Perioperative \( \beta \)-blocker withdrawal and mortality in vascular surgical patients

Jonathan B. Shammash, MD, a Jeffrey C. Trost, MD, f, Julie M. Gold, BA, b Jesse A. Berlin, ScD, c Michael A. Golden, MD, d and Stephen E. Kimmel, MD, MS e New York, NY, and Philadelphia, Pa

Objective Our purpose was to determine the effect of postoperative \( \beta \)-blocker withdrawal on mortality and cardiovascular events after vascular surgery.

Methods Detailed data were collected on perioperative cardiovascular medication use and discontinuation and cardiovascular risk factors among consecutive major vascular surgical procedures at two university hospitals.

Results A total of 140 patients received \( \beta \)-blockers preoperatively. Mortality in the 8 patients who had \( \beta \)-blockers discontinued postoperatively (50%) was significantly greater than in 132 patients who had \( \beta \)-blockers continued (1.5%, odds ratio 65.0, \( P < .001 \)). The effect of \( \beta \)-blocker discontinuation was unaffected by adjustment by stratification for risk factors (all \( P \leq .01 \)), for contraindications to restarting \( \beta \)-blockers (\( P = .006 \)), and by multivariable analyses adjusting for potential confounders (adjusted odds ratio 17.0, \( P = .01 \)). \( \beta \)-Blocker discontinuation also was associated with increased cardiovascular mortality (0% vs 29%, \( P = .005 \)) and postoperative myocardial infarction (odds ratio 17.7, \( P = .003 \)).

Conclusion Discontinuing \( \beta \)-blockers immediately after vascular surgery may increase the risk of postoperative cardiovascular morbidity and mortality. (Am Heart J 2001;141:148-53.)
compared with coronary artery bypass surgery patients. The aim of our study was to examine the impact of postoperative β-blocker withdrawal on mortality and cardiovascular events in vascular surgical patients.

Methods
Study population
A list of consecutive vascular surgical patients at a university hospital (University of Pennsylvania Medical Center) between January 1, 1995, and September 30, 1995, was obtained by a computerized search of the medical records system with use of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) procedure codes, which included endarterectomy (38.1), resection of vessel with anastomosis or replacement (38.2), other shunt or vascular bypass (38.3), revision of vascular procedure (38.4), and other repair of vessels (38.5). Surgeries were excluded if they were associated with a lower level of cardiac risk (posttraumatic, postcomplication, and hemodialysis access procedures) or with a higher level of cardiac risk (any surgery requiring cardiopulmonary bypass).

A similar list of consecutive vascular surgical patients was derived at a second university hospital (New York Presbyterian Hospital–Weill Cornell Center) for patients undergoing the above procedures, excluding carotid endarterectomy, in 1997 and 1998. Carotid endarterectomy was excluded in the second retrospective cohort of patients because these patients were found to have a lower incidence of cardiac events in the first cohort and because experts consider carotid endarterectomy to be surgery associated with intermediate cardiac risk, versus aortic, other major vascular, and peripheral vascular surgery, which are considered high-risk procedures. The list was then reviewed along with Department of Pharmacy data for β-blocker administration, and patients were included if they received preoperative β-blockers.

Data collected
Data were collected to allow assessment of the patients’ postoperative cardiac risk. These factors included a history of known coronary artery disease, previous MI, angina pectoris, congestive heart failure (CHF), hypertension, and history of diabetes mellitus requiring therapy (Table I). These risk factors were considered present only if they were documented in the patient’s medical record.

Data regarding the administration of β-blockers, calcium-channel antagonists, and angiotensin-converting enzyme inhibitors also were collected. Medications on admission were defined as those taken as an outpatient on a long-term basis. Inpatient preoperative medications included those given from admission up to the time of surgery. Postoperative medications included all doses from the time the patient left the operating room until discharge or the 30th postoperative day.

Exposure
Perioperative withdrawal of β-blocker therapy was defined as a patient treated with β-blockers before surgery (at least up to within 1 day of the procedure) who did not receive the medication postoperatively. Possible contraindications to postoperative β-blocker readministration were also measured in all patients (those with and those without β-blocker discontinuation). Those possible contraindications (postoperative CHF, need for postoperative vasopressor administration, or bradyarrhythmia requiring therapy or medication withdrawal) were considered present if they occurred in the postoperative period before β-blocker readministration in patients who had β-blockers restarted. The contraindications to β-blocker administration were considered present at any time postoper-
Cardiac mortality* 0 (0) 2 (28.6) —

P

One patient having *OR not calculable because no events in the unexposed group.

