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Effect of β-blocker Prescription on the Incidence of Postoperative Myocardial Infarction after Hip and Knee Arthroplasty

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CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

Background: **American College of Cardiology/American Heart Association guidelines recommend β-blockade for selected low- and intermediate-risk noncardiac surgery patients. The authors evaluated the effect of perioperative β-blockade on postoperative myocardial infarction (POMI) in low-risk patients undergoing intermediate-risk surgery.**

Methods: **Patients who underwent elective hip or knee arthroplasty between January 1, 2002 and June 30, 2006 were identified. POMI was defined as a Troponin T value of more than 0.1 ng · ml^{-1}. Patients were divided into three groups: those prescribed a β-blocker on the day of surgery and throughout their hospital stay (or 7 days, whichever came first), those prescribed a β-blocker on the day of surgery but discontinued during the first 7 days, and those not prescribed a β-blocker on the day of surgery. Propensity analysis and logistic regression were used to determine the independent association of β-blocker exposure on POMI.**

Results: **Of the 5,158 arthroplasty patients, 992 (18%) were treated with β-blockers on the day of surgery. This β-blocker was discontinued in 252 patients (25%). POMI occurred in 77 patients (1.5%). Discontinuation of β-blocker prescription was significantly associated with POMI (odds ratio 2.0; 95% CI 1.1–3.9) and death (odds ratio 2.0; 95% CI 1.0–3.9).**

Conclusion: **After adjustment for confounders, discontinuation of β-blocker prescription during the first week after surgery was significantly associated with POMI and death. These findings confirm the American College of Cardiology/American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery, which recommend not to withdraw β-blocker therapy.**

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

◆ This article is accompanied by an Editorial View. Please see: London MJ: Perioperative β-blockade, discontinuation, and complications: Do you really know it when you see it? ANESTHESIOLOGY 2009; 111:690–4.

PERIOPERATIVE heart rate control with β-adrenoreceptor blockers (β-blockers) to prevent myocardial ischemia and infarction after noncardiac surgery is recommended in the 2007 American College of Cardiology/American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery.[1] These class II recommendations were largely based on two small trials, one of which enrolled very high-risk patients with multiple cardiovascular risk factors, and the methodology of the other has been the subject of discussion.[2,3] In contrast, several larger-sized trials failed to demonstrate benefit of perioperative β-blockade in terms of a reduced incidence of myocardial infarction.[4–7] Moreover, the recently published PeriOperative Ischemic Evaluation Study (8,351 patients) found that β-blockers reduced postoperative myocardial infarction, but at the cost of an increased stroke and mortality rate.[8] Untoward adverse events from β-blockers are of particular concern among lower-risk patients who contribute nearly 90% of the perioperative deaths but in whom the benefit of therapy has been questioned. Evaluation of a large administrative data set identified that patients with one or fewer cardiac risk factors showed no improvement in outcome (death) associated with β-blockade.[9] Although this study was designed carefully, its results must be interpreted with caution as the timing of β-blocker prescription and outcome could not be determined in the administrative database used. It is possible that the association between β-blockade and adverse outcomes resulted from appropriate prescriptions of β-blockers to patients who had suffered an adverse event (confounding by indication) rather than a failure of prophylaxis.

We performed this study to estimate the impact of perioperative β-blocker prescription on the occurrence of postopereative myocardial infarction (POMI) in a large cohort of low-risk patients undergoing joint arthroplasty in whom the timing of both β-blocker prescription and adverse events could be determined.

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Materials and Methods

Patients

After approval of the local Research Ethics Board (The Ottawa Hospital, Ottawa, Ontario, Canada), all patients undergoing elective hip or knee arthroplasty at The Ottawa Hospital between January 1, 2002 and June 30, 2006 were identified. The Ethics Board waived the need for written informed consent, as data were retrospective and anonymous. The Ottawa Hospital is a regional referral center and teaching hospital that provides approximately 1,400 hip and knee replacements annually. No restrictions on perioperative care were imposed during the time period in question. Patient fitness for surgery was assessed by an anesthesiologist in the Preoperative Assessment Unit, and preoperative testing was indicated by institutional guidelines. Patients felt to be at increased risk of perioperative complications could be referred for preoperative investigation and treatment at the discretion of the anesthesiologist performing the preoperative evaluation. Choice of intraoperative anesthetic and surgical technique was made by the attending anesthesiologist and surgeon, respectively. Daily postoperative care was provided by the orthopedic surgeons.

