 patients; $P = 0.008$) and days 0–7 (atenolol, 24 of 99 patients; placebo, 39 of 101 patients; $P = 0.029$). Patients with episodes of myocardial ischemia were more likely to die in the next 2 yr ($P = 0.025$).**

Conclusions: **Perioperative administration of atenolol for 1 week to patients at high risk for coronary artery disease significantly reduces the incidence of postoperative myocardial ischemia. Reductions in perioperative myocardial ischemia are associated with reductions in the risk for death at 2 yr. (Key words: Beta blockade; cardiac morbidity; cardiac mortality; myocardial infarction; surgery.)**

This article is accompanied by an Editorial View. Please see: Warltier DC: Beta-adrenergic-blocking drugs: Incredibly useful, incredibly underutilized. ANESTHESIOLOGY 1998; 88:2-5.

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Received from the Departments of Anesthesia, Medicine, and Epidemiology and Biostatistics, San Francisco VA Medical Center, University of California, San Francisco, and the Ischemia Research and Education Foundation. Submitted for publication January 20, 1997. Accepted for publication August 5, 1997. The Ischemia Research and Education Foundation (IREF) supported this trial in its entirety. This study was not supported by any pharmaceutical company. However, the IREF has received major funding from Gensia, UCB, Farmos, Jansen, ICI, Zeneca, Anaquest, and Berlex.

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Perioperative Cardiac Complications

SIXTY-FIVE million Americans have cardiovascular disease, resulting in 1 million deaths per year. Of the 400,000 patients per year in the United States having cardiac surgery and the 30 million having noncardiac surgery, approximately 100,000 and 1.5 million patients, respectively, suffer perioperative cardiovascular morbidity at an annual cost exceeding $20 billion.[1,2] One approach to this problem is to identify the predictors of perioperative complications and then design therapeutic trials to reduce the number of poor outcomes. Recently we showed that perioperative administration of atenolol reduced the risk of death and cardiovascular complications for as long as 2 yr after surgery.[3]

The present investigation examined the perioperative risk factors that may be associated with this reduction in deaths after surgery.

The most significant perioperative risk factors for in-hospital adverse outcome have been identified as congestive heart failure, myocardial infarction within 6 months, unstable angina, left ventricular hypertrophy, aged ≥ 65 yr, male sex, cigarette smoking, diabetes, hypertension, increased serum cholesterol, peripheral vascular disease, and postoperative myocardial ischemia.[1,4] Although many of these risk factors are difficult to modify, postoperative myocardial ischemia is a potentially avoidable risk factor that is associated with a ninefold increase in cardiac complications before hospital discharge and a twofold greater long-term (2 yr) risk.[5,6] Thus therapeutic trials aimed at mitigating ischemia are indicated.

Several small studies have investigated both the prophylactic and therapeutic effects of nitrates, beta adrenergic, or calcium channel blockers on intraoperative ischemia. The effectiveness of prophylactic nitrates is controversial: An equal number of studies support as refute their use during operation to blunt myocardial ischemia.[7,8] Calcium channel blockers have been given prophylactically during cardiac surgery[7,9,10] and in cardioplegic solutions,[11] but they have not been shown yet to prevent perioperative myocardial ischemia.[12] Many trials of beta blocker use demonstrate benefits in nonsurgical patients with acute myocardial infarction or myocardial ischemia, including the ISIS-1[13] (International Study of Infarct Survival), the MIAMI[14] (Metoprolol In Acute Myocardial Infarction), the MAPHY[15] (Metoprolol versus thiazide diuretics in hypertension), and the ASIST[16] (Atenolol Silent Ischemia Study) trials. Although these trials clearly show that beta blockade is effective in reducing cardiac complications in patients with ambulatory ischemia and death in patients after myocardial infarction, they do not address whether prophylactic beta blockade is beneficial in the perioperative period.

Prophylactic atenolol given to patients who have or are at risk for coronary artery disease, during hospitalization for noncardiac surgery, has been shown to reduce deaths at 2 yr.[3] The present trial examined the perioperative period of these patients in detail to identify a possible cause for this reduction in deaths at 2 yr. We tested the hypothesis that prophylactic administration of the beta blocker atenolol reduces the incidence and severity of myocardial ischemia during the first perioperative week, and that such reduction is associated with long-term survival benefits.

Methods

Consent

This study was approved by the Committee for Human Research and performed with written informed consent from all patients. Two hundred patients at high risk for coronary artery disease who were scheduled to undergo noncardiac surgery at the San Francisco Veterans Administration Hospital were enrolled in this randomized, double-blinded, placebo-controlled clinical trial.

