Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 5, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.03.059

Should Major Vascular Surgery Be Delayed Because of Preoperative Cardiac Testing in Intermediate-Risk Patients Receiving Beta-Blocker Therapy With Tight Heart Rate Control?

Don Poldermans, MD, PHD,* Jeroen J. Bax, MD, PHD,† Olaf Schouten, MD,‡ Aleksandar N. Neskovic, MD, PHD,§ Bernard Paelinck, MD, PHD,‖ Guido Rocci, MD, PHD,¶ Laura van Dortmont, MD, PHD,# Anai E. S. Durazzo, MD, PHD,** Louis L. M. van de Ven, MD, PHD,†† Marc R. H. M. van Sambeek, MD, PHD,‡ Miklos D. Kertai, MD, PHD,* Eric Boersma, PHD,‡‡ for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo Study Group

Rotterdam, Leiden, Schiedam, and Amsterdam, the Netherlands; Belgrade, Serbia and Montenegro; Antwerp, Belgium; Bologna, Italy; and São Paulo, Brazil

OBJECTIVES The purpose of this study was to assess the value of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate (HR) control scheduled for major vascular surgery.

BACKGROUND Treatment guidelines of the American College of Cardiology/American Heart Association recommend cardiac testing in these patients to identify subjects at increased risk. This policy delays surgery, even though test results might be redundant and beta-blockers with tight HR control provide sufficient myocardial protection. Furthermore, the benefit of revascularization in high-risk patients is ill-defined.

METHODS All 1,476 screened patients were stratified into low-risk (0 risk factors), intermediate-risk (1 to 2 risk factors), and high-risk (≥3 risk factors). All patients received beta-blockers. The 770 intermediate-risk patients were randomly assigned to cardiac stress-testing (n = 386) or no testing. Test results influenced management. In patients with ischemia, physicians aimed to control HR below the ischemic threshold. Those with extensive stress-induced ischemia were considered for revascularization. The primary end point was cardiac death or myocardial infarction at 30-days after surgery.

RESULTS Testing showed no ischemia in 287 patients (74%); limited ischemia in 65 patients (17%), and extensive ischemia in 34 patients (8.8%). Of 34 patients with extensive ischemia, revascularization before surgery was feasible in 12 patients (35%). Patients assigned to no testing had similar incidence of the primary end point as those assigned to testing (1.8% vs. 2.3%; odds ratio [OR] 0.78; 95% confidence interval [CI] 0.28 to 2.1; p = 0.62). The strategy of no testing brought surgery almost 3 weeks forward. Regardless of allocated strategy, patients with a HR <65 beats/min had lower risk than the remaining patients (1.3% vs. 5.2%; OR 0.24; 95% CI 0.09 to 0.66; p = 0.003).

CONCLUSIONS Cardiac testing can safely be omitted in intermediate-risk patients, provided that beta-blockers aiming at tight HR control are prescribed. (J Am Coll Cardiol 2006;48:964–9)
© 2006 by the American College of Cardiology Foundation

According to the guidelines of the American College of Cardiology /American Heart Association (ACC/AHA), all patients scheduled for major vascular surgery who have clinical features associated with increased cardiac risk should undergo noninvasive cardiac stress-testing (1). Perioperative beta-blocker therapy is recommended for patients with inducible ischemia undergoing major vascular surgery. The guidelines also recommend coronary angiography for patients with high-risk noninvasive test results and myocardial revascularization in patients with prognostic high-risk anatomy in whom long-term outcome is likely to be improved. However, noninvasive testing might delay surgery and run the risk of aortic aneurysmal rupture or exacerbation of critical limb ischemia. Furthermore, a recent randomized, controlled trial of preoperative myocardial revascularization in vascular surgery patients showed no improvement in perioperative or long-term outcome associated with prophylactic revascularization (2).

See page 970

In a previous retrospective observational study of 1,351 patients undergoing major vascular surgery, we found that counting clinical risk factors effectively stratified vascular surgery patients into low-risk (0 risk factors), intermediate-

From the *Departments of Anesthesiology, ‡Vascular Surgery, and ‡‡Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands; †Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; #Department of Vascular Surgery, Vlietland Hospital, Schiedam, the Netherlands; ††Merck BV, Amsterdam, the Netherlands; §Dedinje Cardiovascular Institute, Belgrade University School of Medicine, Belgrade, Serbia and Montenegro; ‖Department of Cardiology, University of Antwerp, Antwerp, Belgium; ¶Department of Cardiology, University of Bologna, Bologna, Italy; and the **Vascular Surgery Section, Department of Surgery, Health and Medical Sciences Sector, Lusiada Foundation, Santos, São Paulo, Brazil.

