THE EFFECT OF BISOPROLOL ON PERIOPERATIVE MORTALITY AND MYOCARDIAL INFARCTION IN HIGH-RISK PATIENTS UNDERGOING VASCULAR SURGERY

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ABSTRACT

Background Cardiovascular complications are the most important causes of perioperative morbidity and mortality among patients undergoing major vascular surgery.

Methods We performed a randomized, multicenter trial to assess the effect of perioperative blockade of beta-adrenergic receptors on the incidence of death from cardiac causes and nonfatal myocardial infarction within 30 days after major vascular surgery in patients at high risk for these events. High-risk patients were identified by the presence of both clinical risk factors and positive results on dobutamine echocardiography. Eligible patients were randomly assigned to receive standard perioperative care or standard care plus perioperative beta-blockade with bisoprolol.

Results A total of 1351 patients were screened, and 846 were found to have one or more cardiac risk factors. Of these 846 patients, 173 had positive results on dobutamine echocardiography. Fifty-nine patients were randomly assigned to receive bisoprolol, and 53 to receive standard care. Fifty-three patients were excluded from randomization because they were already taking a beta-blocker, and eight were excluded because they had extensive wall-motion abnormalities either at rest or during stress testing. Two patients in the bisoprolol group died of cardiac causes (3.4 percent), as compared with nine patients in the standard-care group (17 percent, $P=0.02$). Nonfatal myocardial infarction occurred in nine patients given standard care only (17 percent) and in none of those given standard care plus bisoprolol ($P<0.001$). Thus, the primary study end point of death from cardiac causes or nonfatal myocardial infarction occurred in 2 patients in the bisoprolol group (3.4 percent) and 18 patients in the standard-care group (34 percent, $P<0.001$).

Conclusions Bisoprolol reduces the perioperative incidence of death from cardiac causes and nonfatal myocardial infarction in high-risk patients who are undergoing major vascular surgery. (N Engl J Med 1999;341:1789-94.)

PATIENTS undergoing major vascular surgery are at risk for serious perioperative cardiac complications, such as nonfatal myocardial infarction and death.[1] A combination of clinical assessment and noninvasive cardiac testing can be used to identify patients at high risk.[2] Various interventions have been proposed to reduce the risk of cardiac complications in such patients after noncardiac surgery, but none have been found to be efficacious.

Drugs that block beta-adrenergic receptors prevent cardiac complications in patients with acute myocardial infarction, silent ischemia, and heart failure.[3-6] Perioperative blockade of beta-adrenergic receptors has been proposed to reduce the risk of perioperative cardiac complications.[7-9] However, previous trials lacked the statistical power to evaluate the cardioprotective effect of beta-blockade on the incidence of serious cardiac events, such as death or nonfatal myocardial infarction.

We hypothesized that perioperative beta-blockade with bisoprolol would reduce the perioperative incidence of death from cardiac causes and nonfatal myocardial infarction in high-risk patients undergoing major vascular surgery. We therefore performed a multicenter study of a subgroup of high-risk patients who had clinical predictors of cardiac risk together with positive results on dobutamine echocardiography.

METHODS

Study Protocol

Between 1996 and 1999, we prospectively screened all patients undergoing elective abdominal aortic or infrainguinal arterial reconstruction at seven participating centers. The ethics committee at each center approved the study protocol. The patients were

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*The members of the study group are listed in the Appendix.

screened for the following cardiac risk factors: age over 70 years; angina; prior myocardial infarction on the basis of history or a finding of pathologic Q waves on electrocardiography; compensated congestive heart failure or a history of congestive heart failure; current treatment for ventricular arrhythmias; current treatment for diabetes mellitus; or limited exercise capacity, defined as the inability to perform most normal daily activities. Any patient with a risk factor underwent dobutamine echocardiography. Patients who had a positive result on dobutamine echocardiography were considered at high risk.

Patients were excluded if they had extensive wall-motion abnormalities (wall-motion index more than 1.70 at rest), asthma, or strong evidence during stress testing of left main or severe three-vessel coronary artery disease. Patients were also excluded if they were already taking a beta-adrenergic–receptor antagonist. These patients either continued their usual medication or were switched to bisoprolol. They were treated similarly to patients assigned to the bisoprolol group, but their data were analyzed separately.

