

# Chronic $\beta$ Blockade Is Associated with a Better Outcome after Elective Noncardiac Surgery than Acute $\beta$ Blockade

## A Single-center Propensity-matched Cohort Study

Christoph Ellenberger, M.D.,\* Gordon Tait, Ph.D.,† W. Scott Beattie, M.D., Ph.D., F.R.C.P.C.‡

### ABSTRACT

**Background:** Current guidelines on perioperative care recommend the prophylactic use of  $\beta$  blockers in high-risk patients undergoing noncardiac surgery. However, recent studies show that, in some instances, perioperative  $\beta$  blockade can cause harm. Furthermore, chronic  $\beta$  blockade, titrated to effect before surgery, may be superior to acute perioperative  $\beta$  blockade. The primary objective of this study was to compare major cardiac outcomes in patients who underwent surgery with chronic  $\beta$  blocker therapy with those in patients with acute  $\beta$ -blocker therapy.

**Methods:** Data were collected for 10,691 consecutive patients undergoing elective noncardiac surgery between April 1, 2008, and April 30, 2010. Propensity scores, estimating the probability of receiving a preoperative  $\beta$  blocker, were calculated to match (1:1) the patients with acute and chronic  $\beta$ -blocker therapy. The primary outcome was a composite of myocardial infarction, nonfatal cardiac arrest, and perioperative mortality. The rate of cardiac events was compared in the matched cohorts.

**Results:** A total of 962 patients were chronically treated with a  $\beta$  blocker before surgery; in 436 patients, the  $\beta$  blocker was administered acutely. Propensity score matching created 301 patient pairs who were well-balanced for major comorbidities, concomitant drug use, and type of surgery. The primary outcome was observed in 9 (3.0%) chronic versus 24 (8.0%) acute  $\beta$ -blocked patients (relative risk, 2.67; 95% CI, 1.27–5.60;  $P = 0.011$ ).

\* Staff Anesthesiologist, Department of Anesthesiology, Pharmacology and Intensive Care, University Hospital of Geneva, Geneva, Switzerland; † Assistant Professor ‡ Professor, Department of Anesthesia and Pain Management, University Health Network, and Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada.

Received from the Department of Anesthesia and Pain Management, University Health Network, Toronto, Ontario, Canada. Submitted for publication September 24, 2010. Accepted for publication January 7, 2011. Supported by the R. Fraser Elliot Chair in Cardiac Anesthesia and the Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada (to Dr. Beattie).

Address correspondence to Dr. Ellenberger: Department of Anesthesiology, Pharmacology and Intensive Care, University Hospital of Geneva, Rue Gabrielle-Perret-Gentil 4, CH-1211 Geneva, Switzerland. christoph.ellenberger@hcuge.ch. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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### What We Already Know about This Topic

- $\beta$  Blockers may decrease the risk of myocardial infarction in patients undergoing noncardiac surgery, although acute  $\beta$  blockade may also increase the risk of stroke and all-cause mortality.

### What This Article Tells Us That Is New

- In a propensity-matched cohort, major adverse cardiac events were reduced by chronic, compared with acute,  $\beta$  blockade in patients undergoing noncardiac surgery.

**Conclusions:** Acute  $\beta$  blockade, initiated within the first 2 days after surgery, was associated with worse cardiac outcome compared with a matched cohort of patients who underwent surgery on chronic  $\beta$  blockade. These results should be validated in a larger prospective trial.

THE 2009 updated guidelines of the American College of Cardiology/American Heart Association on perioperative cardiovascular evaluation and care for noncardiac surgery gave perioperative  $\beta$  blockade (“heart rate control”) a class IIa recommendation in patients at cardiac risk.<sup>1</sup> If a patient is at risk and not already treated,  $\beta$ -blocker administration during surgery should be considered. The recommendation is based on the fact that several analyses of randomized perioperative  $\beta$ -blocker trials clearly indicate a reduction of perioperative cardiac events, although the magnitude of the effect varies considerably among the studies.<sup>2</sup> The Perioperative Ischemic Evaluation study,<sup>3</sup> a double-blind, randomized, controlled trial, showed that, despite a decrease in myocardial infarction, metoprolol succinate was associated with increased bradycardia and hypotension that, in turn, was associated with increased stroke rate and all-cause mortality. In light of the results of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography studies,<sup>4–6</sup> chronic  $\beta$  blockade, titrated to effect 30 days

Presented at the Best Abstracts of the Meeting Session of the American Society of Anesthesiologists Annual Meeting, October 18, 2010.