Study Criteria

Inclusion criteria required that patients (1) were scheduled for elective noncardiac surgery; (2) could sign informed consent before surgery; and (3) had definite coronary artery disease as indicated by previous myocardial infarction, typical angina, or atypical angina with electrocardiographic (ECG) changes indicative of ischemia in response to exercise or scintigraphic evidence of a myocardial perfusion defect; or, presence of the risk factor of previous or current vascular surgery, or presence of at least two of the following risk factors (in addition to male sex): aged ≥ 65 yr, hypertension, current smoking, serum cholesterol level ≥ 240 mg/dl, or diabetes mellitus. Previous myocardial infarction was defined as either a positive history (using the criteria of the Coronary Artery Surgery Study[17]) or ECG evidence of a previous myocardial infarction (using the Minnesota Code criteria[18]). Typical angina was defined as a history of chest pain with at least three of the following four characteristics: substernal location, precipitation by exercise or stress, duration of < 15 min, and resolution after rest or nitroglycerin treatment. Atypical angina required two of these characteristics in addition to an ischemic ECG response to exercise. Exclusion criteria included the presence of (1) left bundle branch block, (2) cardiac pacemaker dependency, or (3) marked resting ST-T wave abnormalities that precluded ECG interpretation.[6] All patients scheduled to undergo major noncardiac surgery requiring general anesthesia and a hospital stay, who qualified under the inclusion and exclusion criteria, were approached for consent. Major surgery included major vascular, intraabdominal, orthopedic, neurosurgical, intrathoracic, head and neck, and plastic procedures.

Study Evaluations

Before operation, after a detailed history and physical examination, we obtained complete blood cell counts, serum electrolyte levels, and 12-lead ECG with a rhythm strip. Three-channel Holter ECG monitoring was begun 24 h before surgery and continued for 7 days after operation. Three sets of blood pressure (systolic [SBP], diastolic [DBP], and mean arterial [MAP]) and heart rate (HR) measurements were obtained during the 24 h before surgery and averaged to establish baseline measurements.

Study Drug Administration

Patients were randomly assigned to one of two study groups (atenolol and placebo) by a computer-generated list compiled before the start of the study and retained by the hospital pharmacy. Both oral and intravenous preparations of active study drug (atenolol) and placebo were prepared by the hospital pharmacy, and both were labeled "study drug." All other beta blockers were withheld from patients in both the atenolol and placebo groups. On entry into the preoperative area, blood pressure was recorded using an automated cuff, and five-lead ECG monitoring (with display of leads II and V) was begun. Administration of study drug was begun 30 min before entry into the operating room. The study drug was delivered in two 5-ml syringes, both containing 5 mg atenolol or placebo. The study drug was withheld if the following conditions were present at the time of administration: (1) HR $<$ 55 beats/min, (2) SBP $<$ 100 mmHg, (3) current evidence of congestive heart failure, (4) third-degree heart block, or (5) an acute episode of bronchospasm. If the none of these conditions was present, the first syringe was infused over 5 min. The patient was then observed for 5 min and if none of these conditions developed, the second syringe was infused over 5 min.

After operation, the study drug was infused in the recovery room using the technique just described. No time limit for minimum case length was used. For 7 days thereafter, patients received study drug every 12 h using the same technique. If the patient could take oral medications, a tablet of atenolol (50 or 100 mg) or placebo was given twice daily. For patients with HRs $>$ 65 beats/min and SBP $>$ 100 mmHg, the 100-mg dose was given orally; for those with HRs between 55 and 65 beats/min and SBP $>$ 100 mmHg, the 50-mg dose was administered; and for those with HR $<$ 55 beats/min or SBP $<$ 100 mmHg, the study drug tablet was withheld. The oral study drug was administered by the nursing staff blinded to the patient's study group. Infusions of the study drug were given by research personnel blinded to the study drug and not involved in the patient's clinical care. The anesthesiologist providing clinical care was not allowed to observe the study drug infusion. Patient data were analyzed by intention to treat, not by actual drug or amount of drug administered.

Anesthetic Management

All patients received general anesthesia including endotracheal intubation. All preoperative medications were continued until the time of surgery, excluding beta blockers. If the patient was receiving a beta blocker before operation, it was discontinued and the randomized study drug was substituted. There were no other protocol-based restrictions of anesthetic technique. Postoperative analgesic management was not mandated but consisted of intramuscular, intravenous, or epidural administration of opiates.

Holter Electrocardiography

Patients were monitored using a three-channel AM Holter ECG recorder (Marquette Electronics, series 8500) before operation, during operation, and for 7 days after operation. Patients were monitored for at least 12 h after discontinuation of study drug administration. Three bipolar leads, CC5, CM5, and ML, were recorded using silver/silver chloride electrodes. Lead resistance was tested daily, and faulty leads (resistance greater than 5 kφ) were replaced. The effect of patient positional variation on ECG pattern was measured before the study in the supine, upright, and left and right lateral decubitus positions.

Holter ECG data were analyzed for ST segment deviation (Marquette laser Holter analysis system SXP software version 5.8) indicative of ischemia after all abnormal QRS complexes were excluded, such as ventricular ectopic beats and beats with conduction abnormalities. Then the ST segments were trended continuously in three leads for the duration of the tape. The baseline ST segment level was defined as the average ST segment during a stable period (usually 15–60 min) preceding each ischemic episode. All possible ischemic episodes were reviewed independently by two investigators blinded to patient randomization and clinical course.[6] Disagreements were resolved by consensus, and if consensus could not be reached, a third blinded investigator, unaware of the other two assessments, evaluated the data.

