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Michael Zaugg, Lukas Bestmann, Johannes Wacker, Eliana Lucchinetti ...+11 more authors

Institutions: University of Zurich, Triemli Hospital

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Abstract

BACKGROUND: Neuraxial blockade is used as primary anesthetic technique in one third of surgical procedures. The authors tested whether bisoprolol would protect patients at risk for cardiovascular complications undergoing surgery with spinal block. METHODS: The authors performed a double-blinded, placebo-controlled, multicenter trial to compare the effect of bisoprolol with that of placebo on 1-yr composite outcome including cardiovascular mortality, nonfatal myocardial infarction, unstable angina, congestive heart failure, and cerebrovascular insult. Bisoprolol was given orally before and after surgery for a maximum of 10 days. Adrenergic receptor polymorphisms and safety outcome measures of bisoprolol therapy were also determined. RESULTS: A total of 224 patients were enrolled. Spinal block could not be established in 5 patients. One hundred ten patients were assigned to the bisoprolol group, and 109 patients were assigned to the placebo group. The mean duration of treatment was 4.9 days in the bisoprolol group and 5.1 days in the placebo group. Bisoprolol therapy reduced mean heart rate by 10 beats/min. The primary outcome was identical between treatment groups and occurred in 25 patients (22.7%) in the bisoprolol group and 24 patients (22.0%) in the placebo group during the 1-yr follow-up (hazard ratio, 0.97; 95% confidence interval, 0.55-1.69; P = 0.90). However, carriers of at least one Gly allele of the beta1-adrenergic receptor polymorphism Arg389Gly showed a higher number of adverse events than Arg homozygous (32.4% vs. 18.7%; hazard ratio, 1.87; 95% confidence interval, 1.04-3.35; P = 0.04). CONCLUSIONS: Perioperative bisoprolol therapy did not affect cardiovascular outcome in these elderly at-risk patients undergoing surgery with spinal block.

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Adrenergic Receptor Genotype but Not Perioperative Bisoprolol Therapy May Determine Cardiovascular Outcome in At-risk Patients Undergoing Surgery with Spinal Block

The Swiss Beta Blocker in Spinal Anesthesia (BBSA) Study: A Double-blinded, Placebo-controlled, Multicenter Trial with 1-Year Follow-up

Michael Zaugg, M.D., Lukas Bestmann, Ph.D.,† Johannes Wacker, M.D.,‡ Eliana Lucchinetti, Ph.D.,§ Anita Boltres, M.D.,‖ Christian Schulz, M.D.,‖ Martin Hersberger, Ph.D.,# Gabriela Kälin, B.Sc.,** Lukas Furrer, M.D.,†† Christoph Hofer, M.D.,‡‡ Stephan Blumenthal, M.D.,§§ Annabelle Müller, Ph.D.,‖‖ Andreas Zollinger, M.D.,## Donat R. Spahn, M.D.,*** Alain Borgeat, M.D.†††*

Background: **Neuraxial blockade is used as primary anesthetic technique in one third of surgical procedures. The authors tested whether bisoprolol would protect patients at risk for cardiovascular complications undergoing surgery with spinal block.**

Methods: **The authors performed a double-blinded, placebo-controlled, multicenter trial to compare the effect of bisoprolol with that of placebo on 1-yr composite outcome including cardiovascular mortality, nonfatal myocardial infarction, unstable angina, congestive heart failure, and cerebrovascular insult. Bisoprolol was given orally before and after surgery for a maximum of 10 days. Adrenergic receptor polymorphisms and safety outcome measures of bisoprolol therapy were also determined.**

Results: **A total of 224 patients were enrolled. Spinal block could not be established in 5 patients. One hundred ten patients were assigned to the bisoprolol group, and 109 patients were assigned to the placebo group. The mean duration of treatment was 4.9 days in the bisoprolol group and 5.1 days in the placebo group. Bisoprolol therapy reduced mean heart rate by 10 beats/min. The primary outcome was identical between treatment groups and occurred in 25 patients (22.7%) in the bisoprolol group and 24 patients (22.0%) in the placebo group during the 1-yr follow-up (hazard ratio, 0.97; 95% confidence interval, 0.55–1.69; $P = 0.90$). However, carriers of at least one Gly allele of the β_1-adrenergic receptor polymorphism Arg389Gly showed a higher number of adverse events than Arg homozygous (32.4% *vs.* 18.7%; hazard ratio, 1.87; 95% confidence interval, 1.04–3.35; $P = 0.04$).**

Conclusions: **Perioperative bisoprolol therapy did not affect cardiovascular outcome in these elderly at-risk patients undergoing surgery with spinal block.**

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CARDIOVASCULAR morbidity and mortality after major noncardiac surgery is high in patients with or at risk of coronary artery disease. Approximately 1 in 10 patients must be expected to have cardiovascular complications.[1]‡‡‡ The costs and disease burden arising from these complications form the rationale for preoperative risk assessment and preventive medical therapies.[2,3] Based on two randomized trials[4,5] and smaller clinical trials[6–8] reporting short- and long-term cardiovascular benefits with perioperative β blockade, the American Heart Association and the American College of Cardiologists recommended the use of β blockers among high-risk patients undergoing noncardiac surgery.[2,3] However, three recent placebo-controlled trials[9–11] could not confirm these initial promising results, calling into question whether the previous findings can be generalized to the majority of surgical patients.

Neuraxial blockade is used as primary anesthetic technique in one third of surgical procedures, but its interaction with the putative benefits of β blockade remains elusive. Neuraxial blockade *per se* has several physiologic effects that could potentially improve cardiovascular outcome.[12] Direct administration of drugs to the spinal cord completely blocks pain fibers, thus preventing activation of the sympathetic nerve system, a key element in the pathogenesis of perioperative myocardial ischemia.[13] In fact, a large meta-analysis reported a reduction in mortality and myocardial infarction (of approximately 30%) in patients undergoing surgery with this technique compared with general anesthesia.[14] Conversely, the combination of two antiadrenergic strategies may harbor the threat of severe bradycardia and hypotension precipitating myocardial injury and cardiac ar-

* Privatdozent and Director, § Senior Researcher, Cardiovascular Anesthesia Research Laboratory, Institute of Anesthesiology, ‡ Attending Anesthesiologist, ‖ Resident in Anesthesiology, Institute of Anesthesiology, † Head, General Analytics, # Head, Special Analytics, ** Biomedical Scientist, Institute of Clinical Chemistry, ‖‖ Pharmacist, Cantonal Pharmacy KAZ, University Hospital Zurich. †† Resident in Anesthesiology, ‡‡ Attending anesthesiologist, ## Professor and Chief, Institute of Anesthesiology and Intensive Care Medicine, Triemli Hospital Zurich, Zurich, Switzerland. §§ Attending Anesthesiologist, †††; Professor and Chief, Department of Anesthesiology, Orthopedic University Clinic Balgrist Zurich, Zurich, Switzerland. *** Professor and Chair, Institute of Anesthesiology, University Hospital Lausanne, Lausanne, Switzerland.

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Address correspondence to Dr. Zaugg: Institute of Anesthesiology, E-HOF, University Hospital Zurich, and Zurich Center of Integrative Human Physiology ZIHP, University of Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland. michael.zaugg@usz.ch.

‡‡‡ http://www.ncepod.org.uk/20001.htm. Accessed December 13, 2006.

rest, which could abrogate the benefits of β blockade.[15] To date, no study has systematically investigated the short- and long-term cardiovascular effects of acute β blockade in patients undergoing surgery with neuraxial blockade.

Genetic polymorphisms of the β-adrenergic receptor genes alter receptor physiology and act as important disease modifiers.[16–19] Sequence variants were recently reported to influence the response to β-blocker treatment and to affect outcome.[20] Therefore, "average" beneficial and detrimental effects observed in clinical trials may result from subgroups of patients with a particular genetic background. To address this important confounding variable, four physiologically relevant nonsynonymous coding variants of the β-adrenergic receptor were determined in the study population.