◇ This article is featured in “This Month in Anesthesiology.” Please see this issue of ANESTHESIOLOGY, page 9A.

before surgery, may be superior to acute  $\beta$  blockade, administered at surgery.<sup>7</sup> We are not aware of any studies making a direct comparison between chronic treatment and acute dosing.

Therefore, the purpose of this study is to compare the incidence of major adverse cardiac outcomes in patients who undergo surgery on chronic  $\beta$  blockade with the incidence in patients who undergo surgery with acute  $\beta$ -blocker therapy.

## Materials and Methods

### Study Setting, Patient Sample, and Data Collection

This article was prepared to conform to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.<sup>8</sup> The University Health Network (UHN) is a tertiary medical center in Toronto, Ontario, affiliated with the University of Toronto. UHN comprises three teaching hospitals: Toronto General Hospital, Princess Margaret Hospital, and Toronto Western Hospital. Noncardiac surgical services at UHN offer all types of surgery, including vascular, thoracic, visceral, head and neck, urologic, gynecologic, plastic, orthopedic, and spine surgery and neurosurgery. After obtaining approval from the UHN Research Ethics Board, we prospectively collected a detailed preoperative history for 10,691 consecutive adult patients (aged older than 18 yr) undergoing elective noncardiac surgery from April 1, 2008, to April 30, 2010, using an electronic structured questionnaire (Clinical Anesthesia Information System [CAIS] PreOp Clinic, Adjuvant Informatics, Flamborough, Ontario, Canada). The CAIS uses branched logic and is administered uniformly to all elective surgical patients at UHN by trained critical care nurses. The data set included patient demographics (*i.e.*, age, height, weight, and sex), history of anesthesia and surgery, comorbidities, a detailed list of medications, and information (such as date and type) on past noninvasive cardiac investigations (*i.e.*, stress testing, echocardiography, and Holter monitoring) and coronary revascularization procedures (*i.e.*, coronary bypass surgery and/or percutaneous coronary interventions). The CAIS prospectively calculates a Charlson score<sup>9</sup> and a revised cardiac risk index in each patient.

Information related to the surgery and postoperative events, including perioperative death, was downloaded to the Enterprise Electronic Data Warehouse from the hospital electronic charting system (MISYS CPR; Quadramed Corp., Reston, VA). The results of laboratory tests (*i.e.*, troponin, hemoglobin, and creatinine concentrations) were retrieved from the laboratory data warehouse. In-hospital drug administration was retrieved from the pharmacy database (PYXIS®; Pyxis Corp., San Diego, CA). The data from the different databases were linked using the patient's unique hospital identification number to create a comprehensive report of each patient in-hospital visit. Patients undergoing cardiac surgery or solid organ transplantation were not included in the database. If a patient underwent more than one surgery during the study period, only the last procedure was consid-

ered for this analysis. For the current study, we excluded all patients discharged the day of surgery or one day after because of a low risk for adverse events.<sup>10</sup> In a random sample of 50 patients, the electronic data were validated against the hospital record.

### Exposures and Outcomes

The main exposure variable was chronic *versus* acute  $\beta$  blockade. *Chronic  $\beta$  blockade* was defined as already receiving  $\beta$ -blocker therapy when presenting for the anesthesia consultation. The consultation takes place 7 to 10 days before surgery; therefore, treatment duration before surgery in patients who undergo surgery with chronic  $\beta$  blockade is at least 7 to 10 days. In addition, inclusion in the study required treatment continuation after surgery (no withdrawal). *Acute  $\beta$  blockade* was defined as not chronically using a  $\beta$  blocker when evaluated in the preoperative assessment clinic but taking a  $\beta$  blocker within the first 2 days after surgery. Administration during surgery was not considered because the pharmacy database does not allow for retrieval for intraoperative administration of any drug.