Any death or MI 10 (7.6) 5 (62.5) 20.2 (3.2-142)

P

All cause mortality 2 (1.5) 4 (50) 65.0 (6.3-815)

P

Event continued discontinued OR (95% CI) significance

P

MI† 7 (5.3) 4 (50) 17.7 (2.6-113)

P = .003

Table II. Effect of β-blocker discontinuation on outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>β-Blockers continued</th>
<th>β-Blockers discontinued</th>
<th>Unadjusted OR (95% CI)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>2 [1.5]</td>
<td>4 [50]</td>
<td>65.0 [6.3-815]</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Cardiac mortality*</td>
<td>0 [0]</td>
<td>2 [28.6]</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>MI†</td>
<td>7 [5.3]</td>
<td>4 [50]</td>
<td>17.7 [2.6-113]</td>
<td>P = .005</td>
</tr>
<tr>
<td>Any death or MI</td>
<td>10 [7.6]</td>
<td>5 [62.5]</td>
<td>20.2 [3.2-142]</td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>

* OR not calculable because no events in the unexposed group.
† One patient having β-blockers restarted after infarction considered “discontinued.” One patient with intraoperative MI was excluded.

Results
Prevalence of β-blocker administration and discontinuation
Sixty-one of 222 vascular surgical patients (27%) in the first cohort were receiving β-blockers before surgery. Fifty-five patients had documented use of β-blockers as outpatients and the other 6 received β-blockers in the inpatient preoperative period. β-Blockers were discontinued in 6 (10%) of 61 patients who received β-blockers preoperatively.

All 79 patients in the second cohort received preoperative β-blockers (by design). β-Blockers were discontinued in 2 (2.5%) patients.

Patient demographics and surgery type
Of the 140 patients receiving β-blockers preoperatively, 30 underwent carotid endarterectomy (21%), 34 abdominal aortic aneurysm repair (24%), 73 peripheral arterial surgery (52%), and 3 other major vascular surgeries (2%). The prevalence of risk factors for postoperative cardiac events or possible contraindications to β-blocker readministration are listed in Table I. Patients in this vascular surgery cohort had an expected high prevalence of hypertension, prior MI, angina, advanced age, and diabetes mellitus. Patients who had β-blockers discontinued did not have statistically significant differences with respect to age, history of MI, angina, diabetes mellitus, CHF, and bradycardia. Patients who had β-blockers discontinued had a higher prevalence of relative contraindications to restarting β-blockers postoperatively. No patients with β-blocker discontinuation had a history of asthma, chronic obstructive pulmonary disease, or ventricular arrhythmia requiring therapy.

Postoperative β-blocker discontinuation and outcomes
The overall mortality incidence was 3.6%, with 10 deaths in 275 patients. Among those patients receiving β-blockers preoperatively, there were 6 deaths (4.3%). There were 5 deaths in patients who underwent periph-
eral arterial revascularization, and 1 death in a patient undergoing thoracic abdominal aortic aneurysm repair. Two deaths were cardiac related; both occurred in patients who underwent peripheral arterial revascularization and both were confirmed at autopsy by evidence of acute MI. Eleven patients who received β-blockers preoperatively had postoperative nonfatal MIs (7.9%). One patient receiving β-blockers preoperatively in the first cohort had evidence of MI occurring preoperatively (an elevated creatine kinase with elevated CK-MB relative index recorded during surgery) and was therefore excluded from the analysis of postoperative MI.

Postoperative β-blocker withdrawal was associated with an increased risk of events (Table II). Four of 8 patients (50%) whose β-blocker therapy was discontinued died compared with 2 of 132 patients (1.5%) who were continued on β-blocker therapy (unadjusted OR 65, 95% CI 6.3-815, Table II). This association persisted after controlling, in stratified analyses, for each risk factor: history of angina (OR 46, 95% CI 5.0-669), MI (OR 95% CI 5.8-676), diabetes mellitus (OR 100, 95% CI 7.8-5914), CHF (OR 82, 95% CI 6.6-4778), age (OR 47, 95% CI 5.3-626), and surgery type (OR not calculable, P < .001).

