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, 192 of these were followed for two years. Overall mortality after discharge from the hospital was significantly lower 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.)

©1996, Massachusetts Medical Society.
agreed to participate in the study, 200 were enrolled and under-
than 1 patient per day was enrolled, and of the 204 patients who
Survival
spasm (as defined in the first International Study of Infarct
of congestive heart failure, third-degree heart block, or broncho-
heart rate was below 55 or the systolic blood pressure was below
65 and the systolic blood pressure was 100 mm Hg or higher, one
given orally; if the heart rate was 55 or higher but no higher than
given daily. If the heart rate was above 65 beats per minute and
radioartery, the intravenous administration of the study drug was
continued to be met, the second syringe was infused over a period
observed for an additional five minutes, and if the criteria con-
drug was infused over a period of five minutes, the patient was
operative procedure was recorded. Thirty minutes before entry into the
recorded with an automated cuff, and a five-lead continuous elec-
ated, randomized list that was retained only by the pharmacy
oral preparations of the active drug (atenolol) and placebo were
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-gen-
erated, 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 preparative area, their blood pressure was
recorded with an automated cuff, and a five-lead continuous elec-
trocardiogram 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 broncho-
4
spasm (as defined in the first International Study of Infarct Survival20). 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 con-
tinued 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 cli-
nician was allowed to observe administration of the study drug
either before or after surgery.

METHODS

Study Population

Eligible patients were those with or at risk for coronary artery
disease who were scheduled for elective noncardiac surgery re-
quiring general anesthesia at the San Francisco Veterans Affairs
Medical Center. The presence of coronary artery disease was in-
dicated 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.34 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 under-
went 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 sur-
gery, 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-gen-
erated, 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 preparative area, their blood pressure was
recorded with an automated cuff, and a five-lead continuous elec-
trocardiogram 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 broncho-
spasm (as defined in the first International Study of Infarct Survival20). 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 con-
tinued 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 cli-
nician was allowed to observe administration of the study drug
either before or after surgery.

Clinical Care

All patients underwent general anesthesia with endotracheal in-
tubation; 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 restric-
tions of anesthetic or surgical technique, and clinical decisions
were not controlled by the study protocol. Perioperative informa-
tion, which was recorded and analyzed for outcomes, consisted of
variables, including the type and duration of surgery, the anesthetic
methods and medications, hemodynamic variables, electrocardio-
graphic 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 per-
formed after he received the study drug. Six months, one year, and
two years after surgery, study physicians conducted scheduled eval-
uations 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 fail-
ure caused primarily by a cardiac condition. The diagnosis of my-
ocardial infarction required at least one of the following: develop-
ment 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 hospitaliza-
tion with an elevation of total creatine kinase and creatine kinase
MB isoenzyme values; evidence at autopsy of acute myocardial in-
faction; or documentation of myocardial infarction in the hospi-
tal 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 con-
gestive 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 S1
sound, jugular venous distention, and peripheral edema), abnor-
mal results on chest radiography (vascular redistribution, intersti-
tial edema, and alveolar edema), and a change in medication in-
volving at least the institution of treatment with diuretic agents.4

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 out-
come variable combined myocardial infarction, unstable angina
or congestive heart failure requiring hospital admission and clin-
ical diagnosis and treatment, myocardial revascularization (coro-
nary-artery bypass graft surgery or percutaneous transluminal cor-
ony angioplasty), and death. Autopsy data, if available for patients
who died during the two-year period, were reviewed at the cen-
tral laboratory (at the Ischemia Research and Education Founda-
tion) by a pathologist who was blinded to the patients’ treatment
assignments.

Statistical Analysis

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

Copyright © 1996 Massachusetts Medical Society. All rights reserved.
ischemia\textsuperscript{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,\textsuperscript{22} after we first verified that the assumption of the hazards model was valid.\textsuperscript{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.

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).
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).

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 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).

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.

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

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariable models</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.4 (0.2–0.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.1 (1.4–6.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Oral hypoglycemic treatment</td>
<td>2.6 (1.1–6.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Insulin treatment</td>
<td>2.6 (1.0–6.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ischemia on Holter monitoring</td>
<td>2.3 (1.0–5.3)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Multivariable models</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.8 (1.4–6.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0.5 (0.2–1.1)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*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.

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.
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. 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). 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, 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. 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 3. Use of Cardiovascular Medications before and after Surgery, According to Study Group.***

<table>
<thead>
<tr>
<th>Study Period</th>
<th>No. with Data</th>
<th>Beta-Blockers</th>
<th>Calcium-Channel Blockers</th>
<th>Nitrates</th>
<th>ACE Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATENOLOL PLACEBO</td>
<td>ATENOLOL PLACEBO</td>
<td>ATENOLOL PLACEBO</td>
<td>ATENOLOL PLACEBO</td>
<td>ATENOLOL PLACEBO</td>
</tr>
<tr>
<td>Before admission</td>
<td>99</td>
<td>101</td>
<td>19.4</td>
<td>8.2</td>
<td>0.02†</td>
</tr>
<tr>
<td>At hospital discharge†</td>
<td>95</td>
<td>99</td>
<td>14.0</td>
<td>7.1</td>
<td>0.12</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>93</td>
<td>91</td>
<td>13.8</td>
<td>8.3</td>
<td>0.27</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>90</td>
<td>85</td>
<td>16.7</td>
<td>13.7</td>
<td>0.61</td>
</tr>
<tr>
<td>At 24 mo</td>
<td>84</td>
<td>78</td>
<td>15.5</td>
<td>13.9</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*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 nitrates 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).
perioperative myocardial ischemia and outcomes at six months (short-term results) and one year (intermediate results). 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, 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. 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-

### Table 4. Daily Dose and Side Effects of Atenolol.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>BEFORE SURGERY</th>
<th>AFTER SURGERY</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doses†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage‡</td>
<td>Full dose</td>
<td>69</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Half dose</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Not treated</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>Systolic BP &lt; 90 mm Hg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;20% decrease in systolic BP</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia§</td>
<td>Heart rate &lt; 40 bpm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;20% decrease in heart rate</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia and hypotension</td>
<td>Systolic BP &lt; 90 mm Hg and heart rate &lt; 40 bpm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;20% decrease in heart rate and systolic BP</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bronchospasm¶</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*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.
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.5-5 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.3,4,9,10,24,26 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 unproven 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 × 2 percent reduction in mortality × 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.

Supported by the Ischemia Research and Education Foundation.

**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**

17. Merin RG. Calcium channel blocking drugs and anesthetics: is the drug interaction beneficial or detrimental? Anesthesiology 1987;66:111-3.
CORRECTION

Effect of Atenolol on Mortality and Cardiovascular Morbidity after Noncardiac Surgery

Effect of Atenolol on Mortality and Cardiovascular Morbidity after Noncardiac Surgery. On page 1718, two lines from the bottom of the right-hand column, and on page 1719, in the sixth line of the left-hand column, Table 3 should have been cited, not Table 4. We regret the error.