The expected incidence for a single adverse cardiac event in this elective patient population is low; therefore, we chose a composite of major cardiac events, including myocardial infarction, nonfatal cardiac arrest, and 30-day postoperative mortality, as the primary outcome. A patient with more than one single event was counted only once in the composite outcome. *Myocardial infarction* was defined as postoperative troponin I concentrations greater than 0.7  $\mu\text{g/L}$  (the institutional definition for myocardial infarction). Troponin I was measured using an assay (Dade Behring Dimension assay; Siemens Healthcare Diagnostics, Deerfield, IL). Nonfatal cardiac arrest was retrieved by analyzing the World Health Organization *International Classification of Diseases 10* codes, entered at hospital discharge. As secondary outcomes, we assessed the incidence of atrial fibrillation, postoperative stroke, congestive heart failure, and pulmonary embolism (all retrieved from the *International Classification of Diseases 10* codes).

### Analysis

Computer software (SAS version 9.1; SAS Institute, Inc., Cary, NC) was used for the statistical analysis. We used propensity scores, estimating the probability of receiving a preoperative  $\beta$  blocker, to adjust for baseline characteristics between the two cohorts. A nonparsimonious model predicting chronic  $\beta$  blockade was constructed using logistic regression. The following factors were considered: patient demographics (*i.e.*, age, sex, height, and body weight), relevant comorbidities (*i.e.*, diabetes mellitus, hypertension, coronary artery disease, history of congestive heart failure, cerebrovascular disease, and chronic obstructive lung disease), and preoperative cardiac medication (*i.e.*, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiplatelets, and statins). We also adjusted for the type of  $\beta$  blocker (*i.e.*, metoprolol, atenolol, bisoprolol, and

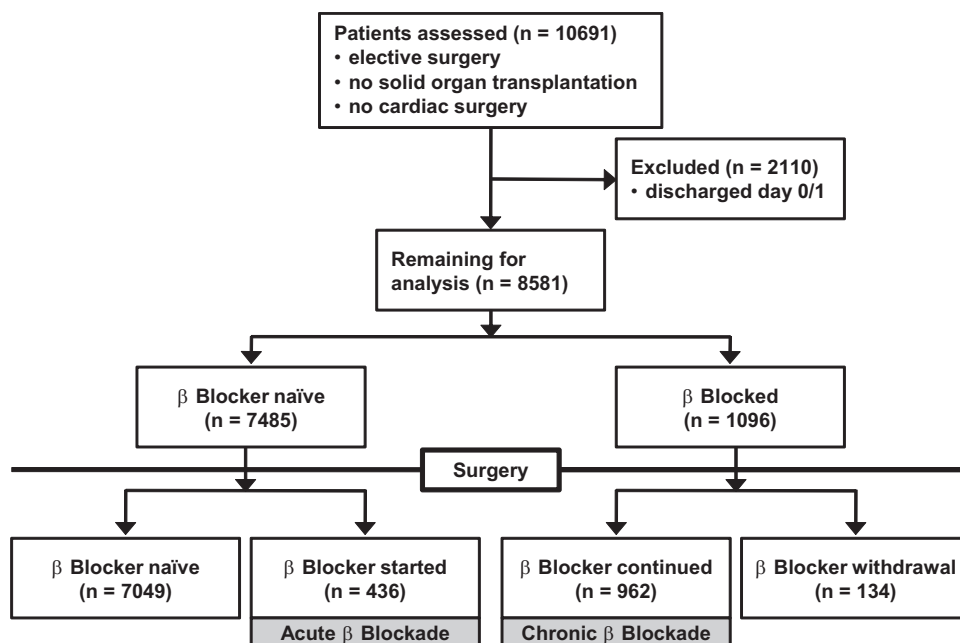


Fig. 1. Patient enrollment.

others) and the type of surgery (*i.e.*, cancer-related surgery and high-risk surgery [either vascular or thoracic]). We specifically did not include the individual risk scores in the matching algorithm (American Society of Anesthesiology physical status classification, revised cardiac risk index, and Charlson comorbidity score). In addition, no postoperative variables were included in the derivation of the model.