After giving written informed consent, eligible patients were randomly assigned to receive either standard perioperative care or standard care plus bisoprolol. A computer algorithm was used at each center to assign patients randomly, in a one-to-one ratio, to one of the two study groups. Treatment with bisoprolol, a selective β_1-adrenergic–receptor antagonist, was started at least 1 week before surgery and continued for 30 days postoperatively.

The initial dose of bisoprolol was 5 mg orally once a day. Approximately one week after starting bisoprolol, the patients were reassessed, and the dose was increased to a maximum of 10 mg once daily if the heart rate remained above 60 beats per minute. The same dose of bisoprolol was continued postoperatively except in patients who were unable to take medication orally or by nasogastric tube postoperatively. In these patients, the heart rate was monitored continuously in the intensive care unit or hourly on the ward, and intravenous metoprolol was administered at a dose sufficient to keep the heart rate below 80 beats per minute. The heart rate and blood pressure were measured immediately before each scheduled dose of bisoprolol. Bisoprolol was withheld if the heart rate was under 50 beats per minute or the systolic blood pressure was under 100 mm Hg.

Dobutamine Echocardiography

Dobutamine echocardiography was performed as described previously.[10] The left ventricle was divided into 16 segments, and wall motion was scored on a 5-point scale (with a score of 1 indicating normal, 2 mild hypokinesis, 3 severe hypokinesis, 4 akinesis, and 5 dyskinesis). The results were considered positive if wall motion in any segment decreased by one or more grades during testing. The extent and location of ischemia were evaluated in every patient, and a wall-motion index was calculated at rest.

Perioperative Management

Anesthetic management, monitoring, surgical technique, and other aspects of perioperative management were at the discretion of the attending physicians. The attending physicians were aware of the patients' echocardiographic results and treatment groups. If symptoms or signs of perioperative myocardial ischemia accompanied by tachycardia developed in a patient in the standard-care group, the attending physician was permitted to administer beta-adrenergic–receptor antagonists.

Follow-up

The patients were monitored for cardiac events for 30 days after surgery. Twelve-lead echocardiography was performed and the serum creatine kinase level (with the MB fraction) was determined one, three, and seven days after surgery. Additional measurements were performed at the discretion of the attending physician. Outpatient follow-up was performed at 30 days if a patient had been discharged from the hospital. All data were collected by the participating centers and evaluated in a masked fashion by members of the adverse-events committee. The primary end points were death from cardiac causes or nonfatal myocardial infarction during the perioperative period. The cause of death was determined by reviewing the clinical presentation, including serum cardiac isoenzyme levels, 12-lead electrocardiograms, and, when available, autopsy results. Nonfatal myocardial infarction was defined by a serum creatine kinase level of more than 110 U per liter, with an MB isoenzyme fraction of more than 10 percent, and a finding of new Q waves lasting more than 0.03 second on the electrocardiogram.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	BISOPROLOL GROUP (N=59)	STANDARD-CARE GROUP (N=53)
Age — yr		
Mean	68	67
Range	60–73	61–75
Male sex — no. (%)	52 (88)	44 (83)
Previous myocardial infarction — no. (%)	32 (54)	26 (49)
Angina pectoris — no. (%)	21 (36)	15 (28)
Limited exercise capacity — no. (%)	16 (27)	23 (43)
Congestive heart failure — no. (%)	6 (10)	8 (15)
Diabetes mellitus — no. (%)	8 (14)	9 (17)

*There were no significant differences between the two groups.

TABLE 2. RESULTS OF DOBUTAMINE ECHOCARDIOGRAPHY.*

CHARACTERISTIC	BISOPROLOL GROUP (N=59)	STANDARD-CARE GROUP (N=53)
Resting wall-motion index		
Mean	1.31	1.44
Range	1.00–1.81	1.00–1.81
Angina during testing — no. (%)	14 (24)	12 (23)
ST changes during testing — no. (%)	25 (42)	23 (43)
No. of ischemic segments — no. of patients		
1 or 2	28	19
3 or 4	25	24
>4	6	10

*There were no significant differences between the two groups.