Manuscript received January 27, 2006; revised manuscript received March 7, 2006, accepted March 17, 2006.

Abbreviations and Acronyms

ACC/AHA = American College of Cardiology/ American Heart Association
CI = confidence interval
MI = myocardial infarction
OR = odds ratio

risk (1 to 2 risk factors), and high-risk (≥3 risk factors) categories (3). Among patients receiving beta-blockers, perioperative cardiac event rates were 0% and 0.9% in low- and intermediate-risk patients, respectively. Of all intermediate-risk patients studied, only a minority (2%) experienced extensive stress-induced myocardial ischemia (3). These data do not support the routine use of preoperative noninvasive testing in intermediate-risk patients, who constitute more than 50% of the major vascular surgery population, provided that perioperative beta-blockade is employed.

We therefore undertook the second multi-center DECREASE-II (Dutch Echocardiographic Cardiac Risk Evaluation) study to prospectively assess the value of cardiac testing according to the ACC/AHA guidelines in intermediate-risk patients receiving beta-blocker therapy with tight heart rate (HR) control scheduled for major vascular surgery.

METHODS

Study protocol. Between 2000 and 2005, we enrolled 1,476 patients undergoing elective open abdominal aortic or infrainguinal arterial reconstruction at 5 participating centers. Patients were screened for the following cardiac risk factors: age over 70 years, angina pectoris, prior myocardial infarction (MI) 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, drug therapy for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/l), and prior stroke or transient ischemic attack.

On the basis of previous study results, patients were divided into 3 groups: 0 risk factors (low-risk), 1 or 2 risk factors (intermediate-risk), ≥3 risk factors (high-risk) (3). Low-risk patients were referred for surgery with beta-blocker therapy without additional testing. Intermediate-risk patients were randomly (1:1) assigned to preoperative cardiac stress-testing or no testing. Cardiac testing was performed by dobutamine echocardiography or dobutamine or dipyridamole perfusion scintigraphy, as previously described (4,5). Test results were scored by the extent of stress-induced ischemia with a 16-segment model in dobutamine echocardiography and a 6-wall model in stress perfusion scintigraphy. In addition during dobutamine echocardiography, the HR at which ischemia occurred (i.e., ischemic HR threshold) was noted. Limited ischemia was defined by the presence of 1 to 4 ischemic segments or 1 to 2 ischemic walls, whereas extensive ischemia was defined by ≥5 ischemic segments or ≥3 ischemic walls. Patients without ischemia as well as those with limited ischemia were referred for surgery with beta-blocker therapy. In patients with extensive ischemia, test results were discussed with the treating physicians and only in those patients in whom the index surgical procedure could be delayed was coronary angiography performed and revascularization considered after the angiography data were obtained. The type of coronary revascularization, bypass surgery or percutaneous coronary intervention, was decided by the treating physicians on the basis of coronary anatomy and the possible delay of the index surgical procedure. High-risk patients were referred for additional cardiac testing. All patients provided written informed consent, and the study was approved by the Erasmus Medical Center medical ethics committee and local research ethics committees.

Beta-blocker therapy. Perioperative beta-blocker therapy was installed in all patients. Patients receiving chronic beta-blocker therapy continued their medication. Patients without beta-blockers started with bisoprolol 2.5 mg once/day at the screening visit. Beta-blocker dose was adjusted in all patients at admission to the hospital and on the day before surgery to achieve a resting HR of 60 to 65 beats/min. The same dose of beta-blockers was continued postoperatively except in patients who were unable to take medication orally or by nasogastric tube postoperatively. In these patients, the HR was monitored continuously in the intensive care unit or hourly at the ward, and intravenous metoprolol was administered at a dose sufficient to keep the HR between 60 and 65 beats/min. The HR and blood pressure were measured immediately before each scheduled dose of beta-blockers. Beta-blockers were withheld if the HR was under 50 beats/min or the systolic blood pressure was under 100 mm Hg. After discharge, patients continued beta-blocker therapy and dose adjustments were carried out during outpatient visits to achieve a resting HR of 60 to 65 beats/min.