Chronically  $\beta$ -blocked patients were then individually matched (1:1) with patients in whom  $\beta$  blockers were initiated after the surgery based on the similarity of the propensity score.<sup>11</sup> A 5 $\leftarrow$ 1 computerized greedy matching technique was used for the matching process, whereby patients who underwent acute  $\beta$  blockade were first matched to patients who underwent chronic  $\beta$  blockade and had a propensity score that was identical in all five digits. Those who did not match were then matched to controls on four digits of the propensity score. This continued down to a one-digit match on propensity score for those who remained unmatched.<sup>§</sup>

If, after the matching, one or more variables remained unbalanced, interaction terms were included in the model. This multiple iterative procedure continued, without knowledge of the outcome, until the cohorts were balanced for all baseline covariates. We assessed the ability of the model to balance the two cohorts by using a standardized difference.<sup>12</sup> Differences of the absolute value lower than 10% indicate that the covariates are well-balanced. In the final model, only

one interaction term between cardiac ischemia and cardiac revascularization was needed to achieve good balance. Outcomes were compared using the McNemar test for paired categorical variables.

### Sensitivity Analysis

We found that the measurement of troponin was not balanced in the study sample in the matched cohorts. Troponin is not measured routinely, but its measurement is ordered as a result of intraoperative and postoperative events. The measurement can be considered as the result of an outcome or as a marker for increased morbidity. In fact, the mere act of ordering the assay has been associated with an increased relative risk of both in-hospital and 1-yr mortality, even if the test result was negative.<sup>13</sup> However, it cannot be denied that an imbalance in the number of troponin measurements between the two groups of interest may introduce a detection bias for myocardial infarction. To evaluate this bias, a *post hoc* sensitivity analysis was performed to assess the effect of chronic and acute  $\beta$  blockade on adverse cardiac outcomes after balancing troponin measurement in both cohorts. For the sensitivity analysis, the same statistical model was used, with the exception that troponin measurement was included.

### Results

Patient enrollment is shown in figure 1. Characteristics in patients who undergo surgery with chronic and acute  $\beta$ -blocker therapy before and after propensity score matching are shown in table 1. Those who underwent surgery on chronic  $\beta$  blockade were potentially at higher risk of postoperative cardiovascular morbidity. They were more likely to have hypertension, coronary artery disease, and a history of

§ Parsons L: Reducing bias in a propensity score matched-pair sample using greedy matching techniques, Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference, Long Beach, California, April 22–25, 2001. <http://support.sas.com/events/sasglobalforum/previous/index.html>. Accessed September 24, 2010.