We here report the results of a double-blinded, placebo-controlled clinical trial designed to test the hypothesis that the perioperative administration of bisoprolol reduces the incidence of cardiovascular complications defined as cardiovascular death, nonfatal myocardial infarction, congestive heart failure, and cerebral stroke in patients with or at risk for coronary artery disease undergoing surgery with spinal nerve block.

Materials and Methods

The Swiss Beta Blocker in Spinal Anesthesia (BBSA) study is a placebo-controlled, randomized trial with 1-yr follow-up, four participating centers (University Hospital Zurich, Orthopedic University Clinic Balgrist Zurich, Triemli Hospital Zurich, and University Hospital Lausanne), and blinding of all involved personnel. Blinding was maintained through selection, treatment, follow-up, data management, and analysis. The local ethics committees of the four hospital centers approved this study, and written informed consent was obtained from all patients.

Study Population and Treatment

Between January 2003 and January 2005, 224 patients scheduled to undergo surgery with spinal block were enrolled in this study. The randomization process used block randomization in a 1:1 ratio stratified by center. Inclusion criteria were (1) presence of coronary artery disease indicated by previous myocardial infarction, typical angina, atypical angina with a positive stress test, or history of coronary surgery and/or coronary intervention; (2) presence of at least two risk factors for coronary artery disease, including hypertension, diabetes, hypercholesterolemia (total serum cholesterol concentration $\geq$ 240 mg/dl or low-density lipoprotein cholesterol $\geq$ 160 mg/dl and high-density lipoprotein cholesterol $\leq$ 40 mg/dl), age older than 65 yr, and active smoking; and (3) duration of in-hospital stay of at least 24 h. Exclusion criteria were (1) chronic β blockade, (2) manifest congestive heart failure, (3) high-degree heart block, (4) active asthma necessitating daily medical treatment, and (5) left ventricular bundle branch block.

All patients received bisoprolol or placebo orally at least 3 h before spinal block and surgery. The study drug was titrated to heart rate and blood pressure. If systolic blood pressure was greater than 120 mmHg and heart rate was greater than 65 beats/min, 10 mg of study drug was given. If systolic blood pressure was less than 100 mmHg or heart rate was less than 50 beats/min, the study drug was withheld. In all other cases, 5 mg of study drug was given. In case of impossible oral administration of the study drug, intravenous metoprolol or matching placebo could be given, but was only necessary for a single application in one patient. All patients received 500 ml Ringer's solution before induction of spinal block. Spinal block was achieved in lateral or supine position at the L3–L4 or L4–L5 segment with 12–15 mg hyperbaric bupivacaine, 0.5%, and supplemented with clonidine (1–2 μg/kg) as per the attending anesthesiologist. Episodes of hypotension (systolic blood pressure $<$ 100 mmHg) and bradycardia ($<$ 50 beats/min) were treated with changing positioning, additional fluid administration, ephedrine, and atropine, respectively. Study drug was again administered within the first 6 h after the end of surgery. The treatment was continued until hospital discharge or for a maximum of 10 days. Administration of the study drug was always titrated to heart rate and blood pressure.

Outcome Measures and Follow-up

The primary outcome measure was time to the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, unstable angina, congestive heart failure, and cerebrovascular insult. In the presence of more than one outcome, the time of the first event was recorded. Death was considered a result of cardiovascular cause if the patient died of myocardial infarction, arrhythmia, congestive heart failure, or cerebral stroke. The diagnosis of a nonfatal myocardial infarction required a new Q wave, persistent ST–T-segment changes as defined by Minnesota Codes,[21] and/or association with elevated creatine kinase MB isoenzyme activity (above double the upper normal concentration) and/or troponins, or documentation of myocardial infarction in the medical chart. Unstable angina was diagnosed in patients with typical pain but no rise in cardiac enzymes together with an *ad hoc* medical intervention for unstable angina, or ST-segment depression, or T-wave inversion. The following events were used for the diagnosis of congestive heart failure: (1) a change in cardiovascular medication including start of medication, increasing dose of existing medication, or new class of medication for heart failure together with (2) at least one of the following two criteria: (a) clinical signs of pulmonary congestion or (b) abnormal results on chest x-ray. The

diagnosis of a cerebrovascular insult required the presence of clinical symptoms and a positive computer-assisted tomography scan. Short-term follow-up included perioperative Holter electrocardiography, collection of blood samples (before surgery, immediately after surgery, at 24, 48, and 72 h, and at discharge), and pulmonary function measurements before and after study drug administration. All patients had prospectively scheduled medical consultations at 6 and 12 months after the operation, independent of their usual clinical care, with 12-lead electrocardiogram and collection of blood samples. In addition, each patient's general physician was asked to prospectively record information on cardiovascular events and medication. Serious adverse events leading to withdrawal of the study drug were also recorded. Secondary outcomes were related to safety of perioperative bisoprolol therapy in patients undergoing surgery with spinal block and included perioperative occurrence of bradycardia (< 50 beats/min), hypotension (systolic blood pressure < 100 mmHg), and pulmonary function. From all blood samples, cardiac enzymes and N-terminal pro brain natriuretic peptide were determined. Pregnancy-associated plasma protein A and cystatin C were measured before surgery, 24 h (pregnancy-associated plasma protein A) or 72 h (cystatin C) after surgery, and 6 and 12 months later.

Cardiovascular Biomarkers

Blood samples were stored at −80°C until analysis. The following parameters were determined using the Roche Modular Analytics P or the Roche Modular Analytics E170 (Roche Diagnostics, Mannheim, Germany) as previously described[22]: N-terminal brain natriuretic peptide (electrochemiluminescence immunoassay)—sensitivity > 5 ng/l; intraassay and interassay coefficients of variance $< 3\%$; normal value (97.5th percentile) for men aged > 50 yr, < 334 ng/l; normal value for women aged > 50 yr, < 227 ng/l; cardiac troponin T (electrochemiluminescence immunoassay)—sensitivity > 0.01 μg/l; intraassay and interassay coefficients of variance $> 2.5\%$; normal value < 0.01 μg/l; total creatine kinase (enzymatic reaction with formation of reduced nicotinamide adenine dinucleotide phosphate)—sensitivity 2 U/l; intraassay and interassay coefficients of variance $< 2\%$; normal value for men ≤ 170 U/l; normal value for women ≤ 145 U/l; creatine kinase MB activity (immunologic ultraviolet assay)—sensitivity 5 U/l; intraassay and interassay coefficients of variance $< 2\%$; normal value ≤ 24 U/l; pregnancy-associated plasma protein A assays, purchased from Brahms, Henningsdorf, Germany (immunometric assay based on time resolved amplification cryptate emission)—sensitivity 0.004 U/l; intraassay and interassay coefficients of variance $< 2\%$; normal range (healthy male) < 0.01 U/l; and cystatin C assays, purchased from Dako A/S, Goldstrup, Denmark (particle-enhanced turbidimetric assay)—sensitivity > 0.2 mg/dl; intraassay and interassay coefficients of variance $< 3.5\%$; normal range 0.74–1.5 mg/l.

Holter Electrocardiography

Analysis of Holter electrocardiography data was performed as previously described.[23] Briefly, three-channel digital Holter electrocardiography monitoring was begun at least 2 h before surgery and continued for 24 h postoperatively (8500 series; GE Marquette Medical Systems, Milwaukee, WI). Seven bipolar leads were simultaneously recorded using silver–silver chloride electrodes. The effect of patient positional variation was measured in supine and upright positions. Holter electrocardiography data were analyzed for cardiac rhythm and ST-segment changes (Marquette Holter analysis system software version 8500; GE Marquette Medical Systems) indicative of ischemia after exclusion of abnormal QRS complexes. ST-segment changes were trended in three leads for the duration of the recording. Baseline ST-segment levels were defined as the average ST-segment during stable periods (at least 10 min) preceding each ischemic period. Electrocardiographic ischemic periods were defined as reversible ST-segment changes lasting at least 1 min and involving either a shift from baseline of ≥ 0.1 mV of ST depression or a shift from baseline of ≥ 0.2 mV of ST–T elevation at the J point. ST-segment depression was measured 60 ms after the J point, unless that point fell within the T wave, in which case it was shortened to the J point plus 40 ms. Holter analysis was corrected for positional variation by taking the maximum shift noted by positional changes. The following parameters were measured as indicators of the severity of each ischemic episode: total episodes per patient with ischemia, maximal ST depression, duration of longest ischemic episode, total area under the curve (defined as the integral of ST depression in mV × duration), and maximal area under the curve. Perioperative time was divided into three separate episodes (preoperative period, intraoperative period, postoperative period). Holter electrocardiography recordings were also analyzed for the occurrence of dysrhythmias using the aforementioned software. Ventricular and supraventricular ectopic beats were identified and counted. The number of runs and the percentage of recorded time with atrial fibrillation were calculated separately for each period.