Perioperative management. Anesthetic management, monitoring, surgical technique, and other aspects of perioperative management were at the discretion of the attending physician. Results of preoperative testing and coronary revascularization were discussed with the attending physicians. In patients with limited or extensive ischemia, HR and hemodynamic management during surgery was implemented to control HR below the ischemic threshold and otherwise below 65 beats/min. Anticoagulant and antiplatelet therapy were continued for a period of at least 4 weeks after percutaneous coronary intervention and continued during surgery. Intraoperative ischemia was treated at the discretion of attending physicians, and additional beta-blockers were permitted.

End point definition. All patients were monitored for cardiac events during hospital stay after surgery. Twelve-lead electrocardiography and serum troponin-T level was determined 1, 3, 7, and 30 days after surgery. Additional tests 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. At the outpatient clinic all patients were screened at 3-month

JACC Vol. 48, No. 5, 2006
September 5, 2006:964–9

intervals for cardiac events by clinical history, troponin-T measurements, and 12-lead electrocardiography recording. All data were collected by the participating centers and evaluated in a blinded fashion by members of the adverse-events committee. The median follow-up was 2.0 years (25th and 75th percentile: 0.8 and 3.1, respectively).

The primary end point was a composite of cardiac death and nonfatal MI at 30 days after surgery. Cardiac death was defined as a death caused by acute MI, significant cardiac arrhythmias, or refractory congestive heart failure or as a death occurring suddenly without another explanation. A nonfatal MI was defined by both a positive troponin-T level and a finding of new Q waves lasting more than 0.03 s on the electrocardiogram. We also report the incidence of the composite end point during long-term follow-up. A nonfatal MI during follow-up was defined by new Q waves lasting more than 0.03 s on the electrocardiogram with or without positive troponin-T level.

Sample size. The primary objective of this trial was to demonstrate that the strategy of no testing is non-inferior to the strategy of cardiac testing in intermediate-risk patients. In a previous study we noted a 5% incidence of perioperative cardiac death or nonfatal MI in intermediate-risk patients (3). We judged that the strategy of no testing is non-inferior to testing if the difference in primary end point is not more than 4%. On the basis of these assumptions, a total of 734 patients are needed to demonstrate non-inferiority with an alpha level of 5% and a power of 80%.

Statistical analysis. Continuous data are presented as median values and corresponding 25th and 75th percentiles, whereas dichotomous data are presented as percentages. Differences in clinical and surgical characteristics between patients allocated to no testing or testing were evaluated by chi-square tests. Differences in the incidence of the primary end point were evaluated by a chi-square test. The incidence of cardiac events over time was further examined by the Kaplan-Meier method, whereas a log-rank test was applied to evaluate differences between the allocated treatment strategies. Analyses were performed according to the intention to treat principle. All statistical tests were 2-sided and a p value < 0.05 was considered significant.

RESULTS

Characteristics of patients. A total of 1,476 patients were enrolled and screened for cardiac risk factors, and 354 patients (24%), 770 patients (52%), and 352 patients (23%) were classified as low-, intermediate- and high-risk, respectively (Fig. 1). A total of 386 intermediate-risk patients were assigned to cardiac testing and 384 patients were assigned to no testing. There were no differences in the presence of ischemic heart disease (i.e., previous MI and angina pectoris) between the 2 groups (Table 1). Testing showed no ischemia in 287 patients (74%); limited ischemia in 65 patients (17%), and extensive ischemia in 34 patients (8.8%). No serious side effects occurred during stress-testing. Stress-induced ischemia during dobutamine echocardiography was noted in 90 patients. The median HR at which ischemia occurred was 112 beats/min (range 92 to 120 beats/min). Of 34 patients with extensive stress-induced ischemia, revascularization before surgery was considered feasible by the treating physicians in 12 patients (35%), percutaneous intervention in 10 patients, and bypass surgery in 2 patients. Coronary angiography showed 2-vessel disease in 5 patients (42%) and 3-vessel disease in 6 patients (50%). Complete revascularization was achieved in 6 patients (50%).