**Table 1.** Patient Characteristics before and after Propensity Score Matching

Characteristics	Entire Sample			Propensity Matched Cohort		
	Chronic $\beta$ Blockade (n = 962)	Acute $\beta$ Blockade (n = 436)	<i>d</i>	Chronic $\beta$ Blockade (n = 301)	Acute $\beta$ Blockade (n = 301)	<i>d</i>
<b>Demographics</b>						
Age, yr*	68.3 $\pm$ 11.0	66.1 $\pm$ 12.6	-18.3	67.1 $\pm$ 12.6	67.5 $\pm$ 11.3	2.6
Height, cm*	165.7 $\pm$ 11.2	166.8 $\pm$ 11.1	9.8	165.5 $\pm$ 10.8	166.1 $\pm$ 11.1	5.4
Weight, kg*	82.5 $\pm$ 18.8	81.4 $\pm$ 19.7	-5.3	81.5 $\pm$ 18.4	81.4 $\pm$ 19.1	-0.7
Male sex	564 (58.6)	243 (55.7)	5.0	159 (52.8)	159 (52.8)	0
<b>Preoperative</b>						
<b>Comorbidities</b>						
Hypertension	830 (86.3)	314 (72.0)	-27.9	229 (76.1)	232 (77.1)	1.9
COPD	71 (7.4)	42 (9.6)	6.5	23 (7.6)	25 (8.3)	2.0
Stroke/TIA	167 (17.4)	70 (16.1)	-2.9	48 (16.0)	48 (16.0)	0
CAD	416 (43.2)	127 (29.1)	-24.6	80 (26.6)	90 (29.9)	6.1
CHF	78 (8.1)	20 (4.6)	-12.4	12 (4.0)	14 (4.7)	2.7
Coronary Revascularization	244 (25.4)	59 (13.5)	-25.7	37 (12.3)	42 (14.0)	4.1
Diabetes Mellitus	246 (25.6)	100 (22.9)	-5.1	68 (22.6)	74 (24.6)	3.9
Renal Disease	42 (4.4)	16 (3.7)	-2.9	12 (4.0)	13 (4.3)	1.4
Oncology Related	512 (53.2)	171 (39.2)	-23.2	135 (44.9)	130 (43.2)	-2.7
RCRI $\geq$ 2	246 (25.2)	82 (18.8)	-13.0	59 (19.6)	57 (18.9)	-1.4
Charlson Score $\geq$ 2	376 (39.0)	123 (28.2)	-18.5	87 (28.9)	92 (30.6)	1.8
<b>Medications</b>						
CCB	307 (31.9)	40 (9.2)	-51.9	36 (12.0)	40 (13.3)	3.3
ACE Inhibitors	398 (41.4)	65 (14.9)	-53.1	56 (18.6)	63 (20.9)	4.8
ARB	194 (20.2)	40 (9.2)	-27.2	45 (15.0)	38 (12.6)	-5.5
Antiplatelets	92 (9.6)	10 (2.3)	-28.3	10 (3.3)	8 (2.7)	-3.1
Statins	566 (58.8)	100 (22.9)	-65.8	84 (27.9)	92 (30.6)	4.8
Heparin	82 (8.5)	15 (3.4)	-16.5	17 (5.7)	15 (5.0)	-2.4
<b><math>\beta</math> Blocker Agent</b>						
Metoprolol	376 (39.1)	242 (55.5)	27.3	140 (46.5)	139 (46.2)	-0.5
Atenolol	299 (31.1)	67 (15.4)	-29.8	71 (23.6)	67 (22.3)	-2.6
Bisoprolol	167 (17.4)	65 (14.9)	-5.3	46 (15.3)	49 (16.3)	2.2
Other	120 (12.5)	62 (14.2)	4.3	44 (14.6)	46 (15.3)	-1.5
High-risk Surgery†	235 (24.4)	85 (19.5)	-8.0	63 (20.9)	61 (20.3)	-1.3
Major Cardiac Event‡	45 (4.7)	36 (8.3)	12.5	9 (3.0)	24 (8.0)	19.5

Data are given as number (percentage) of each group unless otherwise indicated.

\* Data are given as mean  $\pm$  SD. † Either vascular or thoracic surgery. ‡ The composite of cardiac arrest, myocardial infarction, and in-hospital death. Some patients may have had more than one outcome but are only counted once in the composite outcome.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCB = calcium channel blocker; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; *d* = standardized difference; RCRI = revised cardiac risk index; TIA = transient ischemic attack.

cardiac heart failure. Those on chronic  $\beta$  blockade also more frequently used the following medications: calcium channel blockers, statins, antiplatelets, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. In addition, patients with chronic  $\beta$ -blocker therapy underwent more cardiac revascularization procedures in their past and more patients had a revised cardiac risk index of 2 or greater. Metoprolol tartrate was the most frequently used  $\beta$  blocker; atenolol was used twice as often in patients with chronic treatment than in patients with acute  $\beta$ -blocker therapy. In the total cohort, the incidence of major cardiac events was 1.0% in  $\beta$  blocker-naïve patients, 4.7% in patients who received a chronic  $\beta$  blocker, 8.3% in patients who received an

acute  $\beta$  blocker, and 9.7% in patients in whom the  $\beta$  blocker was withdrawn.