Pulmonary Function

Vital capacity, forced vital capacity, forced expiratory volume in 1 s, mid expiratory flow, and peak expiratory flow were determined in an upright position of the upper body at the preoperative assessment (baseline without study drug) and 24 h after surgery using a portable spirometer (MicroLab ML3500; Labhardt AG, Basel, Switzerland). The physiologic parameters were

compared between the bisoprolol and the placebo group and related to the ADRB2 polymorphisms.

Genotyping

One hundred eighty-nine patients consented to genetic analysis. Two polymorphisms in the β_1-adrenergic receptor (ADRB1), namely ADRB1 Ser49Gly (refSNP ID§§§: rs1801252) and ADRB1 Arg389Gly (refSNP ID: rs1801253), and two polymorphisms in the β_2-adrenergic receptor (ADRB2), namely ADRB2 Gly16Arg (refSNP ID: rs1042713) and ADRB2 Gln27Glu (refSNP ID: rs1042714), were determined. Blood was obtained in 5-ml EDTA tubes. DNA was isolated either by a standard rapid lysis technique using the Qiagen QIAamp Blood kit (Qiagen, Hilden, Germany) or on a MagNA Pure LC system (Roche Diagnostics, Rotkreuz, Switzerland) and genotyped on a LightCycler instrument (Roche Molecular Biochemicals, Rotkreuz, Switzerland). The LightCycler is a combined microliter volume thermal cycler and fluorometer suitable for fast real-time fluorescence polymerase chain reaction. It is also designed for mutation detection by melting point analysis with fluorescent hybridization probes using the fluorescence energy transfer principle. LightCycler polymerase chain reaction protocols for the detection of the polymorphisms were developed. Usually, the test setup for the detection of the single nucleotide polymorphism is based on the principle of mutation detection by melting curve analysis with fluorescence energy transfer hybridization probes, using 6-carboxyfluorescein as donor molecule and LCRed 640 or LCRed 705 as acceptor molecules. The probes for the detection of the single nucleotide polymorphisms on the ADRB1 and ADRB2 segments were covered with only one dual-labeled probe, either fitting with the wild type or fitting with the mutation sequence. Hence, the probes were designed as beacons; the reporter dye was 6-carboxyfluorescein (detection channel 530 nm) for the wild type or Yakima Yellow (detection channel 560 nm) for the mutated alleles and the quenching molecule dabcyl. The modifications for the LightCycler setup (originally designed for the TaqMan instrument) were done as previously described.[24] The presence of a wild type evoked a clear amplification signal at the detecting wavelength of the wild-type probes, the homozygous mutated at the wavelength at which the mutated probes were labeled, and the heterozygous gave at both wavelengths a clear signal. For the analysis of the selected polymorphisms in the ADRB2, a single primer pair was used because the polymorphisms are in close proximity on the segment. Primers and probes were as previously published.[24] Additional technical information regarding the genotyping protocols is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org (table S1). In separate experiments, DNA samples from 12 randomly selected patients were tested with these LightCycler protocols and afterward subjected to sequencing for the ADRB1 and ADRB2 on the ABI 310 prism sequencer (PerkinElmer, Schwerzenbach, Switzerland) and used as controls.

Statistical Analysis

Mangano *et al.*[4] reported an event-free survival of 92% in the atenolol group and of 78% in the placebo group at 1 yr of follow-up. Based on these data, we estimated a minimum sample size of 101 patients in each group with a two-sided $\alpha = 0.05$ and a power of 80% (log rank test of event-free survival in two groups followed for a fixed time; nQuery Advisor, Statistical Solutions, Cork, Ireland) was required. Kaplan-Meier event-free survival curves were compared by log rank test. For biochemical and physiologic parameters, repeated-measures analysis of variance was used to evaluate differences over time between groups. All other data were analyzed using an unpaired *t* test for parametric data, or Mann–Whitney tests for nonparametric data. Categorical variables were summarized by proportions and compared using the Fisher exact test or the chi-square test, if appropriate. Cox proportional hazards regression was used to analyze the effect of several risk factors (predictor variables) on the occurrence of an event (coded "Y" if present and "N" if absent). A screening of all putative predictor variables was conducted using chi-square tests (contingency tables) in the case of nominal/categorical variables and using unpaired *t* tests in the case of continuous variables. All *P* values were recorded. In a first step, all variables with $P < 0.20$ entered a Cox proportional hazards regression, and the model coefficients were computed. Subsequently, all nonsignificant variables were removed in a stepwise manner. Odd ratios and confidence intervals (CIs) were computed using univariate Cox proportional hazards regression models. The interaction between bradycardia (or hypotension) and clinical predictors or genotype was tested using multivariate logistic regression. $P < 0.05$ was considered significant. Data are given as mean ± SD or median and quartiles, as appropriate. Analyses were performed using StatView Version 5 (SAS Institute, Chicago, IL).

Results

Two-hundred twenty-four patients were randomly assigned to bisoprolol and placebo. All patients were followed up for 1 yr. In 5 patients (2 bisoprolol, 3 placebo), the spinal block could not be successfully established. These patients underwent surgery in general anesthesia and thus were excluded from the final analysis. From the remaining 219 patients, 110 were assigned to the bisoprolol group and 109 patients to the placebo group. Patient

§§§ http://www.ncbi.nlm.nih.gov/SNP/index.html. Accessed January 2007.

Table 1. Characteristics of Patients

	Bisoprolol (n = 110)	Placebo (n = 109)
Demographics		
Age, mean (SD), yr	69 (11)	71 (10)
Number of women (%)	48 (44)	51 (47)
BMI, mean (SD), kg/m^2	28 (5)	28 (5)
Heart rate, mean (SD), beats/min	75 (11)	75 (12)
Systolic blood pressure, mean (SD), mmHg	146 (22)	144 (18)
Diastolic blood pressure, mean (SD), mmHg	81 (10)	79 (10)
Cardiovascular disease		
Heart failure (%)	5 (4.5)	6 (5.5)
Angina pectoris (%)	8 (7.3)	5 (4.6)
History of hypertension (%)	96 (87.3)	91 (83.5)
Hypercholesterolemia (%)	47 (42.7)	43 (39.4)
Previous myocardial infarction (%)	9 (8.2)	8 (7.3)
Pathologic Q waves on ECG (%)	3 (2.7)	7 (6.4)
Previous PTCA (%)	4 (3.6)	3 (2.8)
Previous CABG (%)	4 (3.6)	6 (5.5)
Previous stroke (%)	11 (10.0)	10 (9.2)
Limb arteriopathy		
Number of patients (%)	12 (10.9)	11 (10.1)
Diabetes mellitus		
Non–insulin dependent (%)	23 (20.9)	14 (12.8)
Insulin dependent (%)	7 (6.4)	7 (6.4)
Smoking		
Current smoker (%)	26 (23.6)	32 (29.4)
Former smoker (%)	60 (54.5)	64 (58.7)
COPD		
Number of patients (%)	16 (14.5)	17 (15.6)
Impaired renal function		
Number of patients (%)	10 (9.1)	18 (16.5)
Risk factors (DECREASE)*		
Number of patients (%) with score 0	28 (25.5)	25 (22.9)
Number of patients (%) with score 1 or 2	76 (69)	74 (67.9)
Number of patients (%) with score ≥ 3	6 (5.5)	10 (9.2)
Cumulative Cardiac Risk Index (Lee)†		
Number of patients (%) with score 0	55 (50.0)	57 (52.3)
Number of patients (%) with score 1 or 2	51 (46.4)	49 (45.0)
Number of patients (%) with score ≥ 3	4 (3.6)	3 (2.8)
Type of surgery		
Orthopedic surgery (%)	75 (68.2)	72 (66.1)
Urologic surgery (%)	26 (23.6)	29 (26.6)
Abdominal surgery (%)	4 (3.6)	2 (1.8)
Gynecologic surgery (%)	1 (0.9)	0 (0.0)
Plastic surgery (%)	1 (0.9)	4 (3.7)
Arterial vascular surgery (%)	1 (0.9)	0 (0.0)
Venous vascular surgery (%)	2 (1.8)	2 (1.8)
Duration of surgery		
Mean (range), min	97 (7–240)	93 (9–253)
Duration of anesthesia		
Mean (range), min	136 (41–290)	131 (28–253)