The ECG ischemic episodes were defined as reversible ST segment changes lasting at least 1 min and involving either a shift from baseline (adjusted for positional changes) of ≥ 0.1 mV of ST depression (with slope ≤ 0), or a shift from baseline of ≥ 0.2 mV of ST-T elevation at the J-point. ST segment depression was measured 60 msec after the J-point, unless that point fell within the T wave, in which case it was shortened to a minimum of J +40 msec. Holter analysis was corrected for positional variation by taking the maximum shift noted by positional changes. If positional changes during Holter setup caused a 0.05 mV of baseline shift, then the criteria for ischemia was increased by 0.05 mV. This technique decreases the sensitivity of Holter ECG detection of ischemia, because more episodes fail to make baseline, but it makes the results more specific. The following parameters were measured as indications of severity of each episode: (1) duration, (2) maximum ST change, (3) total area-under-the-curve (defined as the integral of ST depression in mV *vs.* time), and (4) heart rate (at 5 and 10 min before onset of an episode, at onset, at maximum ST change, at offset, and at maximum heart rate during an episode).[6]

Ischemic episodes were divided into two separate postoperative endpoints (days 0 - 2 and days 0 - 7) specified before the study began. The choice of emphasis on postoperative days (0 - 2) was guided by previous studies[19,20] by the SPI Research Group that found that ischemic episodes during this interval predominated and were associated with adverse events.

Dysrhythmia Analysis

Holter ECG data were analyzed for the occurrence of dysrhythmias using validated Marquette laser Holter analysis system software version 5.8. Ventricular and supraventricular ectopic complexes were identified and counted as isolated, bigeminal cycles, couplets, and runs. The beats in each run, beats in the longest run, rate of the longest run, beats in the fastest run, and rate of the fastest run were calculated. Minimum, average, and maximum heart rate values were calculated. Totals of each variable were calculated for the preoperative day and each postoperative day.

Twelve-lead Electrocardiograph

Twelve-lead ECGs were obtained before operation and daily for the first 7 days after surgery, on the 10th and 14th days, weekly thereafter, on the day of discharge, and whenever clinically indicated (by shortness of breath, chest pain, or syncope). The ECG data were checked at the time of acquisition by study investigators to determine if additional creatinine phosphokinase (CPK) samples were warranted. All ECG data were subsequently analyzed by two investigators unaware of clinical data. Minnesota codes I1 or 2 were used to identify new Q waves. Persistent changes in the ST-T waves were identified by Minnesota codes IV or V.[18]

Hemodynamics

Beginning 1 h before surgery and continuing until 1 h after surgery, SBP, DBP, MAP, and HR were recorded at least every 5 min using continuous five-lead ECG and noninvasive blood pressure monitoring. If blood pressure was measured invasively, the intra-arterial pressure was recorded as the study value. Episodes of hemodynamic abnormality were defined by prespecified criteria: SBP < 80 mmHg or > 180 mmHg; DBP < 50 mmHg or > 100 mmHg; HR < 50 beats/min or > 100 beats/min. An episode of hemodynamic abnormality was defined as two sequential recordings exceeding these limits.

Creatinine Phosphokinase with Myocardial Banding Measurements

Blood samples were obtained on postoperative days 1 and 5 for analysis of CPK and CPK with myocardial banding (CPK with MB). Additional CPK and CPK-MB samples were drawn if clinical condition or ECG changes suggested myocardial ischemia or infarction. (As noted before, all ECGs were checked by a study physician when obtained to determine whether additional CPK analysis was warranted.) The CPK concentrations were determined using the Kodak Ektachem (Rochester, NE) technique and CPK-MB using an Abbott (North Chicago, IL) IMX immunoassay at the hospital laboratory (San Francisco Veterans Administration Hospital). A CPK-MB isoenzyme concentration of 0.83 $mM \cdot l^{-1} \cdot s^{-1}$ (or 50 units/l) was chosen as the threshold for biochemical evidence of myocardial infraction.[6]

Cardiac Adverse Events

All definitions of cardiac adverse events were defined by protocol before the initiation of data collection. The diagnosis of myocardial infarction required: (1) a CPK-MB isoenzyme concentration greater than or equal to threshold (0.83 mmol per liter per second [or 50 units/liter]), and (2) either new Q waves (Minnesota Code I1 or 2), or persistent (4 days) changes in the ST-T wave (Minnesota Code IV or V), or autopsy evidence of acute infarction. Cardiac death was defined as death from

dysthymia, myocardial infarction, or congestive heart failure caused by a cardiac condition. Unstable angina required severe precordial chest pain that was nonsurgical, lasting ≥30 min, unresponsive to standard therapeutic maneuvers (nitroglycerin and rest), and associated with transient changes in the ST segment or T-wave without the development of Q waves or diagnostic enzyme abnormalities. Congestive heart failure required symptoms or signs of pulmonary congestion (shortness of breath and rales), signs of new left or right ventricular failure (cardiomegaly, S3, 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) treatment with diuretic agents. A diagnosis of ventricular tachycardia required five or more consecutive beats at a rate of at least 100 beats/min.[6,21]

The primary endpoints for the perioperative trial were defined as the incidence and severity of myocardial ischemia, occurring on postoperative days 0–2, detected using Holter ECG monitoring. Incidence was defined as the number of patients having at least one episode of ST segment change. Severity was defined by the six previously described criteria.[6] The secondary endpoints were the incidence and severity of myocardial ischemia on postoperative days 0–7. Safety endpoints included hypotension, bradycardia, bronchospasm, cardiac death, myocardial infarction, heart failure, and life-threatening dysrhythmia. Differences in hemodynamics and requirements for inotropic, vasopressor, or anticholinergic support were recorded. Safety endpoints were validated by two investigators blinded to patient study group and monitoring data.