### Adjustment for Confounders Using Propensity Score Matching

The algorithm matched 301 (69%) patients with acute  $\beta$  blockade to the cohort of patients who underwent surgery on chronic  $\beta$  blockade, with similar propensity scores. The matching process achieved a good balance for comorbidities, type of surgery, and medications, including the type of  $\beta$  blocker used. Again, metoprolol tartrate was the most frequently used  $\beta$  blocker, followed by atenolol and bisoprolol. Other  $\beta$  blockers used were acebutolol (more than 75% of

**Table 2.** Outcomes before and after Propensity Score Matching

Outcome	Entire Sample		Propensity-matched Cohort		RR (95% CI)	P Value
	Acute $\beta$ Blockade (n = 436)	Chronic $\beta$ Blockade (n = 962)	Acute $\beta$ Blockade (n = 301)	Chronic $\beta$ Blockade (n = 301)		
Major Cardiac Event	36 (8.3)	45 (4.7)	24 (8.0)	9 (3.0)	2.67 (1.27–5.60)	0.011
Infarct	32 (7.3)	39 (4.0)	20 (6.6)	6 (2.0)	3.33 (1.39–8.00)	0.007
Postoperative Death	2 (0.5)	11 (1.1)	2 (0.7)	2 (0.7)	1.00 (0.14–7.10)	1.000
Cardiac Arrest	3 (0.7)	7 (0.7)	2 (0.7)	4 (1.3)	0.50 (0.09–2.73)	0.688
Secondary Outcomes						
Atrial Fibrillation	17 (3.9)	14 (1.5)	13 (4.3)	6 (2.0)	2.17 (0.87–5.41)	0.144
Stroke/TIA	0 (0.0)	3 (0.3)	0 (0.0)	1 (0.3)	NA	NA
CHF	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.3)	NA	NA
Pulmonary Embolism	3 (0.7)	2 (0.2)	2 (0.7)	0 (0.0)	NA	NA

Data are given as number (percentage) of each group unless otherwise indicated.

CHF = congestive heart failure; CI = confidence interval; NA = not available; RR = relative risk; TIA = transient ischemic attack.

the remaining  $\beta$  blockers), carvedilol, labetalol, nadolol, propranolol, and sotalol. However, none of the patients was treated with esmolol.

The outcomes are shown in table 2. A total of 24 (8.0%) adverse cardiac events were observed in patients with acute  $\beta$ -blocker therapy compared with 9 (3.0%) events in patients who underwent surgery on chronic  $\beta$  blockade (relative risk, 2.67; 95% CI, 1.27–5.60;  $P = 0.011$ ). The most frequent event was myocardial infarction (2.0% in patient with chronic  $\beta$ -blockade and 6.6% in patients with acute  $\beta$ -blockade). Perioperative death and nonfatal cardiac arrest were rare events. There were four cardiac arrests in patients with chronic  $\beta$  blockade compared with two arrests in patients with acute  $\beta$  blockade, but the difference was not statistically significant (relative risk, 0.50; 95% CI, 0.09–2.73;  $P = 0.688$ ).

The incidence of new atrial fibrillation was higher in patients with acute  $\beta$ -blocker therapy, but did not reach statistical significance (relative risk, 2.17; 95% CI, 0.87–5.41;  $P = 0.144$ ). There was one stroke and one postoperative congestive heart failure in the cohort with chronic treatment, whereas two of the patients with acute  $\beta$ -blocker therapy had a pulmonary embolism.

To assess if  $\beta$  blockers were given as a result of an adverse cardiac event, we studied the records of the 20 patients with myocardial infarction who underwent surgery with acute  $\beta$ -blocker therapy. This analysis indicates that two patients may have received the  $\beta$  blockers as a direct result of an adverse cardiac event. However, excluding the two patients did not significantly influence the study result (relative risk, 2.44; 95% CI, 1.15–5.18;  $P = 0.024$ ).