No significant differences were found between groups.

* As defined by the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) Study Group. Cardiac risk factors were age 70 yr or older, previous myocardial infarction, congestive heart failure, cerebrovascular event, diabetes mellitus, and impaired renal function (creatinine > 170 μM). † Revised Cardiac Risk Index score: ischemic heart disease, cerebrovascular disease, impaired renal function, and diabetes mellitus.

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; PTCA = percutaneous transluminal coronary angioplasty.

and perioperative characteristics were similar between groups (table 1). Recruitment of patients as per Mangano's criteria resulted in approximately 75% of patients having at least one risk factor as defined by the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) Study Group[25] or in approximately 50% of patients having one risk factor as defined by Lee *et al.*[26] Framingham Risk assessment[27] to estimate 10-yr risk for myocardial infarction and coronary death yielded a risk greater than 20% in 63% of the study patients (fig. S1, available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). The majority of patients were undergoing orthopedic (67%) or urologic (25%) surgery. Eight patients in the bisoprolol group and 9 patients in the

Table 2. Medical Therapy at the Start of the Trial and during the 1-Year Follow-up

	Cardiovascular Medication															
	Ca^{2+} Antagonists		Diuretics		ACEIs		AT II Receptor Blockers		Nitrates		Statins		Acetylsalicylic Acid		β Blockers	
	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P
Preoperative	20 (18)	19 (17)	35 (32)	45 (41)	34 (31)	34 (31)	19 (17)	19 (17)	6 (5)	2 (2)	26 (24)	23 (21)	31 (28)	26 (24)	0 (0)	0 (0)
Discharge	20 (18)	19 (17)	35 (32)	45 (41)	34 (31)	34 (31)	19 (17)	19 (17)	6 (5)	2 (2)	25 (23)	23 (21)	35 (32)	25 (23)	2 (2)	1 (1)
6 months	18 (17)	18 (17)	39 (36)	44 (40)	36 (33)	31 (28)	20 (18)	19 (17)	8 (7)	4 (4)	25 (23)	26 (24)	38 (35)	27 (25)	6 (6)	5 (5)
12 months	21 (19)	17 (16)	39 (36)	45 (42)	35 (32)	34 (32)	20 (19)	19 (18)	8 (7)	3 (3)	27 (25)	29 (27)	38 (35)	30 (28)	8 (7)	9 (8)

	Diabetes Medication						Other			
	Insulin		Sulfonylureas		Other Antidiabetics		COX-2 Inhibitors		NSAIDs	
	B	P	B	P	B	P	B	P	B	P
Preoperative	6 (5)	7 (6)	7 (6)	5 (5)	24 (22)	10 (9)	6 (5)	6 (6)	8 (7)	6 (6)
Discharge	6 (5)	7 (6)	7 (6)	5 (5)	17 (15)	6 (6)	12 (11)	11 (10)	7 (6)	6 (6)
6 months	6 (6)	7 (6)	8 (7)	5 (5)	19 (17)	9 (8)	7 (6)	10 (9)	9 (8)	5 (5)
12 months	6 (6)	7 (7)	8 (7)	6 (6)	20 (19)	11 (10)	6 (6)	10 (9)	9 (8)	5 (5)

Data are number of patients (%). The use of cardiovascular medication was similar in the two groups.

6 months = medication at 6 months postoperatively; 12 months = medication at 12 months postoperatively; ACEI = angiotensin-converting enzyme inhibitor; AT II = angiotensin II; B = bisoprolol; COX-2 = cyclooxygenase-2; Discharge = medication at discharge; NSAID = nonsteroidal antiinflammatory drug; P = placebo; Preoperative = medication at hospital admission.

placebo group had received β blockers during their follow-up (table 2).

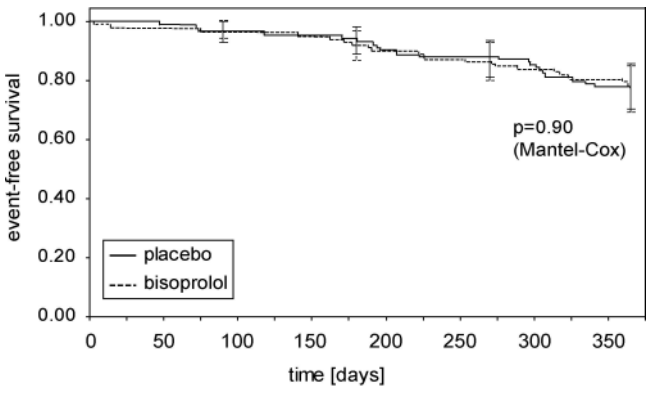
Primary Outcome

Four patients (2 bisoprolol patients with fatal cerebral stroke and fatal myocardial infarction, 2 placebo patients with cardiac death and death due to prostate cancer) died during the 1-yr follow-up. Twenty-five patients in the bisoprolol group (22.7%) and 24 in the placebo group (22.0%) had a positive primary outcome (table 3). Figure 1 shows the Kaplan-Meier estimates of the primary outcome measure in the two groups (log rank test, $P = 0.90$). Primary outcome was equally distributed over the follow-up period, and occurred in 2 bisoprolol-treated patients during the hospital stay or within 30 days postoperatively. Table 4 shows the predictors of the primary outcome in univariate Cox regression models. No significant effect of bisoprolol compared with placebo was observed (hazard ratio, 0.97; CI, 0.55–1.69; $P = 0.90$). Lee score, occurrence of perioperative hypotension or bradycardia, or presence of statin therapy did not provide prognostic information.

Table 3. Primary Outcomes

	Bisoprolol (n = 110)	Placebo (n = 109)
Cardiovascular death	2	1
Myocardial infarction	2	1
Stroke	2	2
Unstable angina	3	4
Congestive heart failure	16	16
All	25	24

One hundred eighty-nine patients were genotyped (86.3%). Genotyping success rate was 100% for the adrenergic receptor polymorphisms rs1801252, rs1042713, and rs1042714. For the ADRB1 Arg389Gly (rs1801253), genotype determination was successful in 92 bisoprolol- and 94 placebo-treated patients, respectively (186 of 189 patients,



number at risk

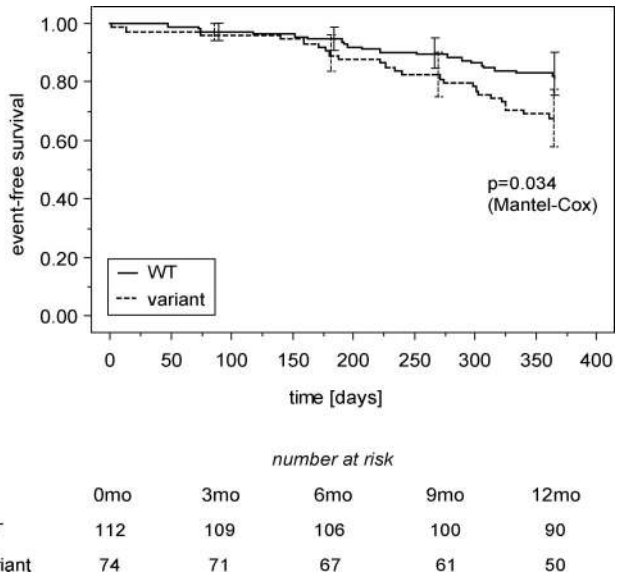
	0mo	3mo	6mo	9mo	12mo
placebo	109	106	103	96	84
bisoprolol	110	107	102	96	85

Fig. 1. Kaplan-Meier plot for adverse events during 1 yr of follow-up after perioperative bisoprolol and placebo therapy in 219 patients undergoing surgery in spinal block. Each *curve* represents the cumulative percentage of patients remaining event free. There is no difference in event-free survival in patients with bisoprolol compared with patients with placebo (77.3% *vs.* 78.0%, Mantel-Cox log rank rest; $P = 0.90$). Ninety-five percent confidence intervals are shown at 3, 6, 9, and 12 months.