Statistical Analysis

The calculation of sample size was based on a previous study in which we noted a 28 percent incidence of serious perioperative cardiac events in patients who had clinical risk factors as well as positive results on dobutamine echocardiography.[11] We calculated that the inclusion of 266 patients would allow us to detect a reduction in the incidence of the primary end point from 30 percent to 15 percent with an alpha level of 0.05 and a statistical power of 0.80. As part of the study design, an interim analysis by an independent safety committee was planned after enrollment of the first 100 patients. In accordance with the O'Brien and Fleming criteria,[12] the protocol specified that the trial would be stopped if there was a significant difference in the rate of the primary end point between the bisoprolol group and the control group ($P=0.001$).

Continuous data are presented as median values and corre-

sponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences between the groups of patients in clinical and surgical characteristics and in the results of dobutamine echocardiography were evaluated by Wilcoxon's nonparametric test or Fisher's exact test, whichever was appropriate. Differences between the groups in the rates of occurrence of the primary end point were evaluated by Fisher's exact test. Event rates were further examined by the Kaplan–Meier method and a corresponding log-rank test. Cox proportional-hazards regression analysis was performed to estimate the relative risk of the end point. Analyses were performed according to the intention to treat.

RESULTS

Characteristics of the Patients

A total of 1351 patients were screened, and 846 were found to have one or more cardiac risk factors. Stress-induced ischemia occurred in 173 of the 846 patients (20 percent) during dobutamine echocardiography. Of these patients, 112 underwent randomization: 59 were assigned to receive bisoprolol plus standard care and 53 to receive standard care alone. All but one patient underwent the planned vascular surgical procedure after randomization. Sixty-one patients did not undergo randomization: 53 were already taking a beta-blocker at enrollment and underwent the planned vascular surgical procedure while continuing to take this medication, and 8 had extensive wall-motion abnormalities.

The clinical characteristics of the randomized patients are presented in Table 1. The results of dobutamine echocardiography, details of the surgical procedure, and important aspects of perioperative management are presented in Tables 2 and 3. There were no significant differences between the groups with respect to any of these variables. Patients in the bisoprolol group had significantly lower heart rates before surgery and during the perioperative period than did those given standard care (Table 4).

TABLE 3. CHARACTERISTICS OF SURGICAL PROCEDURES.*

CHARACTERISTIC	BISOPROLOL GROUP (N=59)	STANDARD-CARE GROUP (N=53)
Duration — hr		
Mean	4.0	3.4
Range	3.0–5.5	2.6–5.0
Type of surgery — no.		
Aortic-aneurysm resection	13	8
Aortofemoral bypass	25	27
Infrainguinal arterial reconstruction	21	18
Type of anesthesia — no. (%)		
General	34 (58)	32 (60)
Epidural or spinal	4 (7)	4 (8)
Combined	21 (36)	17 (32)
Stay in intensive care unit — days		
Mean	1	2
Range	0–2	1–2
Postoperative analgesia — no. (%)		
Epidurally administered	24 (41)	22 (42)
Patient-controlled	5 (8)	7 (13)
Opioids as needed	30 (51)	24 (45)

*There were no significant differences between the two groups.

TABLE 4. MEAN HEART RATES OF RANDOMIZED PATIENTS AT BASE LINE AND ONE, THREE, AND SEVEN DAYS POSTOPERATIVELY.*

TIME OF MEASUREMENT	BISOPROLOL GROUP (N=59)	STANDARD-CARE GROUP (N=53)	P VALUE
	beats/min		
Before surgery			<0.001
Mean	66	79	
Range	58–78	72–82	
Day 1			<0.001
Mean	71	82	
Range	62–80	76–88	
Day 3			<0.001
Mean	71	84	
Range	65–80	76–88	
Day 7			<0.001
Mean	69	80	
Range	63–74	69–82	