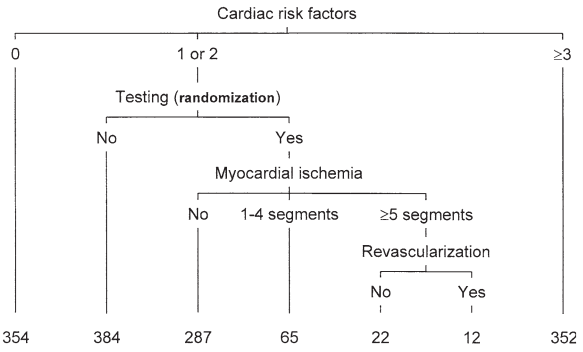

Figure 1. Flow chart of the study. Cardiac risk factors included: age over 70 years, angina pectoris, prior myocardial infarction on the basis of history or a finding of pathologic Q waves on electrocardiography, compensated congestive heart failure or a history of congestive heart failure, current treatment for diabetes mellitus, renal dysfunction (serum creatinine >160 μmol/l), and prior stroke or transient ischemic attack. Patients with 1 or 2 cardiac risk factors were randomly (1:1) assigned to cardiac testing or no testing. Test results were classified as no ischemia, limited ischemia, and extensive ischemia. Patients with extensive ischemia were considered for coronary revascularization.

The median duration of screening to operation was 53 days (range 13 to 121 days) in patients assigned to testing and 34 days (range 7 to 88 days) in the no-testing group ($p < 0.001$). The HR decreased from a median of 70 beats/min at the screening visit to 60 beats/min before operation and was similar in both groups (Fig. 2).

Perioperative cardiac events. The incidence of the 30-day end point in low-, intermediate-, and high-risk patients was 0.3%, 2.2%, and 8.5%, respectively ($p < 0.001$) (Table 1).

No difference in 30-day outcome was observed in intermediate-risk patients with and without testing, (2.3% vs. 1.8%; odds ratio [OR] 0.78, 95% confidence interval [CI] 0.28 to 2.1) (Table 2). The upper limit of the 95% CI of the absolute risk difference in favor of cardiac testing was 1.2%, indicating non-inferiority of the no-testing strategy according to our pre-specified criteria. The incidence of the primary end point in patients without, limited, and extensive ischemia was 0%, 6.2%, and 14.7%, respectively ($p < 0.001$). In intermediate-risk patients with extensive ischemia, revascularization did not improve 30-day outcome (25.0% vs. 9.1% events; OR 3.3, 95% CI 0.5 to 24; $p = 0.32$). One patient died after successful revascularization before surgery because of a ruptured aortic aneurysm.

Late cardiac events. The incidence of the 3-year end point in low-, intermediate-, and high-risk patients was 0.7%, 3.7%, and 14.8%, respectively. No difference in 2-year

Table 1. Baseline Characteristics

Characteristic	All Patients	Patients With 1 or 2 Cardiac Risk Factors*	
		Testing	No Testing
No. of patients	1,467	386	384
Age (yrs)	67.0 (59.5, 73.8)	67.3 (60.9, 73.9)	68.0 (60.9, 73.5)
Men (%)	73.3	77.5	72.1
History of diabetes (%)	21.8	22.3	21.9
History of angina pectoris (%)	55.1	67.6	63.8
History of myocardial infarction (%)	27.0	18.7	15.9
History of congestive heart failure (%)	11.5	3.9	3.7
History of cerebrovascular accident (%)	19.1	16.1	16.7
History of renal failure (%)	8.5	4.9	6.0
Statin use (%)	42.1	42.8	42.2
ACE inhibitor use (%)	32.6	31.6	33.1
Aspirin use (%)	45.3	47.2	44.5
Type of surgery			
Thoraco-abdominal (%)	4.9	5.2	4.4
Tube graft (%)	12.6	15.0	10.7
Bifurcated graft (%)	38.1	38.9	34.1
Femoro-popliteal (%)	44.4	40.9	50.8

*Cardiac risk factors include: age ≥70 yrs, angina pectoris, myocardial infarction, congestive heart failure, cerebrovascular accident, diabetes mellitus, and renal failure (3).
ACE = angiotensin-converting enzyme.

outcome was observed in intermediate-risk patients with and without testing (4.3% vs. 3.1%; p = 0.30) (Fig. 3).