### Sensitivity Analysis

To assess possible selection bias, a *post hoc* sensitivity analysis was conducted, in which the propensity score–matching algorithm was programmed to balance the number of troponin measurements. The algorithm created 300 patient pairs who were well matched for all baseline variables, including tro-

ponin measurement. Balancing troponin measurement resulted in a slight decrease in the relative risk for major adverse cardiac events in patients who underwent surgery with acute  $\beta$ -blocker therapy (relative risk, 2.20; 95% CI, 1.04–4.65;  $P = 0.05$ ).

### Discussion

This analysis found that, in patients undergoing elective noncardiac surgery, acute  $\beta$  blockade is associated with a significantly higher incidence of postoperative adverse cardiac events than chronic  $\beta$  blockade. Our analysis suggests that acute  $\beta$  blockade does not possess the magnitude of cardioprotective effects evident in patients presenting for surgery on chronic  $\beta$  blockade.

$\beta$  Blockers protect the heart by preventing myocardial oxygen supply–demand imbalance in the situation of surgical stress *via* reduction of the incidence of tachycardia.<sup>14</sup> Postoperative myocardial ischemia and infarction are typically preceded by an increase in heart rate, and tight heart rate control is associated with improved  $\beta$ -blocker efficacy.<sup>15,16</sup>  $\beta$  Blockers have antiinflammatory effects and may, therefore, protect the heart by stabilizing arteriosclerotic plaques and slowing down the progression of coronary atherosclerosis.<sup>17–19</sup> The course of these effects may require weeks to develop, which could partially explain the superior nature of chronic  $\beta$  blockade in our study. A further explanation may be that patients with chronic  $\beta$ -blocker therapy underwent a *de facto* titration process. Follow-up visits to the prescribing physicians would have allowed for dose adjustment, resulting in decreased side effects, and for drug substitution in intolerant patients.

### Comparison with Other Studies

To our knowledge, this is the first study making a direct comparison between chronic and acute  $\beta$  blockade. However, previous studies<sup>3,20–22</sup> in which  $\beta$ -blocker therapy was begun the day of surgery appeared to be less cardioprotective

than studies<sup>5,6</sup> in which the  $\beta$  blockade was titrated to effect well before surgery. For example, the Perioperative Ischemic Evaluation study showed a 16% relative risk reduction in the incidence of major cardiac events in patients treated with metoprolol succinate just before surgery.<sup>3</sup> The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography-IV trial showed a 67% relative risk reduction in the incidence of cardiac death or myocardial infarction in patients receiving bisoprolol, titrated to effect on average more than 30 days before surgery.<sup>5</sup>

Most studies investigating perioperative  $\beta$  blockade targeted high-risk patients and/or patients undergoing vascular surgery. In contrast, our study population includes all types of noncardiac surgery; most patients were at low to moderate risk for cardiac complications. The better part of our patients likely received  $\beta$  blockers to treat hypertension, not to prevent ischemic events.<sup>5</sup>

A recent study by Wallace *et al.*<sup>23</sup> assessed the effect of different patterns of use of perioperative  $\beta$  blockade on postoperative mortality. Although not a study outcome, acute  $\beta$  blockade appeared to be associated with a greater reduction in perioperative mortality than chronic  $\beta$  blockade. Our study sample is too small to comment on mortality rates; however, before matching, 11 deaths (1.1%) occurred in patients who underwent surgery on chronic  $\beta$  blockade compared with only 2 (0.5%) in patients with acute  $\beta$ -blocker therapy. It cannot be determined if this trend is a result of the higher risk seen in patients with chronic  $\beta$ -blocker therapy or if there is a relation with pattern of  $\beta$ -blocker use. The causes of death in the two patients with acute  $\beta$ -blocker therapy were pneumonia and intraabdominal sepsis. The causes of death in patients with chronic treatment were infection or sepsis ( $n = 4$ ), pulmonary embolism ( $n = 2$ ), congestive heart failure ( $n = 1$ ), myocardial infarction ( $n = 1$ ), and unwitnessed cardiac arrest ( $n = 1$ ).