Table 4. Cox Proportional Hazard Models for Primary Outcome

	Hazard Ratio (95% CI)	*P* Value
Univariate models		
Group	0.97 (0.55–1.69)	0.90
Age	0.99 (0.97–1.03)	0.97
Sex	0.98 (0.56–1.71)	0.93
β_1 Ser49Gly-variant	1.57 (0.82–2.98)	0.17
β_1 Arg389Gly-variant	1.87 (1.04–3.35)	0.04
β_2 Gly16Arg-variant	0.62 (0.35–1.11)	0.11
β_2 Gln27Glu-variant	1.40 (0.73–2.66)	0.31
Bradycardia	1.22 (0.65–2.26)	0.54
Hypotension	1.51 (0.85–2.66)	0.16
Lee score	1.11 (0.82–1.52)	0.50
Use of statins	0.67 (0.36–1.22)	0.19
History of smoking (pack-years)	1.01 (0.99–1.02)	0.12
NT-proBNP perioperative fold-change	0.61 (0.29–1.29)	0.20
Multivariate model		
β_1 Arg389Gly-variant	1.87 (1.04–3.35)	0.04

NT-proBNP = N-terminal pro brain natriuretic peptide.



number at risk

	0mo	3mo	6mo	9mo	12mo
WT	112	109	106	100	90
variant	74	71	67	61	50

Fig. 2. Kaplan-Meier plot for adverse cardiac events during 1 yr of follow-up stratified to the wild type (WT) or the variant (heterozygous and mutant) of the β_1-adrenergic receptor polymorphism Arg389Gly. Each *curve* represents the cumulative percentage of patients remaining event free. There is a significant difference in event-free survival in patients with the wild-type genotype compared with patients with the variant (81.3% *vs.* 67.6%, Mantel-Cox log rank test; $P = 0.034$). Ninety-five percent confidence intervals are shown at 3, 6, 9, and 12 months.

genotyping success rate 98.4%). Measured allele frequencies corresponded to frequencies observed in a Caucasian population. All study subjects had a Caucasian genetic background with Central European roots. The study population was in Hardy-Weinberg equilibrium for the adrenergic receptor polymorphisms rs1801252 ($P = 0.29$), rs1042713 ($P = 0.45$), and rs1042714 ($P = 0.31$) but not for rs1801253 ($P < 0.0001$; fig. S2, available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). In the bisoprolol and placebo groups, approximately 60% of the patients had the wild-type genotype of the ADRB1 Arg389Gly polymorphism (Arg389Arg), whereas approximately 40% of the patients had the variant genotype with at least one mutated allele (Arg389Gly or Gly389Gly). Forty-five of the genotyped patients had a positive primary outcome compared with four primary outcomes occurring in nongenotyped patients (45 of 186 *vs.* 4 of 33; $P = 0.20$). Twenty-one of the primary outcomes (21 of 112 [18.7%]) occurred in patients with wild-type genotype, and 24 (24 of 74 [32.4%]) occurred in patients with the variant genotype. Figure 2 shows the Kaplan-Meier estimates of the primary outcome measure in the two genotypes (log rank test, $P = 0.034$). The variant genotype was associated with a significantly higher number of adverse events (hazard ratio, 1.87; 95% CI, 1.04–3.35; $P = 0.04$). No differences in primary outcome were observed after placebo or bisoprolol treatment within the wild-type group or the variant group (wild-type placebo 13 of 57 [22.8%] *vs.* wild-type bisoprolol 8 of 55 [14.5%], $P = 0.33$; variant placebo 10 of 37 [27.0%] *vs.* variant bisoprolol 14 of 37 [37.8%], $P = 0.45$). No association of primary outcome with any of the other genotypes was observed (table 4).

Short-term Outcome Measures and Safety

Several biochemical markers of cardiovascular outcome, including N-terminal brain natriuretic peptide, cardiac troponin T, pregnancy-associated plasma protein A, and cystatin C, were determined in all patients to detect possible minor perioperative damage or long-term effects that might have escaped from clinical indicators and examinations. Except for perioperative N-terminal brain natriuretic peptide serum levels, for which moderate increases were previously reported after β-blocker therapy,[28] no differences between groups were noted (fig. S3, available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). Twenty-four–hour Holter electrocardiogram detected perioperative ischemic events in 8 patients (6 placebo and 2 bisoprolol patients; $P = 0.13$). Six of the seven genotyped patients with Holter-detected cardiac ischemia were Gly carriers in the ADRB1 Arg389Gly polymorphism (6 of 7 *vs.* 1 of 7; $P = 0.03$). The administration of bisoprolol doubled the number of patients experiencing bradycardia (bisoprolol 47 of 110 [43%] *vs.* placebo 23 of 109 [21%]; $P = 0.02$) (figs. S4–S7, available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). Multivariate logistic regression identified bisoprolol and the level of sympathicus block as important predictors of bradycardia (table 5). Blood pressure was significantly decreased in bisoprolol patients (fig. S7, available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org), but the number of hypotensive episodes did not reach statistical significance (bisoprolol 61 of 110 [55%] *vs.* placebo 49 of 109 [45%]; $P = 0.12$). Predictors of hypotension were the concomitant use of spinal clonidine, bradycardia itself, and the ADRB2 polymorphism Gly16Arg (table 6). Baseline heart rate or peri-

Table 5. Predictors of Bradycardia

	Odds Ratio (95% CI)	*P* Value
Univariate models		
Group	2.95 (1.62–5.38)	0.0004
ASA physical status	0.36 (0.15–0.85)	0.02
Level of sympathicus block (< T4)	1.80(1.00–3.27)	0.05
Clonidine	1.34 (0.71–2.55)	0.37
Bupivacaine	1.03 (0.95–1.13)	0.48
β_1 Ser49Gly-WT	0.97 (0.47–2.01)	0.93
β_1 Arg389Gly-WT	1.62 (0.85–3.07)	0.14
β_2 Gly16Arg-WT	0.82 (0.43–1.54)	0.53
β_2 Gln27Glu-WT	0.67 (0.35–1.30)	0.24
BMI	1.04 (0.96–1.08)	0.64
Age	1.01 (0.98–1.04)	0.58
Multivariate model		
Group	3.22 (1.74–5.98)	0.0002
Level of sympathicus block (< T4)	2.10 (1.12–3.92)	0.02

ASA = American Society of Anesthesiologists; BMI = body mass index; WT = wild type.

operative changes in heart rate were not predicted by any of the determined adrenergic receptor polymorphisms. The average administered dose of bisoprolol per day of treatment did not differ between Arg389Arg genotype and Gly carriers (6.3 ± 2.4 *vs.* 6.7 ± 2.0 mg; $P = 0.42$). Sixty percent of the patients had a history of smoking, and approximately 16% had chronic obstructive pulmonary disease. In each group, one patient experienced bronchospasm necessitating medical therapy. There was a small but significant postoperative decrease in peak expiratory flow in the bisoprolol patients compared with placebo patients (−6 ± 26% *vs.* 4 ± 41%; $P = 0.046$), which was not predicted by any of the determined adrenergic receptor genotypes nor the presence of chronic obstructive pulmonary disease (for detailed lung function analysis, see figs. S8–S10, available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org).