HR control. The incidence of the 30-day end point showed a significant correlation with HR control. The study aimed at a HR between 60 and 65 beats/min before surgery, and the median HR was 60 beats/min. The HR was below 50 beats/min in 1.7% of the intermediate-risk patients and more than 65 beats/min in 16.5% (no difference between allocated groups). Patients with a HR <65 beats/min had lower incidence of the primary end point than the remaining patients (1.3% vs. 5.2%; OR 0.24, 95% CI 0.09 to 0.66; p = 0.003). The incidence of the primary end point increased by a factor 1.5 (95% CI 1.1 to 2.0; p = 0.006) for each 5 beats/min heart-rate increase (Fig. 4).

DISCUSSION

In this randomized, multicenter study, we found that cardiac testing of intermediate-risk patients before major vascular surgery, as recommended by the guidelines of the ACC/AHA, provided no benefit in patients receiving beta-blocker therapy with tight HR control (1). Cardiac test results influenced patients' management. The treating physicians were aware of the presence of stress-induced myocardial ischemia as well as the HR at which ischemia occurred (i.e., ischemic threshold). Physicians were encouraged to control HR below the ischemic threshold. Furthermore, in a selected number of patients with extensive stress-induced ischemia, preoperative coronary revascular-

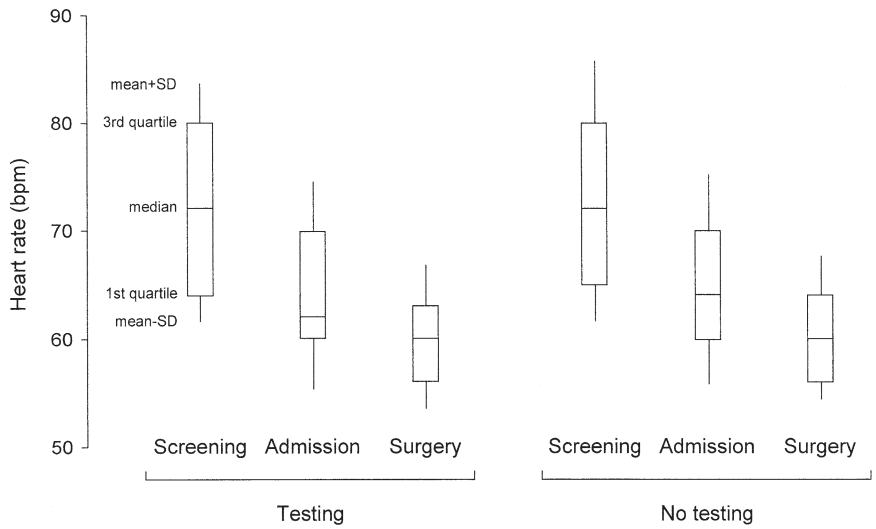

Figure 2. Heart rate at the screening visit, at the day of hospital admission, and immediately before surgery in patients allocated to cardiac testing **(left)** or no testing **(right)**. Heart rate values are presented as beats/min (bpm).

Table 2. Patient Outcome at 30 Days After Surgery

	No. of Patients	All-Cause Death (%)	p Value	Cardiovascular Death (%)	p Value	MI (%)	Cardiovascular Death or MI (%)	Odds Ratio (95% CI)	p Value
All patients	1,476	51 (3.5)		27 (1.8)		39 (2.6)	48 (3.3)		
Cardiac risk factors			0.002		<0.001				<0.001
0	354	6 (1.7)		1 (0.3)		0 (0)	1 (0.3)	1	
1 or 2	770	23 (3.0)		8 (1.0)		13 (1.7)	17 (2.2)	8.0 (1.1, 161)	
≥3	352	22 (6.3)		18 (5.1)		26 (7.4)	30 (8.5)	33 (4.8, ∞)	
Patients with 1 or 2 cardiac risk factors			0.14		0.29				0.62
Allocated to testing	386	15 (3.9)		6 (1.6)		7 (1.8)	9 (2.3)	1	
Allocated to no testing	384	8 (2.1)		2 (0.5)		5 (1.3)	7 (1.8)	0.78 (0.28, 2.1)	
Patients with 1 or 2 cardiac risk factors allocated to testing			<0.001		<0.001				<0.001
No ischemia	287	6 (2.1)		0 (0)		0 (0)	0 (0)	1	
1–4 ischemic segments	65	3 (4.6)		2 (3.1)		4 (6.2)	4 (6.2)	42 (2.2, ∞)*	
≥5 ischemic segments	34	6 (17.7)		4 (11.8)		3 (8.8)	5 (14.7)	107 (5.8, ∞)*	

*These estimators use a correction of 0.5 in the cell that contains a zero.
CI = confidence interval; MI = myocardial infarction.

ization was performed. According to the present guidelines, this is thought to be the optimal strategy. However, interestingly, compared with the no-testing population, a reverse trend in perioperative outcome was observed. An absolute increase in perioperative cardiac death or MI of more than 1.2% in patients assigned to no testing can be excluded with 95% certainty. Importantly, the strategy of no testing brought the operation almost 3 weeks forward.