Two-year follow-up techniques were described previously,[3] and the same definitions and outcomes are used for this analysis.

Statistics

Power analysis was performed before the study was begun to determine sample size for Holter-detected myocardial ischemia as the outcome variable. The study was designed to have 80% power to detect a 50% reduction the incidence of myocardial ischemia detected by Holter ECG during postoperative days 0–2. The expected incidence of myocardial ischemia in this patient population was 40%.[6]

Continuous variables were compared using analysis of variance. Results were confirmed using nonparametric statistics (Kruskal-Wallis test) when appropriate. Incidence was compared using Fisher's exact test (two tailed). Survival analysis was performed with Kaplan-Meier estimated mortality. All values are presented as mean values ± SD. A level of significance was specified as $P \leq 0.05$ before the study began. No corrections were done for multiple comparisons. Analyses were performed using Statistical Analysis System software (version 6.12; SAS Institute, Cary, NC).

Table 1. Patient Demographics

No. of Patients	Atenolol (n = 99)	Placebo (n = 101)	*P* Value*
Cardiac history			
Definite CAD	36	42	0.38
Previous MI	18	26	0.26
Previous CABG	11	17	0.31
Previous PTCA	1	3	0.30
Typical angina	25	36	0.13
History of dysrhythmia	13	13	1.00
History of CHF	9	7	0.61
Cardiac risk factors			
Current smoking	35	38	0.77
Hypertension	71	60	0.075
Cholesterol ≥ 240 mg/dl	10	6	0.31
Diabetes mellitus	28	35	0.36
Age ≥ 65 yr	65	75	0.22
Preoperative medications			
Antidysrhythmic	0	3	0.25
β blocker	18	8	0.020†
Atenolol	4	2	0.44
Calcium channel blocker	22	34	0.11
Diuretics	28	17	0.042†
Antihypertensive	30	19	0.048†
Digoxin	6	10	0.44
Nitrates	8	13	0.36
Age (yr)	68 ± 8.6	67 ± 10.2	0.11
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

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CAD = coronary artery disease; MI = myocardial infarction; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; CHF = congestive heart failure.

* Fisher's Exact Test (two-tailed).

† Statistically significant at $P \leq 0.05$.

Results

Demographics

The two study groups (atenolol and placebo) had similar demographic characteristics (table 1), except for a

Table 2. Intraoperative Hemodynamics

	Atenolol (n = 99)	Placebo (n = 101)	*P* Value*
Systolic blood pressure < 80 mmHg	13	16	0.69
Systolic blood pressure > 180 mmHg	32	42	0.19
Diastolic blood pressure < 50 mmHg	38	37	0.88
Diastolic blood pressure > 100 mmHg	25	31	0.43
Heart rate < 40 bpm	4	2	0.44
Heart rate < 50 bpm	38	15	0.0002†
Heart rate > 100 bpm	35	54	0.019†

* Fisher's Exact Test (two-tailed).

† Statistically significant at $P \leq 0.05$.

Table 4. Holter Detected Arrhythmias for Postoperative Days 0–7

	Atenolol (mean)	Placebo (mean)	*P* Value*
Duration (s)	76,435	78,951	0.12
QRS complexes	88,573	107,819	0.0001†
Ventricular ectopics	824	979	0.61
Supraventricular ectopics	1,234	1,386	0.72
Minimal heart rate (bpm)	50	59	0.0001†
Average heart rate (bpm)	75	87	0.0001†
Maximal heart rate (bpm)	113	130	0.0001†

Data are averages over postoperative days 0–7 given per 24-h recording period.

* ANOVA.

† Statistically significant at $P \leq 0.05$.

significantly higher incidence of chronic preoperative beta blocker and antihypertension therapy on hospital admission in the atenolol group (table 1). The types of operations included major vascular, intra-abdominal, orthopedic, neurosurgical, intrathoracic, head and neck, and other general or plastic surgery (table 1). These population data were presented in the 2-yr follow-up manuscript[3] but are included here for completeness.

Hemodynamics

Intraoperative bradycardia (HR <50 beats/min) was more common in atenolol-treated patients, and intraoperative tachycardia (HR >100 beats/min) was less common (table 2). There was no difference between groups in the incidence of severe bradycardia (HR <40 beats/min; table 2). There also was no difference between groups in the administration of atropine to treat bradycardia, or ephedrine, phenylephrine, dopamine, or epinephrine to treat hypotension (table 3).

Table 3. Intraoperative Cardiovascular Medications

	Atenolol (n = 99)	Placebo (n = 101)	*P* Value*
Dopamine	0	1	1.0
Epinephrine	0	1	1.0
Phenylephrine	5	4	0.74
Ephedrine	8	7	0.79
Atropine	2	1	0.61

* Fisher's Exact Test (two-tailed).