Data

All data were obtained from The Ottawa Hospital Data Warehouse, a peer-reviewed research infrastructure established to facilitate health services research. The Ottawa Hospital Data Warehouse integrates clinical data from laboratory, pharmacy, and radiology information systems with administrative data from patient registration and health records systems. Patients in the Ottawa Hospital Data Warehouse were identified by using encrypted unique identifiers. The linking of appropriate tables and the recoding of important variables of interest was performed by an experienced programmer and overseen by a health services researcher whose primary focus is the use of healthcare databases (Alan J. Forster, M.D., Ph.D., General Internist and Associate Professor, Department Internal Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada).

Patient gender, age, type of surgery, and the occurrence of death during admission were obtained from the patient registration system. Details regarding the dates and type of the β-blocker prescribed were identified by using pharmacy data. Troponin T, hemoglobin, and creatinine values were selected from laboratory data. Preexisting comorbid conditions were identified by using diagnostic codes in the discharge abstracts, except for chronic renal failure, which was defined as a preoperative creatinine value greater than 2 mg · dl^{-1}.

Perioperative β-blockade

The exposure of interest was the prescription of any β-blocker in the perioperative period. In most prospective trials, perioperative β-blockade was initiated on admission (the day before surgery) or at the day of surgery (postoperative day [POD] 0) and continued for at least 1 week or until discharge, but in two trials for up to 30 days after surgery.[2–6,8] In the current study, however, pharmacy data could not distinguish between prescriptions for chronic preoperative β-blocker treatment for hypertension or angina and those initiated prophylactically on admission. Furthermore, β-blockers ordered after the day of surgery may have been prescribed for the treatment of an ongoing adverse postoperative event and could not, for the purposes of this study, be considered a prophylactic risk reduction strategy. Therefore, patients were divided into three β-blocker exposure groups: those prescribed a β-blocker at any time on POD0 in whom prescription was continued for at least 7 days thereafter (or until hospital discharge, whichever came first), those prescribed a β-blocker on POD0 but in whom prescription was discontinued at any time during the first 7 days of surgery, and those not prescribed a β-blocker on POD0.

Outcome

The primary outcome of interest, POMI, was defined by a Troponin T value greater than 0.1 ng · ml^{-1} (highest value). POMI occurring between POD1 and POD10 were included. Coding of pharmacy data precluded the determination of the temporal relationship between exposure (β-blocker) and outcome (POMI) in units of time less than a calendar day. It was likely that a POMI on the day of surgery would prompt a postevent prescription for β-blocker leading to "confounding by indication." POMI occurring more than 10 days after surgery (POD10) could not be reliably recorded or linked to the surgical procedure in our inpatient data set. Death from all causes occurring from POD1 to POD10 was considered as a secondary outcome.

Analysis

SPSS 15.0 (SPSS inc., Chicago, IL) was used for statistical analysis. Baseline characteristics of all patients were described as proportions or mean ± SD as appropriate. Multivariable logistic regression was used to calculate the predicted probability of an individual being prescribed a β-blocker on admission (propensity score). As a Troponin was measured selectively in patients suspected of experiencing a POMI and/or myocardial ischemia, the propensity score included whether or not a Troponin was measured postoperatively. Patients prescribed a β-blocker might be perceived by their attending physicians to be at higher risk, resulting in a greater likelihood of having a Troponin level drawn. A greater frequency of Troponin assay may in turn increase detection of silent POMI in those patients who were on a β-blocker.

Two separate multivariable logistic regression models were subsequently used to determine the association between the β-blockade and outcome. In the first model,

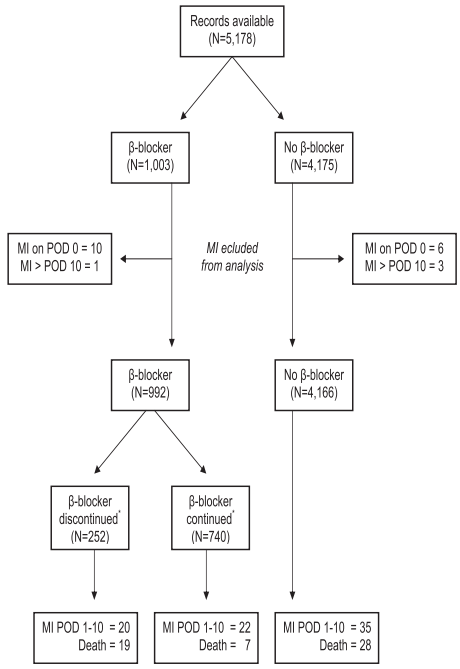

Fig. 1. Patient flow. * β-blocker discontinued means discontinuation of β-blocker prescription during the first week after surgery; β-blocker continued means that β-blocker prescription was continued for at least 1 week or until hospital discharge, whichever came first. MI = myocardial infarction, POD = postoperative day.