Table 6. Predictors of Hypotension

	Odds Ratio (95% CI)	*P* Value
Univariate models		
Group	1.52 (0.90–2.60)	0.12
ASA physical status	1.18 (0.60–2.30)	0.63
Level of sympathicus block (< T4)	1.93 (1.09–3.43)	0.03
Bradycardia	2.45 (1.36–4.43)	0.003
Clonidine	9.42 (4.18–21.2)	<0.0001
Bupivacaine	1.07 (0.99–1.16)	0.09
β_1 Ser49Gly-WT	0.42 (0.20–0.86)	0.02
β_1 Arg389Gly-WT	1.69 (0.93–3.05)	0.08
β_2 Gly16Arg-WT	2.05 (1.12–3.75)	0.02
β_2 Gln27Glu-WT	0.74 (0.41–1.36)	0.33
BMI	1.02 (0.96–1.07)	0.58
Age	1.00 (0.97–1.03)	0.94
Multivariate model		
Bradycardia	2.99 (1.47–6.09)	0.003
Clonidine	11.0 (4.26–28.5)	<0.0001
β_2 Gly16Arg-WT	2.28 (1.15–4.53)	0.02

ASA = American Society of Anesthesiologists; BMI = body mass index; WT = wild type.

Study Drug Administration and Compliance

Before administration of the first dose of study drug, heart rate and blood pressure did not differ between the two groups (table 1). Study drug was administered in all patients before surgery (table 7). The mean duration of drug administration was 4.9 days in the bisoprolol group and 5.1 days in the placebo group. Because of low heart rate and/or blood pressure, several patients received less study drug. During the treatment period, heart rate was on an average 10 beats/min lower in the bisoprolol group compared with the placebo group (figs. S4–S6, available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). In two patients of the bisoprolol group, study drug was discontinued earlier because β-blocker therapy was indicated. Study drug was discontinued earlier in three placebo patients and one bisoprolol patient because of adverse events (table 8).

Discussion

The results of this trial demonstrate that bisoprolol as perioperative adjunct to spinal block has no benefit on cardiovascular long-term outcome in patients with or at risk of coronary artery disease undergoing noncardiac surgery. The event-free survival in bisoprolol- and placebo-treated patients was identical after 1 yr of follow-up. The clinical outcome was corroborated by serial determinations of several sensitive prognostic biomarkers of cardiovascular outcome.[29]

In this study, exclusively patients who met the criteria by Mangano *et al.*[4] were enrolled. More than one third of these patients had overt cardiovascular disease. Despite this disease burden, the immediate perioperative complications were low, and no cardiovascular long-term benefits were observed during 1-yr follow-up after perioperative bisoprolol therapy. The following explanations for the lack of benefit can be offered. First, our study cannot exclude a smaller benefit after bisoprolol treatment than previously observed[4] because of its relatively small sample size. However, the largest difference that our study could have been expected to find with 80% power was 15%, making the current trial reasonably sensitive. Second, patients undergoing surgery with spinal block may have a lower risk *per se* because of the limited invasiveness of surgery conducted with neuraxial blockade[3] as well as its putative cardioprotective properties.[14,30] In fact, nearly all patients underwent orthopedic and urologic procedures with only intermediate surgical risk as classified by the American Heart Association.[2] This idea is further supported by the low incidence of cardiac ischemic events and the fact that pregnancy-associated plasma protein A, a marker of atherosclerotic plaque instability, did not change perioperatively, as opposed to cardiac surgery.[22] Hence, our findings are in line with the conclusions of a large retrospective cohort study[31] and of a

Table 7. Daily Dose of Bisoprolol and Placebo

	Preop		Postop		POD 1		POD 2		POD 3		POD 4		POD 5		POD 6		POD 7		POD 8		POD 9		POD 10	
	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P
Total number of patients	110	109	110	109	110	107	97	93	76	78	63	65	56	58	44	47	36	41	28	33	17	25	12	17
Full dose*	89	85	18	53	45	75	39	65	40	62	31	60	30	53	26	41	21	33	19	27	9	21	9	16
Half dose†	21	24	36	31	49	22	45	20	27	12	27	4	21	4	16	5	12	7	7	6	7	4	3	1
Not treated‡	0	0	54	25	16	10	13	8	9	4	5	1	5	1	2	1	3	1	2	0	1	0	0	0

Data are number of patients.

* Full dose = 10 mg. † Half dose = 5 mg. ‡ Not treated: because of heart rate less than 50 beats/min or systolic blood pressure less than 100 mmHg.

B = bisoprolol; P = placebo; POD = postoperative day; Postop = within 6 h after end of surgery; Preop = preoperative.

recent meta-analysis[32] dissuading from an unselective perioperative β-blocker use in intermediate-risk conditions. A recent guideline update on perioperative β-blocker therapy[3] restricts class I recommendations ("should be given") of perioperative β-blocker therapy to patients receiving β blockers for medical reasons and to patients undergoing vascular surgery at high cardiac risk owing to the finding of ischemia on preoperative testing. For patients with intermediate surgical risk and less prominent medical predictors of perioperative cardiovascular risk, as enrolled in our study, a recommendation class IIa ("are probably recommended") or IIb ("may be considered") can be made for perioperative β-blocker therapy with evidence level B (single randomized trial or nonrandomized studies) or C (consensus opinion of experts, case studies, or standard of care), respectively. Therefore, the findings of this trial certainly add valuable new information in this context.

We found that genetic variations in the ADRB1 at position 389 determined postoperative long-term event-free survival. To date, no perioperative β-blocker trial has addressed the role of adrenergic receptor polymorphisms on outcome or treatment effect. We here show that genetic variations in the ADRB1 at position 389 determined cardiovascular long-term outcome. *In vitro* studies of isoproterenol stimulation showed that Arg389Arg homozygous receptors produce higher levels of cAMP because of enhanced G-protein coupling compared with Arg389Gly and Gly389Gly receptors ("gain-of-function" polymorphism).[33,34] This is consistent with clinical studies showing increased prevalence of hypertension[35] and myocardial infarction in Arg389Arg homozygotes.[36] However, once ischemic heart disease is established, individuals carrying the Arg389Arg homozygous receptor may have a better prognosis. Using a transgenic mouse model with cardiac-specific overexpression of either human Gly389Gly or Arg389Arg ADRB1, Akhter *et al.* [37] showed that the Arg389Arg is linked to improved protection against myocardial ischemia/reperfusion due to adaptive signaling mechanisms. In addition, Arg389 homozygotes are more likely to benefit from β-blocker therapy.[17,38] In the β-Blocker Evaluation of Survival Trial (BEST) heart failure study, Arg389 homozygotes treated with bucindolol had the largest benefit in mortality reduction (−38%), whereas Gly389 carriers (*i.e.*, heterozygotes and Gly homozygotes) had virtually no clinical benefit from bucindolol therapy compared with placebo.[20,39] Taken together, these studies demonstrate a prominent biologic difference between wild-type ADRB1 Arg389Arg and Gly carriers (heterozygous Arg389Gly and homozygous Gly389Gly) and justify the use of a dominant genetic model in our analysis.

Table 8. Reported Serious Adverse Events

	Bisoprolol (n = 110)	Placebo (n = 109)
Cardiovascular		
Stroke	2	0
Bradycardia	0	3*
Hypotension	0	3*
Other		
Bronchospasm	1	1
Psychosis/delirium	4	1
All	7	8

* Three patients having two reported serious adverse events.