Analysis of Dysrhythmia

Holter ECG data were available, on average, for 78% of the 8-day recording interval (1 day before and 7 days after operation), and all patients (200) had 48 h of postoperative Holter data. The percentages of available and interpretable Holter data were day 0-1, 100%; days 2-3, 87%; days 4-5, 68%; and days 6-7, 49%. Thus the daily incidence data represent day 0-1, 200 patients; days 2-3, 174 patients; days 4-5, 137 patients; and days 6-7, 98 patients. Because some patients dropped out of the study early, the data represent the incidence figures for the available data. There was no difference in the frequency of missing or unanalyzable data between the placebo and control groups.

Analysis of preoperative, intraoperative, and postoperative Holter ECG data did not demonstrate any significant differences between groups for any measure of ventricular or supraventricular ectopy, including the number of isolated ectopic beats, bigeminal cycles, couplets, runs, beats in a run, beats in the longest run, beats in the fastest run, and the rates of the longest and fastest runs. However, during the 7 postoperative days, atenolol-treated patients had significantly lower minimum, average, and maximum heart rates (table 7). The number of QRS complexes in the atenolol group was significantly lower than that in the placebo group because of a lower average heart rate.

Myocardial Ischemia

Before and during operation there were no group differences in the incidence of myocardial ischemia (table 5). However, patients given atenolol had a 50%

Table 5. Incidence of Holter Detected 1 mm ST Depression Lasting at Least 1 min

	Atenolol (n = 99)	Placebo (n = 101)	*P* Value*
Preoperative	13	12	0.79
Operative	12	18	0.26
Postoperative days 0–7	24	39	0.03†
Postoperative days 0–2	17	34	0.008†

* Fisher's Exact Test (two-tailed).

† Statistically significant at $P \leq 0.05$.

lower incidence of myocardial ischemia during the first 48 h after operation (atenolol, 17 compared with placebo, 34 patients; $P = 0.008$) and a 40% lower incidence during postoperative days 0–7 (atenolol, 24 compared with placebo, 39 patients; $P = 0.03$; table 5). There was no difference in the severity of ischemic episodes as assessed by any of the six measures of ischemic episode severity (table 6). Heart rate before an episode was lower in the atenolol group (atenolol, 82 ± 14 beats/min compared with placebo, 94 ± 16 beats/min; $P = 0.0027$), as was the maximum heart rate during an ischemic episode (atenolol, 100 ± 20 beats/min compared with placebo, 113 ± 20 beats/min; $P = 0.0043$).

The association between perioperative ischemia and mortality during the 2 yr after surgery can be seen in figures 1 and 2. Figure 1 shows that of the 200 patients enrolled in the trial, 78 (atenolol 31 and placebo 47) had at least one episode of myocardial ischemia during the period of recording (before, during, and after operation). Of the 78 patients who had an episode of myocardial ischemia, 20 (26%) died in the next 2 yr after surgery (atenolol, 6; placebo, 14). Of the 122 patients without an episode of ischemia during the recording period, 16 (13%) died during the next 2 yr. An episode of myocardial ischemia at any time during the perioperative period (before, during, and after operation) increased the incidence of death during the 2 yr after surgery ($P = 0.025$). An episode of myocardial ischemia during postoperative days 0–2 increased the relative risk of death during the next 2 yr (relative risk = 2.06; 95% CI = 1.04–4.06; fig. 2).

Table 6. Severity of ST Depression Lasting at Least 1 min

	Atenolol (n = 24)	Placebo (n = 39)	*P* Value*
Total episodes (per patient with an episode)	3.8 ± 3.7	5.9 ± 6.7	0.15
Maximal ST elevation (mV)	3.0 ± 2.0	2.5 ± 1.2	0.29
Total duration of episodes (min)	230 ± 358	282 ± 369	0.59
Duration of longest episode (min)	148 ± 317	109 ± 124	0.50
Total area under the curve (AUC) (mV/s)	286 ± 439	480 ± 964	0.36
Maximal AUC (mV/s)	161 ± 244	1,173 ± 300	0.87
Heart rate prior to episode (bpm)	82 ± 14	94 ± 16	0.003†
Maximal heart rate during episode (bpm)	100 ± 20	115 ± 20	0.004†

Values are mean ± SD.

* ANOVA.

† Statistically significant at $P \leq 0.05$.

In-hospital Safety Endpoints

As expected because of low event rates, there was no difference between the two treatment groups in the incidence of in-hospital cardiac death (atenolol, 1 compared with placebo, 2 patients; $P = 1.0$), noncardiac death (atenolol, 3 compared with placebo, 0; $P = 0.12$), myocardial infarction (atenolol, 1; placebo, 2; $P = 1.0$), unstable angina (atenolol, 0; placebo, 0), congestive heart failure (atenolol, 9; placebo, 7; $P = 0.61$), ventricular tachycardia (atenolol, 2; placebo, 3; $P = 1.0$), or stroke (atenolol, 4; placebo, 1; $P = 0.21$).