the likelihood of β-blockade (propensity score) and perioperative variables, including type of procedure and preoperative as well as postoperative hemoglobin level, were used to evaluate the relationship between β-blockade and outcome. In the second model the individual predictors form the Revised Cardiac Risk Index (RCRI)[10] were used to adjust the relationship between β-blockade and POMI for known correlates of postoperative cardiac morbidity. To facilitate interpretation, the association between β-blockade prescription status and outcome was stratified by using the four classes of the RCRI and postoperative hemoglobin level. Similar analyses were conducted to evaluate the association between β-blockade and all-cause mortality. The associations between β-blockade and the outcomes of interest were expressed as odds ratios (OR) or mean differences with 95% confidence interval (CI).

Results

In total 5,178 patient records were available, but 20 patients were excluded because they experienced a POMI on POD0 or after POD10 (fig. 1). A β-blocker was prescribed on POD0 to 992 (19%) of the remaining 5,158 patients. This β-blocker was discontinued within 7 days of surgery in 252 (25%) of these 992 patients (fig. 1). Patients who were prescribed a β-blocker were older and were more likely to have significant comorbidities (table 1). The factors associated with POMI and potentially related to prescription of a β-blocker on POD0 are described in table 2.

Of the 5,158 patients, 77 (1.5%) had a POMI between POD1 and POD10 (fig. 1), and 54 (1.0%) died within that interval. The event rate of POMI during the first 10 postoperative days was 3.0% (n = 22) in those who were prescribed a β-blocker during at least 7 days or until hospital discharge, 7.9% (n = 20) in those in whom the β-blocker prescription was discontinued during the first week, and 0.8% (n = 35) in patients who were not prescribed a β-blocker on POD0. Most events occurred

Table 1. Patient Characteristics

	β-blocker Discontinued during First Week (n = 252)	β-blocker Continued for at Least 1 Week or until Discharge (n = 740)	No β-blocker on Day of Surgery (n = 4,166)
Female gender	151 (59.9)	447 (60.4)	2548 (61.2)
Mean age, yrs (SD)	77.8 (10.6)	73.1 (10.3)	66.5 (13.2)
Preexisiting conditions			
Coronary artery disease	37 (14.7)	64 (8.6)	75 (1.8)
Congestive heart failure	24 (9.5)	36 (4.9)	55 (1.3)
Stroke	4 (1.6)	12 (1.6)	10 (0.2)
Chronic renal failure	20 (7.9)	21 (2.8)	42 (1.0)
Diabetes mellitus	27 (10.7)	75 (10.1)	238 (5.7)
Hemoglobin < 100 g $\cdot$ l^{-1}	31 (12.3)	68 (9.2)	427 (10.2)
Surgery			
Total hip arthroplasty	195 (77.4)	352 (47.6)	2,109 (50.6)
Total knee arthroplasty	57 (22.6)	388 (52.4)	2,057 (49.4)
Postoperative outcome			
Myocardial infarction	20 (7.9)	22 (3.0)	35 (0.8)
Death	19 (7.5)	7 (0.9)	28 (0.7)
Myocardial infarction or death	30 (11.9)	27 (3.6)	56 (1.3)
Myocardial infarction and death	9 (3.4)	2 (0.3)	7 (0.2)
Hemoglobin < 100 g $\cdot$ l^{-1}	174 (69.0)	497 (67.2)	2,735 (65.7)
Mean length of stay, days (SD)	11.9 (11.7)	10.3 (11.6)	7.7 (8.2)

Data expressed as number (%) unless otherwise specified.

β-blocker = those patients prescribed a β-blocker on the day of surgery; SD = standard deviation.