Of note, 3 of the 8 patients whose β-blockers were discontinued had hemodynamic events that might have prohibited restarting β-blockade (defined as postoperative CHF, need for postoperative vasopressor administration, or bradyarrhythmia requiring therapy or medication withdrawal). Although adjustment for these potential contraindications diminished the OR, the strong association persisted (adjusted OR 35, 95% CI 3.2-557). After the patients with potential contraindications to restarting β-blockers were excluded, there was still an increased risk of death or MI (OR 18.3, 95% CI 1.8-233; P = .006). For death alone, the results were not statistically significant, but the CIs were very wide (OR 19.7, 95% CI 0.25-451; P = .09). Furthermore, adjusting simultaneously for all variables that reduced the OR and therefore might have created a false association between β-blocker withdrawal and mortality (age, angina, MI, and contraindications to restarting β-blockers), the multivariable OR remained significant (adjusted exact OR 17.0, 95% CI 1.81-224; P = .01). Further adjustment for the other factors would likely have increased the OR but was not possible as discussed in Methods.

The impact of aspirin, warfarin, and class Ia antiarrhythmic medication discontinuation on β-blocker discontinuation and death was assessed in the subset of patients with known status of drug use (University of Pennsylvania Medical Center) because these medications may have an impact on perioperative cardiac outcomes. After adjustment for aspirin or warfarin discontinuation, the results were unchanged. Adjustment for class Ia antiarrhythmic drug discontinuation led to a reduction in the OR for stopping β-blockers and death (unadjusted OR 54 reduced to 41), but the results remained statistically significant (P < .001).

β-Blocker discontinuation was also associated with an
increased risk for cardiovascular outcomes (Table II). There were no cardiac deaths in patients who had β-blockers restarted and 2 deaths (28.6%) in those with β-blocker discontinuation (P = .005). The risk of MI also was elevated in patients withdrawn from β-blockers (Table II). This increased OR for MI, which was statistically significant in its unadjusted form, remained significant with adjustment for age, surgery type, contraindications to restarting β-blockers, angina, heart failure, diabetes, and history of MI (adjusted exact OR 19.4, 95% CI 1.19-1414; P = .03). β-Blocker discontinuation was also associated with an increased risk for any death or MI (Table II), which persisted after adjustment for the same variables discussed above (adjusted exact OR 19.3, 95% CI 1.96-328; P = .007).

Discontinuation of other medications and outcomes
To determine whether bias produced the β-blocker results, the effects of withdrawal of calcium channel antagonists and angiotensin-converting enzyme inhibitors were examined. The discontinuation of calcium channel antagonists and angiotensin-converting enzyme inhibitors were both associated with a modest to moderate increase in risk of mortality and MI, but none of these associations was statistically significant (Figure 1). The ORs (95% CI) for calcium channel antagonists were 1.6 (0.03-21) for death and 5.3 (0.72-30.8) for MI, for angiotensin-converting enzyme inhibitors, they were 13.3 (0.96-708) for death and 6.6 (0.42-97) for MI. There was only one cardiac death among patients who were given angiotensin-converting enzyme inhibitors or calcium channel antagonists preoperatively. Although there was an increased risk of mortality associated with the discontinuation of these medications, the associations were not statistically significant and were of smaller magnitude, albeit with wide CIs.

Discussion
The results of our study suggest an increased risk of mortality and cardiovascular events associated with β-blocker discontinuation in vascular surgery patients, a group of patients with a relatively high prevalence of coronary artery disease and risk factors for perioperative morbidity and mortality. In evaluating the relationship between inpatient postoperative mortality and β-blocker discontinuation, we have tried to account for potential confounders that may have been associated with β-blocker use or withdrawal and with an increased mortality risk. Furthermore, the discontinuation of calcium channel antagonists and angiotensin-converting enzyme inhibitors, medications that often have similar indications for discontinuation but do not have the withdrawal effect seen with β-blockers, were not associated with the same risk as β-blocker withdrawal, although the number of patients are too small to draw any firm conclusions. Nevertheless, our finding of increased mortality and cardiovascular events associated only with β-blocker withdrawal supports the argument that the particular pharmacologic characteristics of β-blockers, and of their discontinuation, contribute to the increased mortality seen with β-blocker withdrawal.