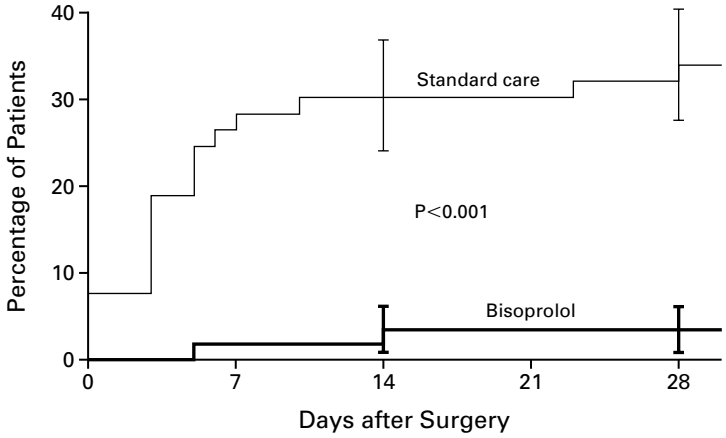
*The mean heart rate was measured in the morning before the next dose of beta-blocker was administered.

Beta-Blockade

In the bisoprolol group, bisoprolol was started an average of 37 days (range, 7 to 89) before surgery. The daily dose was 10 mg in 15 patients and 5 mg in 44. All these patients received bisoprolol orally on the morning of surgery. The day after surgery, bisoprolol was administered either orally or by nasogastric tube in 31 patients and intravenously in 28 patients. By the fourth day after surgery, all patients had resumed oral therapy. No patient in this group had a preoperative exacerbation of underlying peripheral vascular disease.

Cardiac Events in Randomized Patients

Nine patients in the standard-care group (17 percent) died of cardiac causes during the perioperative period, as compared with two patients (3.4 percent) in the bisoprolol group ($P=0.02$). There were no deaths from other causes. Nine patients in the standard-care group (17 percent) had a nonfatal myocardial infarction, as compared with none in the bisoprolol group ($P<0.001$). Eight of the infarctions occurred postoperatively, and one occurred preoperatively. The one preoperative infarction was considered a primary end point, even though the surgery was canceled. The overall rate of the combined end point of death from cardiac causes or nonfatal myocardial infarction was 34 percent (95 percent confidence interval, 21 to 48 percent) in the standard-care group, as compared with 3.4 percent (95 percent confidence interval, 0 to 8.0 percent; $P<0.001$) in the bisoprolol group. The estimated relative risk of death



No. at Risk					
Standard care	53	38	37	37	35
Bisoprolol	59	58	57	57	57

Figure 1. Kaplan–Meier Estimates of the Cumulative Percentages of Patients Who Died of Cardiac Causes or Had a Nonfatal Myocardial Infarction during the Perioperative Period.

I bars indicate standard errors. The difference between groups was significant (P<0.001 by the log-rank test).

from cardiac causes or nonfatal myocardial infarction during the perioperative period among patients receiving bisoprolol therapy, as compared with those receiving standard care, was 0.09 (95 percent confidence interval, 0.02 to 0.37). Four patients in the standard-care group received beta-blockers perioperatively because of severe intraoperative myocardial ischemia or postoperatively because of unstable angina.

The significant difference between groups in the incidence of serious cardiac events prompted the safety committee to interrupt the study after the planned interim analysis. While the safety committee was evaluating the results, six additional patients underwent randomization. The number of patients who reached the end point is presented in Figure 1. The majority of events occurred during the first seven days after surgery.

Cardiac Events in Nonrandomized Patients

Among the 53 patients with positive results on dobutamine echocardiography who were already taking a beta-blocker, 4 (7.5 percent) died of cardiac causes during the perioperative period and none had a myocardial infarction. The eight patients who did not undergo randomization because of extensive resting or stress-induced wall-motion abnormalities (or both) had a median wall-motion index of 1.84 and had new wall-motion abnormalities in seven segments. Four of these patients underwent coronary-artery bypass grafting, and two of them died. The two surviving patients subsequently underwent uneventful vascular surgery. The other four patients underwent vascular surgery without prior myocardial revascularization but with perioperative administration of beta-blockers. None of these four patients died, but one had a perioperative myocardial infarction.