Our study sheds new light on past and future outcome trials investigating the effectiveness of perioperative β blockade. With respect to the study by Poldermans *et al.*,[5] it could be argued that enrollment of patients with a positive dobutamine stress echocardiography might introduce a bias toward the Arg389Arg ADRB1 genotype, because these patients exhibit enhanced responsiveness to catecholamines precipitating cardiac ischemia.[40] Skilled echocardiography investigators were reported to reliably predict a subject being homozygous for the Arg389 allele or homozygous or heterozygous for the Gly389 genotype.[41] Therefore, these preselected patients would profit greatly from perioperative β blockade[20,38] and explain the unusually high or "overestimated" protection observed in this study. Likewise, the benefits observed in the study by Mangano *et al.*[4] might have resulted from an uneven distribution of ADRB1 genotypes within strata. Even few patients could have biased the outcome, as evidenced by the loss of statistical significance in this study, if in-hospital events were included in the analysis. Finally, with respect to future β-blocker trials, our results imply that even large-scale

trials might be unable to ultimately decide whether perioperative β blockade is beneficial, unless detailed pharmacogenomic characterization of the study population will be performed. In support of this idea is the recent experience from the BEST study with more than 1,000 patients enrolled.[39] Bucindolol therapy was only advantageous in the Arg389Arg ADRB1 genotype and related to the degree of antagonized adrenergic activity and not—as previously speculated—by protection against excessive sympatholysis.[20] The question of whether β blockers reduce cardiac complications in patients selected by medical comorbidities is currently being addressed by the PeriOperative ISchemic Evaluation (POISE) trial.[42] However, to generate convincing conclusions on the efficiency of perioperative β blockade, the investigators of this trial will need to determine relevant, *i.e.*, disease-modifying, genotypes in their study population.

The results of our study also show an increased incidence of bradycardia and hypotension in the bisoprolol group, whereas bronchospasm only occurred in one bisoprolol and one placebo patient. Hypotension was particularly occurring if spinal clonidine was added to prolong the duration of the block. In a retrospective analysis, β-blocker use was recently shown to increase all-cause mortality in patients with a Revised Cardiac Risk Index of 0–1.[31] Although we were unable to show an association of hemodynamic sequelae with long-term outcome and some small studies reported good tolerance of neuraxial blockade with β blockers,[5,6] the lack of clear benefit in our patients highlights the need to carefully balance the risk and benefits of preventive perioperative β blockade, specifically in patients undergoing surgery with sympatholytic spinal block. Interestingly, the presence of the ADRB2 Gly16Gly genotype doubled the risk of hypotension. This finding is in contrast to a recent study evaluating the role of ADRB2 polymorphisms in young pregnant women,[43] a condition that is clearly different from the elderly patients with cardiovascular disease and multidrug therapy in our study. Also, the literature on this polymorphism is not conclusive because systemic infusion of isoproterenol evokes greater vasodilation in Arg16 than Gly16 homozygotes,[44] whereas local infusion demonstrates a greater vasodilator response in Gly16 than Arg16 homozygotes.[45] Moreover, there is strong linkage disequilibrium between codons 16 and 27 of the ADRB2 polymorphism, making the interpretation of clinical data difficult. Although polymorphisms of the ADRB2 were previously reported to be of relevance in asthma and chronic obstructive pulmonary disease patients,[46] we were unable to associate baseline or perioperative changes in pulmonary function to any of the investigated polymorphisms.

Recent placebo-controlled studies evaluating the protection of perioperative β blockade used metoprolol as study drug.[9–11] However, metoprolol is subject to extensive stereoselective metabolism. Polymorphic metabolism of β blockers is of clinical importance because poor metabolizers with genetic variants of cytochrome P450 may have increased plasma levels, whereas fast metabolizers may have insufficient β blockade.[47] Stereoselective metabolism related to genetic background was also reported for carvedilol.[48] Therefore, we have chosen bisoprolol as primary study drug because it is independent of clinically relevant genetic heterogeneity of drug metabolism.[49]

Study Limitations

Although all efforts were undertaken to maintain efficient blinding for the study drug throughout the trial, we cannot completely rule out that titration of the study drug to heart rate and blood pressure may have affected blinding. Another limitation of this study is that only 84.9% of the study patients were genotyped for the Arg389Gly polymorphism, which may have biased our findings. However, primary outcome events were evenly distributed between genotyped and nongenotyped individuals, and only 4 of the 49 events occurred in the nongenotyped patients.

We found a significant departure from Hardy-Weinberg equilibrium for ADRB1 Arg389Gly polymorphism with an excess of homozygous mutants (Gly389Gly). To exclude genotyping errors, we have carefully regenotyped patients, and the data were interpreted by three independent individuals. A likely reason for the observed deviation from Hardy-Weinberg equilibrium may be the obvious selection bias introduced in our study population because of inclusion and exclusion criteria of this randomized controlled trial. In fact, patients with a predefined cardiovascular risk and/or disease profile were enrolled. Also, mortality bias (differential survival of marker carriers) due to varying genetic and environmental background may have occurred. This is of particular relevance in our elderly study population at the end of life expectancy. Finally, we cannot rule out that the observed excess of homozygous Gly carriers might have contributed to genotype-related difference in outcome in our study population. Together, our data should be confirmed in a prospective clinical trial specifically designed and adequately powered to detect genotype-specific differences in cardiovascular outcome in patients with or at risk of coronary artery disease.

Conclusions

The results of this study provide evidence that widespread β-blocker prophylaxis for patients with or at risk of coronary artery disease having surgery with spinal block is not indicated. The results of our study also suggest that genetic heterogeneity of ADRB1 may translate into differences in clinical outcome, and further imply that future trials on perioperative β-blocker ther-

apy should genotype the study population to properly interpret study results. Although we were unable to differentiate specific responses of adrenergic receptor genotypes to bisoprolol therapy, an increasing body of evidence suggests that patients with defined adrenergic receptor genotypes may profit from β blockade, whereas others do not. Therefore, adrenergic receptor genotyping could help to optimize drug therapy by maximizing efficacy and limiting toxicity.

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References

1. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, Chong V, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, Irvin G III, McDonald G, Passaro E Jr, Phillips L, Scamman F, Spencer J, Stremple JF: The Department of Veterans Affairs' NSQIP: The first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. Ann Surg 1998; 228:491–507

2. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr: 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

3. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL: ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: Focused update on perioperative beta-blocker therapy: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery), developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine and Biology. Circulation 2006; 113:2662–74

4. 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

5. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H: 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

6. Urban MK, Markowitz SM, Gordon MA, Urquhart BL, Kligfield P: Postoperative prophylactic administration of β-adrenergic blockers in patients at risk for myocardial ischemia. Anesth Analg 2000; 90:1257–61

7. Zaugg M, Tagliente T, Lucchinetti E, Jacobs E, Krol M, Bodian C, Reich DL, Silverstein JH: Beneficial effects from beta-adrenergic blockade in elderly patients undergoing noncardiac surgery. ANESTHESIOLOGY 1999; 91:1674–86

8. Raby KE, Brull SJ, Timimi F, Akhtar S, Rosenbaum S, Naimi C, Whittemore AD: The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. Anesth Analg 1999; 88:477–82

9. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR: Perioperative β-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg 2005; 41:602–9

10. Yang H, Raymer K, Butler R, Parlow J, Roberts R: The effects of perioperative beta-blockade: Results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. Am Heart J 2006; 152:983–90

11. Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, Norgaard P, Fruergaard K, Bestle M, Vedelsdal R, Miran A, Jacobsen J, Roed J, Mortensen MB, Jorgensen L, Jorgensen J, Rovsing ML, Petersen PL, Pott F, Haas M, Albret R, Nielsen LL, Johansson G, Stjernholm P, Molgaard Y, Foss NB, Elkjaer J, Dehlie B, Boysen K, Zaric D, Munksgaard A, Madsen JB, Oberg B, Khanykin B, Blemmer T, Yndgaard S, Perko G, Wang LP, Winkel P, Hilden J, Jensen P, Salas N: Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: Randomised placebo controlled, blinded multicentre trial. BMJ 2006; 332:1482