### Strengths and Limitations of the Study

Our study sample included a wide variety of operative procedures in subjects with different comorbidities, increasing the generalizability of our results. Comorbidities and preoperative medication were collected prospectively, resulting in a higher sensitivity than retrospective data collection.<sup>24</sup> An evaluation of the accuracy of preoperative CAIS assessment revealed only 16 errors in 1,000 entries. However, CAIS is only used in elective patients. The incidence of adverse cardiac events in urgent/emergent patients may be much higher; an analysis of more than 60,000 consecutive noncardiac surgical patients at UHN showed a perioperative mortality rate of 0.66% in elective patients *versus* 4.4% in urgent/emergent patients (25% of all patients).

There are several limitations to be considered when interpreting the results of our study. First, the sample size of this study is small and the 95% CIs are large. The outcome is a result of the higher incidence of myocardial infarction in patients with acute  $\beta$ -blocker therapy. Perioperative death

and nonfatal cardiac arrest are rare; interestingly, more cardiac arrests occurred in patients with chronic treatment than in patients with acute  $\beta$  blockade. However, the numbers are too small to determine whether there is a relation with the pattern of  $\beta$ -blocker use or if the difference is simply because of chance. Furthermore, *International Classification of Diseases 10* codes were used to retrieve several outcomes, including nonfatal cardiac arrest, atrial fibrillation, stroke, congestive heart failure, and pulmonary embolism. Dependent on the outcome, administrative databases may severely underestimate their frequency.<sup>25</sup>

Second, as in any retrospective study, causality cannot be determined. In addition, the effects of unknown or unmeasured confounders on the observed association cannot be excluded. Neither the indication of the  $\beta$  blocker nor the duration of the chronic  $\beta$  blockade before surgery was known; both may have prognostic implications. Analyzing the patient records showed that two patients may have received a postoperative  $\beta$  blocker because of ongoing cardiac ischemia. Excluding these two patients did not change the study results; however, other events may occur, resulting in postoperative  $\beta$  blockade. Although not statistically significant, atrial fibrillation was more frequent in patients with acute  $\beta$  blockade and may, therefore, be another indication to begin  $\beta$ -blocker use. On the other hand, physicians considering postoperative  $\beta$  blockade may also prescribe an electrocardiogram more often and, therefore, detect atrial fibrillation more often. There is a chance that some patients were not receiving a preoperative  $\beta$  blocker (despite an increased risk of cardiac events) because of previous intolerance or a lack of response, which could have resulted in  $\beta$  blockers being administered postoperatively and, thus, being found in the group that underwent surgery with acute  $\beta$  blockade. Unfortunately, hemodynamic data to compare heart rate and blood pressure between the two cohorts are not available.

The database also contains no information regarding dosage of the  $\beta$  blocker; the administration of a small single dose, resulting in insufficient cardioprotection, is possible. Therefore, we reviewed the medical records of 50 randomly selected patients with acute  $\beta$ -blocker therapy. In 25 patients, the  $\beta$  blocker was started the day of surgery; in 20 patients, the  $\beta$  blocker was administered the first postoperative day; and in 5 patients, the  $\beta$  blocker was administered the second postoperative day. The dosage range for metoprolol was from 12.5 to 100 mg/d; atenolol, from 25 to 100 mg/d; and bisoprolol, from 2.5 to 10 mg/d. In all but one patient, the  $\beta$  blocker was given for several days (in most patients, it was given until discharge).

In conclusion, the results of this study suggest that acute  $\beta$  blockade, administered within 48 h after surgery, lacks the magnitude of cardioprotective effects evident in patients who present for elective noncardiac surgery with chronic  $\beta$ -blocker therapy. Perioperative  $\beta$  blockade should, if practicable, be initiated in advance of surgery. However, this does not mean that perioperative  $\beta$  blockade should be avoided in patients

who present with chronic indications but without chronic treatment. Our study does not allow comment on perioperative stroke and mortality, two major concerns associated with perioperative  $\beta$  blockade. Prospective data are needed to determine the influence of dose and timing on these important outcomes.

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