DISCUSSION

In this randomized, multicenter study, we found that perioperative administration of bisoprolol reduced the perioperative incidence of both death from cardiac causes and nonfatal myocardial infarction in high-risk patients undergoing major vascular surgery. The combined incidence of these cardiac events was 34 percent in the standard-care group, as compared with 3.4 percent in the bisoprolol group; this difference caused the safety committee to interrupt the study after the first planned interim analysis. The observed treatment effect is not attributable to differences between the two groups with respect to clinical characteristics, results on dobutamine echocardiography, surgical procedures, anesthetic or analgesic technique, or the duration of hospitalization in the intensive care unit.

At first glance, the 34 percent rate of serious perioperative events in the standard-care group seems high. However, this rate is consistent with the results of a previous study at one of our institutions. In a group of 300 consecutive patients, the incidence of serious cardiac events was 28 percent in patients with one or more risk factors and positive results on dobutamine echocardiography.[11] Other investigators have noted high rates of perioperative cardiac events in patients in whom ischemia can be induced on perioperative testing.[13-15]

The cause of the perioperative cardiac events re-

mains undefined. Such events occur almost exclusively among patients with positive results on dobutamine echocardiography,[11] suggesting that hemodynamically significant coronary-artery stenosis has an essential role in the pathogenesis of perioperative coronary ischemic syndromes. Coronary stenosis may increase a patient's vulnerability to ischemia or infarction caused by perioperative hemodynamic instability, anemia, hypoxemia, hypercoagulability, or rupture of coronary atherosclerotic plaques.

The mechanism by which beta-blockade reduces perioperative cardiac events is also unclear. Several mechanisms have been proposed. Myocardial oxygen balance may be improved by decreases in the heart rate and myocardial contractility, thus preventing myocardial ischemia, reducing the size of the infarct, or both. Beta-blockade may reduce myocardial oxygen consumption by suppressing lipolysis and thus causing the myocardium to metabolize more glucose in relation to free fatty acids. Beta-blocking drugs may increase the stability of coronary atherosclerotic plaques or increase the threshold for ventricular fibrillation in the presence of ischemia.[6] Antagonists of beta-adrenergic receptors have also been shown to improve the outcome among patients with acute myocardial infarction, silent ischemia, and heart failure.[3-5]

The only previous randomized, controlled study evaluating the cardioprotective effect of beta-adrenergic antagonists in patients undergoing major surgery was performed by Mangano and colleagues.[7,8] In this study, 200 patients who had or were at risk for coronary artery disease were randomly assigned to receive atenolol or placebo during the perioperative period. The patients were monitored perioperatively for cardiac events and then followed for two years after surgery. During the first 48 hours after surgery, the incidence of myocardial ischemia, as detected by continuous three-lead Holter monitoring, was reduced by 50 percent in patients given atenolol. During the two-year follow-up period, the mortality rate was 10 percent in patients given atenolol and 21 percent in the controls. However, atenolol did not significantly reduce the incidence of death from cardiac causes during hospitalization or that of perioperative myocardial infarction.

The failure of atenolol to alter the perioperative outcome significantly reflects the low incidence of serious perioperative cardiac events in the study population (3 percent). The study included both patients with known coronary artery disease and those with only coronary risk factors, and the patients underwent various surgical procedures. In contrast, we studied a population of patients who were undergoing vascular surgery who were identified by clinical screening and dobutamine echocardiography as being at high risk, with an anticipated rate of cardiac events of 28 percent. Our results demonstrate the importance of testing risk-reduction strategies in a subgroup of high-risk patients.

Preoperative evaluation offers a unique opportunity to screen patients for underlying coronary artery disease and cardiac risk factors that affect the perioperative outcome. A task force of the American College of Cardiology and the American Heart Association has published guidelines for the preoperative cardiovascular evaluation of patients scheduled for noncardiac surgery.[2] According to these guidelines, patients undergoing vascular surgery who have intermediate risk factors (Canadian Cardiovascular Society class I or II angina, myocardial infarction, congestive heart failure, or diabetes mellitus) or limited exercise capacity should undergo a noninvasive cardiac evaluation before surgery. We prefer dobutamine echocardiography for this purpose, because of its extremely high negative predictive value and because it can be used in patients who cannot exercise. Patients with no clinical risk factors and without stress-induced ischemia have a rate of serious perioperative cardiac events that is close to zero.[12] They can undergo surgery without extra evaluation or extensive monitoring. Patients with a positive test result are at high risk and are candidates for perioperative risk-reduction measures.