12. Liu SS, McDonald SB: Current issues in spinal anesthesia. ANESTHESIOLOGY 2001; 94:888–906

13. Zaugg M, Schaub MC, Foex P: Myocardial injury and its prevention in the perioperative setting. Br J Anaesth 2004; 93:21–33

14. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S: Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: Results from overview of randomised trials. BMJ 2000; 321:1493

15. Zaugg M, Schulz C, Wacker J, Schaub MC: Sympatho-modulatory therapies in perioperative medicine. Br J Anaesth 2004; 93:53–62

16. Donahue MP, Marchuk DA, Rockman HA: Redefining heart failure: the utility of genomics. J Am Coll Cardiol 2006; 48:1289–98

17. Mialet Perez J, Rathz DA, Petrashevskaya NN, Hahn HS, Wagoner LE, Schwartz A, Dorn GW, Liggett SB: β1-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure. Nat Med 2003; 9:1300–5

18. Lanfear DE, Jones PG, Marsh S, Cresci S, McLeod HL, Spertus JA: β2-adrenergic receptor genotype and survival among patients receiving β-blocker therapy after an acute coronary syndrome. JAMA 2005; 294:1526–33

19. Zaugg M, Schaub MC: Genetic modulation of adrenergic activity in the heart and vasculature: Implications for perioperative medicine. ANESTHESIOLOGY 2005; 102:429–46

20. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, Nelson B, Morrison J, Domanski MJ, Wagoner LE, Abraham WT, Anderson JL, Carlquist JF, Krause-Steinrauf HJ, Lazzeroni LC, Port JD, Lavori PW, Bristow MR: A polymorphism within a conserved β1-adrenergic receptor motif alters cardiac function and β-blocker response in human heart failure. Proc Natl Acad Sci U S A 2006; 103:11288–93

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

22. Lucchinetti E, Hofer CK, Bestmann L, Hersberger M, Feng J, Zhu M, Furrer L, Schaub MC, Tavakoli R, Genoni M, Zollinger A, Zaugg M: Gene regulatory control of myocardial energy metabolism predicts postoperative cardiac function in patients undergoing off-pump coronary artery bypass graft surgery: Inhalational *versus* intravenous anesthetics. ANESTHESIOLOGY 2007; 106:444–57

23. Julier K, da Silva R, Garcia C, Bestmann L, Frascarolo P, Zollinger A, Chassot PG, Schmid ER, Turina MI, von Segesser LK, Pasch T, Spahn DR, Zaugg M: Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebo-controlled, multicenter study. ANESTHESIOLOGY 2003; 98:1315–27

24. Ranade K, Jorgenson E, Sheu WH, Pei D, Hsiung CA, Chiang FT, Chen YD, Pratt R, Olshen RA, Curb D, Cox DR, Botstein D, Risch N: A polymorphism in the β1 adrenergic receptor is associated with resting heart rate. Am J Hum Genet 2002; 70:935–42

25. Boersma E, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR: Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. JAMA 2001; 285:1865–73

26. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9

27. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97:1837–47

28. van den Meiracker AH, Lameris TW, van de Ven LL, Boomsma F: Increased plasma concentration of natriuretic peptides by selective β1-blocker bisoprolol. J Cardiovasc Pharmacol 2003; 42:462–8

29. Jaffe AS, Babuin L, Apple FS: Biomarkers in acute cardiac disease: The present and the future. J Am Coll Cardiol 2006; 48:1–11

30. Lee TW, Grocott HP, Schwinn D, Jacobsohn E: High spinal anesthesia for cardiac surgery: Effects on beta-adrenergic receptor function, stress response, and hemodynamics. ANESTHESIOLOGY 2003; 98:499–510

31. 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

32. Biccard BM, Sear JW, Foex P: Acute peri-operative beta blockade in intermediate-risk patients. Anaesthesia 2006; 61:924–31

33. Sandilands AJ, O'Shaughnessy KM, Brown MJ: Greater inotropic and cyclic AMP responses evoked by noradrenaline through Arg389 β1-adrenoceptors *versus* Gly389 β1-adrenoceptors in isolated human atrial myocardium. Br J Pharmacol 2003; 138:386–92

34. Mason DA, Moore JD, Green SA, Liggett SB: A gain-of-function polymorphism in a G-protein coupling domain of the human β1-adrenergic receptor. J Biol Chem 1999; 274:12670–4

35. Bengtsson K, Melander O, Orho-Melander M, Lindblad U, Ranstam J, Rastam L, Groop L: Polymorphism in the β1-adrenergic receptor gene and hypertension. Circulation 2001; 104:187–90

36. Iwai C, Akita H, Kanazawa K, Shiga N, Terashima M, Matsuda Y, Takai E, Miyamoto Y, Shimizu M, Kajiya T, Hayashi T, Yokoyama M: Arg389Gly polymor-

phism of the human β1-adrenergic receptor in patients with nonfatal acute myocardial infarction. Am Heart J 2003; 146:106–9

37. Akhter SA, D'Souza KM, Petrashevskaya NN, Mialet-Perez J, Liggett SB: Myocardial β1-adrenergic receptor polymorphisms affect functional recovery after ischemic injury. Am J Physiol Heart Circ Physiol 2006; 290:H1427–32

38. Bruck H, Leineweber K, Temme T, Weber M, Heusch G, Philipp T, Brodde OE: The Arg389Gly beta1-adrenoceptor polymorphism and catecholamine effects on plasma-renin activity. J Am Coll Cardiol 2005; 46:2111–5

39. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001; 344:1659–67

40. London MJ, Zaugg M, Schaub MC, Spahn DR: Perioperative beta-adrenergic receptor blockade: Physiologic foundations and clinical controversies. ANESTHESIOLOGY 2004; 100:170–5

41. La Rosee K, Huntgeburth M, Rosenkranz S, Bohm M, Schnabel P: The Arg389Gly β1-adrenoceptor gene polymorphism determines contractile response to catecholamines. Pharmacogenetics 2004; 14:711–6

42. Devereaux PJ, Yang H, Guyatt GH, Leslie K, Villar JC, Monteri VM, Choi P, Giles JW, Yusuf S: Rationale, design, and organization of the PeriOperative ISchemic Evaluation (POISE) trial: A randomized controlled trial of metoprolol *versus* placebo in patients undergoing noncardiac surgery. Am Heart J 2006; 152:223–30

43. Smiley RM, Blouin JL, Negron M, Landau R: Beta2-Adrenoceptor genotype affects vasopressor requirements during spinal anesthesia for cesarean delivery. ANESTHESIOLOGY 2006; 104:644–50

44. Gratze G, Fortin J, Labugger R, Binder A, Kotanko P, Timmermann B, Luft FC, Hoehe MR, Skrabal F: β-2 adrenergic receptor variants affect resting blood pressure and agonist-induced vasodilation in young adult Caucasians. Hypertension 1999; 33:1425–30

45. Garovic VD, Joyner MJ, Dietz NM, Boerwinkle E, Turner ST: Beta(2)-adrenergic receptor polymorphism and nitric oxide-dependent forearm blood flow responses to isoproterenol in humans. J Physiol 2003; 546:583–9

46. Ramsay CE, Hayden CM, Tiller KJ, Burton PR, Goldblatt J, Lesouef PN: Polymorphisms in the β2-adrenoreceptor gene are associated with decreased airway responsiveness. Clin Exp Allergy 1999; 29:1195–203

47. Lennard MS, Tucker GT, Silas JH, Freestone S, Ramsay LE, Woods HF: Differential stereoselective metabolism of metoprolol in extensive and poor debrisoquin metabolizers. Clin Pharmacol Ther 1983; 34:732–7

48. Zaugg M, Schaub MC, Pasch T, Spahn DR: Modulation of β-adrenergic receptor subtype activities in perioperative medicine: Mechanisms and sites of action. Br J Anaesth 2002; 88:101–23

49. Leopold G: Balanced pharmacokinetics and metabolism of bisoprolol. J Cardiovasc Pharmacol 1986; 8 (suppl 11):S16–20