Previous studies have documented deleterious effects from β-blocker withdrawal in surgical patients. These effects may be mediated through a hyperadrenergic response to stress, which may occur as the result of an increased number of β-receptors that develops with long-term β-adrenergic receptor blockade. However, heterogeneity among β-blockers, in properties such as lipophilicity, likely results in different mechanisms of β-blocker withdrawal. In a cohort study comparing abrupt withdrawal of propranolol within 24 hours before coronary artery bypass grafting to patients whose dose was tapered over an average of 3 days and then discontinued 24 hours before surgery, abrupt withdrawal resulted in a 4-fold higher rate of perioperative MI (7% vs 32%), and all six patients who died as a result of perioperative MI had been abruptly withdrawn from propranolol. A separate trial with propranolol in aortocoronary bypass surgery showed that patients assigned to be withdrawn from propranolol preoperatively had a higher incidence of perioperative and intraoperative myocardial ischemia and arrhythmias than those patients assigned to continue on propranolol, although they did not have an elevated rate of postoperative MI or mortality. However, this latter small study is difficult to interpret because 25% of patients assigned to have their β-blockers withdrawn did not.

The benefits of perioperative β-blockade in reducing perioperative myocardial ischemia in vascular surgery have been demonstrated. Data from a case-control study involving 2088 vascular surgical patients also found an association between β-blocker use and a decreased incidence of perioperative MI. A randomized controlled trial by Mangano et al in noncardiac surgery patients demonstrated a long-term reduction in postdischarge mortality and cardiac events over a 2-year follow-up period in patients with coronary artery disease or at risk for coronary disease who had received perioperative atenolol versus placebo. The occurrence of perioperative ischemia in this study was associated with long-term postoperative cardiac events. A recent randomized controlled study of high-risk patients undergoing major vascular surgery showed a significant reduction in cardiac death and nonfatal MI in those patients receiving bisoprolol perioperatively. These data suggest that effectively limiting perioperative myocardial ischemia through perioperative β-blocker administration can have significant long-term benefits on reducing cardiac event rates and that discontinuing β-blockers might be deleterious.

The above studies provide data to further assess the impact of perioperative β-blocker withdrawal in noncardiac surgery. Eight of the 101 patients receiving placebo
perioperatively in the atenolol study had received β-blockers before randomization and were therefore at risk for β-blocker withdrawal. While the impact of β-blocker withdrawal on postoperative mortality was not discussed in that publication, Manganese noted, in a separate correspondence, a 12% 2-year postoperative mortality rate (1/8) among patients receiving β-blockers preoperatively but randomized to the placebo group versus 6% (1/18) for patients on β-blockers preoperatively who were randomized to β-blockers postoperatively. That is, in a clinical situation similar to that of our study patients whose preoperative β-blockers were discontinued postoperatively had a mortality rate twice as high as that for patients whose β-blockers were continued. These data, although of small sample size, are suggestive, but certainly not proof, of an increased risk associated with β-blocker withdrawal. Further study of the impact of β-blocker withdrawal on mortality is clearly warranted.

There are several limitations to our study. First, because of the small number of patients withdrawn from β-blockers, it is possible that our finding is a spurious one. Second, the study was not randomized and therefore subject to confounding by indication (ie, that medical conditions associated with increased perioperative mortality influenced the decision to prescribe or withhold β-blockers postoperatively). However, adjustment for contraindications to β-blocker readministration diminished, but did not negate, the finding of increased risk of all-cause mortality in those patients whose β-blockers were discontinued. Although the results were not statistically significant after those with potential contraindications were excluded, the numbers were very small and the CIs very wide. Also, the results remained significant for the combined outcome of death or MI in this subgroup. Furthermore, the results were unchanged after adjusting simultaneously for other risk factors and for possible contraindications to β-blocker readministration. However, these contraindications were determined retrospectively by chart review, and therefore their accuracy and completeness are somewhat limited. A randomized trial of β-blocker discontinuation would overcome these limitations, but we are concerned that such a study may be unethical, given the evidence supporting the adverse effects of β-blocker discontinuation. Another possible explanation for our results is that cause and effect were reversed, that is, death prevented β-blocker readministration. However, if this were so, then the same striking association between mortality and discontinuation seen with β-blockers should have been observed with calcium channel antagonists and angiotensin-converting enzyme inhibitors. Although there was an increased risk of mortality associated with the discontinuation of these medications, the associations were not statistically significant and were of smaller magnitude.

In conclusion, β-blocker discontinuation in vascular surgical patients may be associated with an increased risk of postoperative morbidity and mortality. Further study confirming our results would provide additional support for this conclusion. Meanwhile, in the absence of serious potential contraindications to β-blocker use, and given current evidence, efforts must be made to ensure that patients treated with β-blockers before vascular surgery have their β-blockers continued as soon as possible in the postoperative period.

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References