On the basis of our results, we recommend that high-risk surgical patients receive beta-blockers perioperatively, beginning one to two weeks before surgery. The goal should be to reduce the heart rate to less than 70 beats per minute preoperatively and to less than 80 beats per minute in the immediate postoperative period. Therapy should be continued for at least two weeks postoperatively. An alternative to this approach would be to omit preoperative noninvasive cardiac testing and prescribe a beta-blocker perioperatively for all patients with clinical risk factors who are undergoing high-risk surgery. Although our results applied to patients who were undergoing major vascular surgery, we recommend that high-risk patients undergoing other types of noncardiac surgery receive a beta-blocker perioperatively.

Our study has several limitations. Most important, it was not conducted in a blinded fashion. The attending physicians knew which treatment had been prescribed, and bias on their part may have affected the management and outcome. However, we found no significant differences in major aspects of perioperative treatment (e.g., anesthetic or analgesic technique or duration of hospitalization in the intensive care unit) between the two groups. The rate of events in the standard-care group was not higher than that predicted on the basis of our previous work. It is unlikely that factors other than the use of beta-blockers can account for the reduced rate of events in the bisoprolol group. For such factors to have affected the outcome, physicians at eight different institutions would have had to use — consistently and exclusively — an unproved, but extremely effective, risk-reduction strategy in the bisoprolol group.

The lack of blinding may also have affected the reporting of events. Systematic screening for myocardial infarction with the use of cardiac isoenzyme levels and electrocardiography was performed only during the first week after surgery. Subsequent testing was discretionary and may have been influenced by bias on the part of the investigators. Such bias may have affected the diagnosis and reporting of myocardial infarctions after the first week. However, most infarctions occurred in the first seven days after surgery and would have been detected by routine screening.

Our decision to exclude eight patients with extensive resting or stress-induced wall-motion abnormalities was arbitrary and may have affected the results. Our exclusion criteria were established before the study began and reflected our belief that it would be inappropriate to constrain the perioperative care of these patients in any way. There is little doubt that the randomized patients still constitute an appropriate high-risk group in which to test the value of perioperative beta-blockade.

There were doubtless minor variations between centers in the interpretations of the results of dobutamine echocardiography, but the outcome in the standard-care group shows that the presence of one or more risk factors plus a positive test result does define a high-risk population. Furthermore, since randomization was performed at each participating center, differences in the results of dobutamine echocardiography between centers would not have biased the overall results.

In conclusion, we found that bisoprolol reduces the perioperative incidence of death from cardiac causes and of nonfatal myocardial infarction in high-risk patients undergoing abdominal aortic or infrainguinal arterial reconstructive surgery.

APPENDIX

The members of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography study group and the participating centers were as follows: *Steering committee* — D. Poldermans, I.R. Thomson, H. van Urk, J.J. Bax, P.M. Fioretti, A.J. Man in 't Veld, L.L.M. van de Ven, and J.R.T.C. Roelandt; *Statistical analysis* — E. Boersma; *Data-base management* — V.C. Poldermans and A. Schyns; *Adverse-events committee* — P. van de Meer and P. Klootwijk; *Safety committee* — M.L. Simoons and G.A. van Es; *Participating centers* — the Netherlands: Erasmus Medical Center, Rotterdam (D. Poldermans, M. van Nierop, H. van Urk); Sint Clara Ziekenhuis, Rotterdam (M.G. Scheffer, T.-I. Yo); Twee Steden Ziekenhuis, Tilburg (H.F. Baars, S. Berends, S.E. Kranendonk); Academisch Ziekenhuis, Utrecht (J.D. Blankensteijn, H.W.J. Meijburg, R. Rienks); and Medisch Centrum, Alkmaar (J.H. Cornel, H.A. van Dijk); Belgium: Ziekenhuis Middelheim Antwerp (B. Paelinck); Italy: San Gerardo Hospital, Monza (G. Emanuelli, G. Trocino, A. Virtuani, M. Zerbato); and Istituto di Ricovero e Cura a Carattere Scientifico Hospital, San Giovanni Rotondo (C. Vigna, G. Colacchio).

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