Although testing identified a minority of intermediate-risk patients with an increased risk of perioperative cardiac death or MI, we considered the overall cardiac event rate of 2.2% in this population as sufficiently low to preclude testing.

Preoperative risk stratification with simple clinical cardiac risk markers effectively identified patients at low-, intermediate, and high-risk with a perioperative cardiac event rate of 0.3%, 2.2%, and 8.5%, respectively. The absence of the aforementioned cardiac risk factors identified a population of truly low risk, even in the presence of peripheral atherosclerotic disease. During long-term follow-up a similar trend was observed; the incidence of late cardiac death and MI in low-, intermediate-, and high-risk patients was 0.7%, 3.7%, and 14.8%, respectively (p = < 0.001) (Fig. 3).

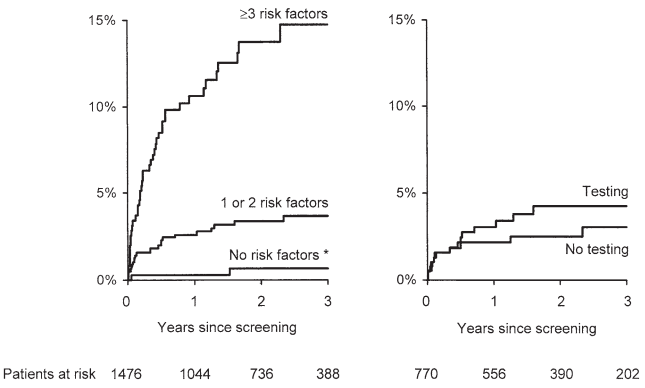

Figure 3. Incidence of cardiac death or myocardial infarction (MI) during 3-year follow-up according to the number of cardiac risk factors **(left)** and allocated strategy in patients with 1 or 2 cardiac risk factors only **(right)**. The incidence of cardiac death or MI was associated with the number of cardiac risk factors at screening (log-rank p < 0.001). There was no significant difference in the long-term incidence of cardiac events between patients allocated to cardiac testing or no testing (log-rank p = 0.30).

Beta-blocker therapy has become an essential part of the medical treatment of patients with acute coronary syndromes, also a major cause of perioperative adverse outcome. Two randomized trials showed that perioperative beta-blocker therapy was associated with an improved outcome in high-risk surgical patients (6,7). A recent large retrospective observational study, evaluating the effect from 663,635 surgical procedures confirmed the benefit of beta-blocker in those with increased risk (8). These promising results were questioned by a recent meta-analysis of 8 randomized clinical trials evaluating a total number of 1,152 patients. This meta-analysis showed only a nominal statistically significant effect of beta-blockers for the composite end point of 30-day cardiovascular mortality, nonfatal MI, and nonfatal cardiac arrest (relative risk 0.44; 95% CI 0.20 to 0.97) (9). Two more recently completed studies failed to show a favorable effect of beta-blockers. In the POBBLE (Perioperative Beta-Blockade) trial metoprolol failed to improve 30-day cardiovascular outcome in 97 low-risk vascular surgery patients; those with a history of ischemic heart disease were excluded (10). The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, involving 921 patients with diabetes undergoing non-cardiac surgery, failed to show that metoprolol significantly reduced the risk of death and cardiac complications after a median follow-up of 18 months (11).