Discussion

This study shows that the incidence of postoperative myocardial ischemia can be reduced by available (and inexpensive) pharmacologic means. Specifically, perioperative atenolol administration, begun 30 min before anesthesia is induced and continued for 7 days after operation, reduces by 30–50% the incidence of postoperative myocardial ischemia and significantly reduces heart rate before and during ischemic episodes. Safety findings indicate that prophylactic perioperative administration of atenolol for 1 week to patients at high risk for cardiac complications and death who are having noncardiac surgery is safe and does not increase the incidence of bronchospasm, hypotension, severe bradycardia, or dysrhythmia. Finally, patients who have at least one episode of myocardial ischemia during the perioperative period are more likely to die in the next 2 yr, a finding that likely explains the long-term survival benefits we recently reported.[3]

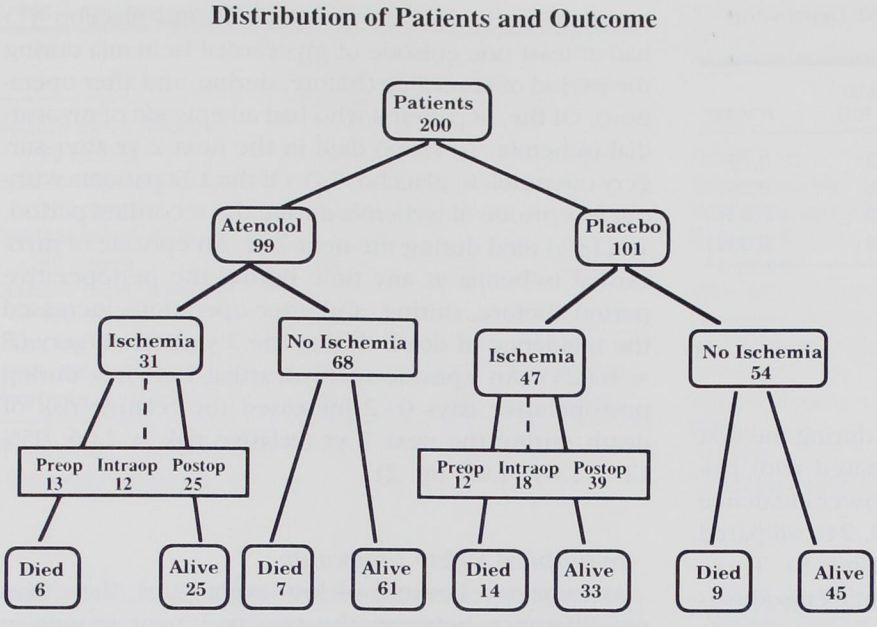

Fig. 1. Distribution of patients and 2-yr survival. Patient are separated by assignment to the atenolol or placebo groups, presence or absence of ischemia during the preoperative, intraoperative, or postoperative recording periods, and 2-yr survival.

Perioperative ST Segment Changes

What is the significance of perioperative ST changes? The criteria used in this study are identical to those used by Mangano *et al.*,[6] and such episodes are associated with a 2.8-fold increase in the odds of all adverse cardiac outcomes (95% CI, 1.6–4.9) and a 9.2-fold increase in the odds of a cardiac adverse event (95% CI, 2–42.0),[6] defined as cardiac death, nonfatal myocardial infarction, and unstable angina during the original hospitalization. Furthermore, patients with such postoperative ischemic episodes have been previously shown to have a twofold decrease in event-free survival during 2-yr follow-up, with survival decreasing from 93% to 78%, compared with patients with no episodes of myocardial

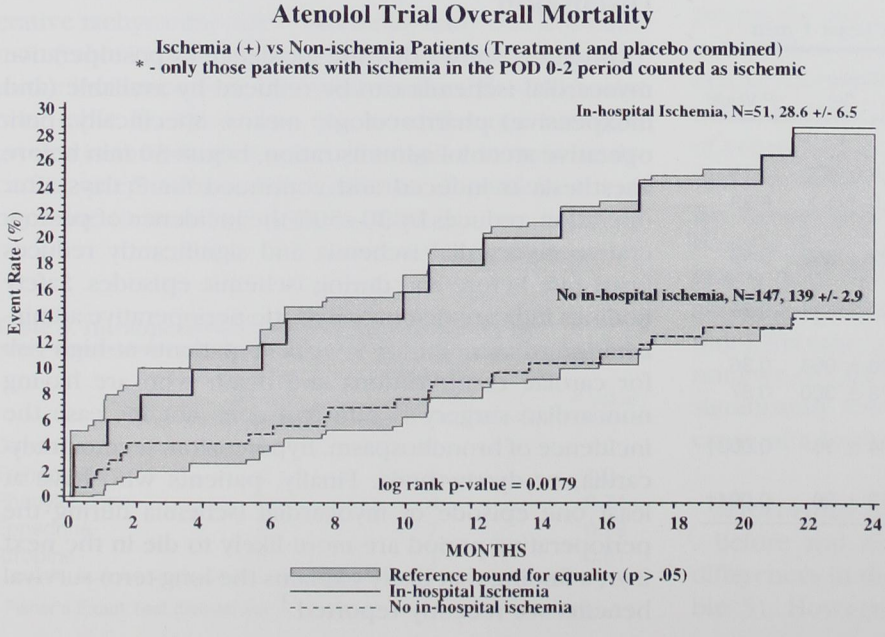

Fig. 2. Kaplan-Meier event curves for death. Patients were separated into presence or absence of ischemia during the preoperative, intraoperative, or postoperative recording periods. The atenolol and placebo groups are combined.

ischemia.[5] The present study confirmed the association between an episode of perioperative myocardial ischemia and reduction in 2-yr survival.

Is it possible to reduce the incidence of myocardial ischemia? We found that perioperative atenolol given for 1 week after operation reduces the incidence of myocardial ischemia during administration, extending the results of other trials that showed a reduction in perioperative ischemia in patients given perioperative beta blockers.[22,23]

What is the effect of reducing the incidence of myocardial ischemia? For patients not having surgery, reducing the incidence of Holter-detected myocardial ischemia reduces adverse outcomes.[16] For patients having surgery, episodes of myocardial ischemia are clearly associated with increases in adverse outcomes.[5,6,24] Our previous report of these patients documented that perioperative atenolol given for 1 week reduces the incidence of death, cardiac death, and serious cardiac complications in the ensuing 2 yr.[3] This report confirms our earlier finding that episodes of myocardial ischemia increase the risk for cardiac complications. It also suggests that atenolol-induced reductions in ischemia may account for our observed long-term reductions in cardiac complications and death. However, we cannot exclude the possibility that other factors may also contribute to the long-term effects. Atenolol may cause a reduction in some type of myocardial injury not identified by this study that contributes to the reduction in death at or after 2 yr.

Sample Size

Our study was designed with sufficient power to detect a difference in the incidence and severity of myocardial ischemia detected by Holter ECG monitoring. It was not designed to detect differences in in-hospital clinical outcomes (death, myocardial infarction, unstable angina, congestive heart failure, or ventricular tachycardia). The in-hospital death rate in our study population was 3%. To have a 80% chance of detecting a 50% reduction in an event with an incidence of 3% would require 1,541 patients per group. Thus our finding of no difference in in-hospital endpoints indicates merely that no difference was detected, not the absence of a difference.

Side Effects

There were no detectable increases in side effects commonly associated with beta blocker use (third-degree heart block, hypotension, bronchospasm, or congestive heart failure)[25] in our patients despite the presence of significant cardiac and pulmonary disease. The average heart rate in the atenolol-treated group, although lower than that in the control group, was not associated with severe bradycardia. Thus patients in the atenolol-treated group did not appear to have profound[26] beta blockade, yet the therapy was still efficacious. We chose the dose regimen for atenolol based on the ISIS[13] data demonstrating efficacy for preventing death after myocardial infarction. A dose-response relation was not defined and thus further investigations should be done to establish the correct level of beta blockade for specific subsets of patients to allow maximum protection with minimal side effects.

Limitations

We measured 21 preoperative historical and clinical variables and found a trend toward more patients with preoperative hypertension in the atenolol-treated group (table 1), as well as more patients treated with long-term beta blockers, diuretics, and anti-hypertensive drugs. It is unclear if this difference implies that these patients were more compromised or were more aggressively managed than those in the control group.

All preoperative cardiac medications, excluding beta blockers, were continued before operation. All long-term preoperative beta blocker therapy was discontinued and replaced by study drug. Thus beta blocker withdrawal may have occurred in the eight patients in the placebo group in whom preoperative beta blockade was discontinued. However, there were no identifiable differences in DBP, SBP, MAP, or HR during the operative period, or in Holter ECG data during the operative and postoperative periods in these patients at risk for beta blocker withdrawal. Further, excluding all patients receiving preoperative beta blockade from the analysis does not alter the results: Atenolol reduced the incidence of myocardial ischemia during postoperative days 0–2 (atenolol, 9; placebo, 32; $P < 0.001$) and days 0–7 (atenolol, 16; placebo, 37; $P = 0.004$).

Considering the long-term follow-up, in the placebo group, one death occurred in the 2 yr after surgery among the eight patients (13%) taking long-term beta-blockers, and 11 deaths occurred among the 91 patients (11%) not taking beta-blockers. For the atenolol group, 1 of 18 patients (6%) receiving beta-blockers, compared with 3 of 75 patients (4%) not receiving beta-blockers, died. These findings suggest that beta-blocker discontinuation in the placebo group patients did not confound the results.

Heart rate before an episode of ischemia was lower in the atenolol group (atenolol, 82 beats/min; placebo, 94 beats/min; $P = 0.003$; table 7). The minimum, average, and maximum HRs during the entire postoperative week were also lower in the atenolol group (table 5). These findings could suggest several hypotheses. (1) Atenolol lowers the HR at which patients become ischemic. This hypothesis is unlikely given the long-term survival benefits of beta-blockers.[14-16,27] (2) Fifty percent or more of ischemic episodes are independent of HR. (3) The present atenolol dose regimen failed to reduce HR enough to suppress all rate-dependent ischemia. (4) The reduced HR observed before ischemic episodes is merely an artifact of lower heart rates in one study group. Nonetheless, atenolol effectively reduced the incidence of myocardial ischemia in the first postoperative week.