A potential factor that might explain these conflicting study outcomes is a difference in dosing and HR control. Beta-blockers reduce HR and myocardial contractility and, subsequently, myocardial oxygen demand. To exert the optimal beneficial effect, dose adjustments for HR control are important. In a small randomized study, the HR threshold at which ischemia occurred was assessed with ambulatory electrocardiographic monitoring in 26 patients (12). These patients were randomized to either tight HR

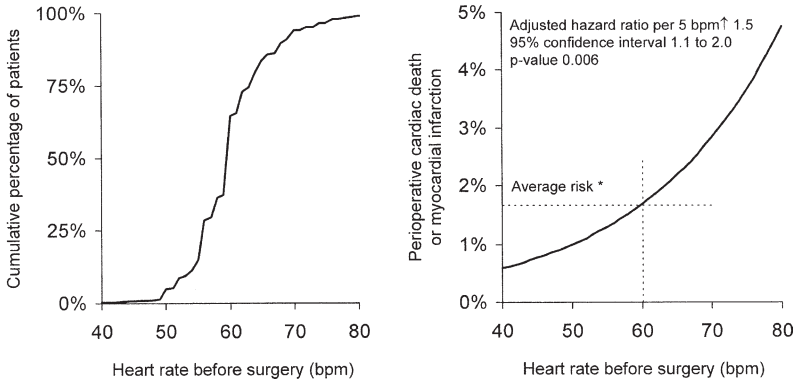

Figure 4. Cumulative distribution of the heart rate before surgery **(left)** and the relation between heart rate and perioperative cardiovascular events **(right)**. For this analysis we included patients with 1 to 2 risk factors. The hazard ratio was adjusted for clinical risk factors. bpm = beats/min.

control (i.e., 20% less than the ischemic threshold but >60 beats/min) or normal, non-adjusted beta-blocker therapy. Tight HR control was associated with a significant reduction of perioperative ischemia in 7.7% versus 92%. We confirmed these findings, because tight HR control was clearly associated with an improved outcome. We believe that for a proper interpretation of the perioperative cardiac protective effect of beta-blockers, the effect on HR control needs to be taken into account. This might be a potential limitation for clinical trials using a study design with blinded randomization and fixed beta-blocker doses.

Study limitations. The assessment of the HR at which ischemia occurred during stress-testing was only feasible in patients evaluated by dobutamine echocardiography. In patients evaluated by nuclear imaging only, the presence and extent of ischemia could be assessed. The effect of coronary revascularization in intermediate-risk patients with extensive stress-induced ischemia can not be assessed, owing to the insufficient number of patients studied.

Conclusions. In conclusion, we found that 30-day and long-term cardiac death and MI rate in intermediate-risk patients undergoing abdominal aortic or infrainguinal arterial reconstruction surgery was sufficiently low to preclude preoperative testing for coronary artery disease.

Acknowledgments

The authors are indebted to Margaret van Nierop for the outstanding care of blood sample collections of the study patients and thank Ian Thomson of the University of Alberta, Winnipeg, Canada, for his critical review of the manuscript.

Reprint requests and correspondence: Dr. Don Poldermans, Room H921, Department of Anesthesiology, Erasmus Medical Center, 3015 GD Rotterdam, the Netherlands. E-mail: d.poldermans@erasmusmc.nl.

REFERENCES

1. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2002;105:1257–67.
2. McFalls EO, Ward HB, Moritz TE, et al. Coronary artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2895–2904.
3. Boersma E, Poldermans D, Bax JJ, et al. Predictors of cardiac events after major vascular surgery: role of clinical characteristics, dobutamine echocardiography, and beta blocker therapy. JAMA 2001; 285:1865–73.
4. McNeill AJ, Fioretti PM, el-Said EM, Salustri A, Forster T, Roelandt JR. Enhanced sensitivity for the detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol 1992;70:41–6.
5. Elhendy A, Schinkel AF, van Domburg RT, Bax JJ, Valkema R, Poldermans D. Prognostic value of stress Tc-99m tetrofosmin SPECT in patients with previous myocardial infarction: impact of scintigraphic extent of coronary artery disease. J Nucl Cardiol 2004;11:704–9.
6. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996;335:1713–20.
7. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999;341:1789–94.
8. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005;353:349–61.
9. Devereaux PJ, Beattie WS, Choi PT, et al. How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials. BMJ 2005;331:313–21.
10. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR, POBBLE Trial Investigators. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg 2005;41:602–9.
11. Juul AB, Wetterslev J, Kofoed-Enevoldsen A, Callesen T, Jensen G, Gluud C. Randomized, blinded trial on perioperative metoprolol versus placebo for diabetic patients undergoing non-cardiac surgery. Circulation 2005;111:1725–8.
12. Raby KE, Brull SJ, Timimi F, et al. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. Anesth Analg 1999;88:477–82.

APPENDIX

For a list of the members of the DECREASE study group and the participating centers, please see the online version of this article.