Conclusions

Perioperative administration of atenolol for 1 week to noncardiac surgical patients at high risk for cardiac morbidity is safe and reduces the incidence of in-hospital postoperative myocardial ischemia. Patients without episodes of ischemia had lower rates of death at or after 2 yr. Thus our observed reductions in perioperative ischemia may explain the reductions in death at 2 yr and cardiac complications by perioperative atenolol administration.

The authors thank the investigators of the Ischemia Research and Education Foundation who contributed to the design, analysis, and publication of this manuscript, and Winifred Von Ehrenburg for editorial assistance.

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, Layug EL, Wallace A, Tateo I, McSPI: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 1996; 335:1713-20

4. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, Burke DS, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Carabello B, Slater EE: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977; 297:845-50

5. Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM: Long-term cardiac prognosis following noncardiac surgery. JAMA 1992; 268:233-9

6. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990; 323:1781-8

7. Knothe C, Boldt J, Zickmann B, Ballesteros M, Haufler G, Bruns F, Hempelmann G: Kardioprotektion bei herzchirurgischen Eingriffen durch prophylaktische Medikamentengabe vor extrakorporaler Zirkulation. Untersuchungen mit Troponin T als Parameter fur perioperative Myokardschaden. [Cardiac protection in heart surgery interventions by preventive drug administration before extracorporeal circulation. Studies with troponin T as a parameter for perioperative myocardial damage]. Herz 1993; 18:379-86

8. Gallagher JD, Moore RA, Jose AB, Botros SB, Clark DL: Prophylactic nitroglycerin infusions during coronary artery bypass surgery. ANESTHESIOLOGY 1986; 64:785-9

9. Hannes W, Seitelberger R, Christoph M, Keilich M, Kulinna C, Holubarsch C, Fasol R: Effect of peri-operative diltiazem on myocardial ischaemia and function in patients receiving mammary artery grafts. Eur Heart J 1995; 16:87-93

10. Dupuis JY, Nathan HJ, Laganiere S: Intravenous nifedipine for prevention of myocardial ischaemia after coronary revascularization. Can J Anaesth 1992; 39:1012-22

11. Trubel W, Zwoelfer W, Moritz A, Laczkovics A, Haider W: Cardioprotection by nifedipine cardioplegia during coronary artery surgery. Eur J Anaesthesiol 1994; 11:101-6

12. Lievre M, Boissel JP: Antagonistes calciques et ischemie ou ischemie/reperfusion myocardiques. [Calcium channel antagonists and myocardial ischemia or ischemia/reperfusion]. Arch Mal Coeur Vaiss 1993; 86(4):91-8

13. First International Study of Infarct Survival Collaborative Group. Mechanisms for the early mortality reduction produced by beta-blockade started early in acute myocardial infarction: ISIS-1. ISIS-1 Lancet 1988; 1:921-3

14. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction. Patients and methods. Am J Cardiol 1985; 56:3G-9G

15. Wikstrand J, Warnold I, Tuomilehto J, Olsson G, Barber HJ, Eliasson K, Elmfeldt D, Jastrup B, Karatzas NB, Leer J, et al: Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY Study. Hypertension 1991; 17:579-88

16. Pepine CJ, Cohn PF, Deedwania PC, Gibson RS, Handberg E, Hill JA, Miller E, Marks RG, Thadani U: 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

17. Manual of operations II: data collection and storage: Collaborative studies in coronary artery surgery. Washington, DC, National Heart, Lung, and Blood Institute, 1978

18. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S: The electrocardiogram in population studies: A classification system. Circulation 1960; 21:1160-75

19. Mangano DT: Myocardial ischemia following surgery: Preliminary findings. J Card Surg 1990; 5:288-93

20. Mangano DT, Hollenberg M, Fegert G, Meyer ML, London MJ, Tubau JF, Krupski WC: 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

21. O'Kelly B, Browner WS, Massie B, Tubau J, Ngo L, Mangano DT: Ventricular arrhythmias in patients undergoing noncardiac surgery. JAMA 1992; 268:217-21

22. Podesser B, Schwarzacher S, Zwolfer W, Binder TM, Spatt J,

Peschl F, Huber S, Seitelberger R: Combined perioperative infusion of nifedipine and metoprolol provides antiischemic and antiarrhythmic protection in patients undergoing elective aortocoronary bypass surgery. Thorac Cardiovasc Surg 1993; 41:173–9

23. Stone JG, Foex P, Sear JW, et al: Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. ANESTHESIOLOGY 1988; 68:495

24. Fleisher LA, Nelson AH, Rosenbaum SH: Postoperative myocardial ischemia: etiology of cardiac morbidity or manifestation of underlying disease? J Clin Anesth 1995; 7:97–102

25. Duffy M: Physicians' desk reference. Oradell, NJ, Medical Economics Company, 1992, pp 1105–10

26. First International Study of Infarct Survival Collaborative Group: Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. Lancet 1986; 2:57–66

27. First International Study of Infarct Survival) Collaborative Group. Mechanisms for the early mortality reduction produced by beta-blockade started early in acute myocardial infarction: ISIS-1. ISIS-1 Lancet 1988; 1:921–3