Table 2. Association between Preoperative Characteristics and POMI

	POMI (n = 77)	No POMI (n = 5,081)	Odds Ratio (95% CI)	*P* Value
β-blocker on day of surgery	42 (54.5)	950 (18.7)	5.2 (3.3–8.2)	< 0.01
Atenolol, bisoprolol	10 (13.0)	271 (5.3)	4.4 (2.1–8.9)	< 0.01
Metoprolol	25 (32.5)	518 (10.2)	5.7 (3.4–9.6)	< 0.01
Other	7 (9.1)	161 (3.2)	5.1 (2.2–12)	< 0.01
Discontinued during first week after surgery	20 (26.0)	232 (4.6)	10 (5.8–18)	< 0.01
Continued for at least 1 week or until hospital discharge	22 (28.6)	718 (14.1)	3.6 (2.1–6.2)	< 0.01
Female gender	39 (50.6)	3,107 (61.1)	0.7 (0.4–1.0)	0.06
Mean age, yrs (SD)	80 ± 8.9	68 ± 13.1		< 0.01
Preexisitng comorbid conditions				
Coronary artery disease	25 (32.5)	151 (3.0)	16 (9.5–26)	< 0.01
Congestive heart failure	21 (27.3)	94 (1.9)	20 (12–34)	< 0.01
Stroke	1 (1.3)	25 (0.5)	2.7 (0.4–20)	0.32
Chronic renal failure	10 (13.0)	73 (1.4)	10 (5.1–21)	< 0.01
Diabetes mellitus	11 (14.3)	329 (6.5)	2.4 (1.3–4.6)	< 0.01
Revised Cardiac Risk Index				
Class I	28 (36.4)	4,502 (88.6)	Reference	
Class II	32 (41.6)	502 (9.9)	10 (6.1–17)	< 0.01
Class III	15 (19.5)	63 (1.2)	38 (19–75)	< 0.01
Class IV	2 (2.6)	14 (0.3)	23 (5.0–106)	< 0.01
Preoperative hemoglobin < 100 g · l^{-1}	20 (26.0)	506 (10.0)	3.2 (1.9–5.3)	< 0.01
Postoperative hemoglobin < 100 g · l^{-1}	67 (87.0)	3,339 (65.7)	3.5 (1.8–6.8)	< 0.01
Knee replacement surgery	15 (19.5)	2,487 (48.9)	0.3 (0.1–0.4)	< 0.01

CI = confidence interval, POMI = postoperative myocardial infarction.

during the first 5 days after surgery (fig. 2). Patients on a β-blocker had a longer hospital stay (table 1).

Age, comorbidity, β-blocker prescription, preoperative, and postoperative hemoglobins < 100 g · l^{-1} and total knee arthroplasty were significantly associated with POMI (table 2). Patients in whom β-blocker prescription was discontinued during the first week had a much higher risk for POMI (OR 10, 95% CI 5.8–18). Increasing cardiovascular risk, as defined by RCRI, was also associated with increased risk of POMI. β-blockers of relatively short and long durations of action had comparable effects on the occurrence of POMI.

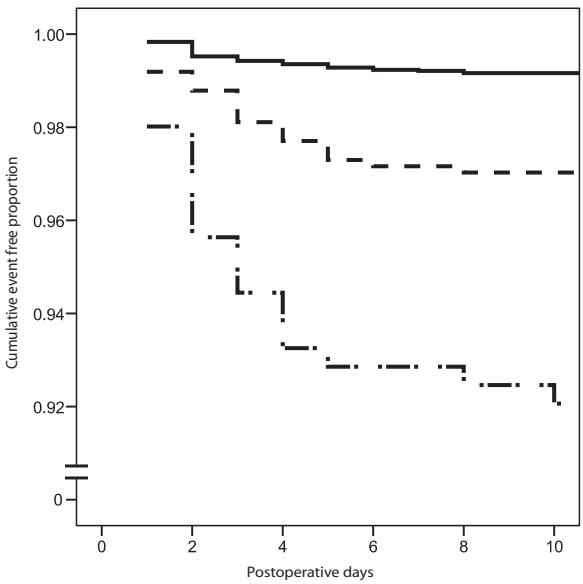

Fig. 2. Kaplan-Meier curve showing the cumulative event-free proportion (a myocardial infarction did not occur) during the first 10 postoperative days. The *solid line* represents patients who were not prescribed a β-blocker on the day of surgery (cumulative event rate 0.8%). The *dashed line* represents those patients who were prescribed a β-blocker on the day of surgery and in whom this prescription was continued for at least 1 week or until hospital discharge, whichever came first (cumulative event rate 3.0%). The *dashed - dotted line* represents those who were prescribed a β-blocker on the day of surgery and in whom this prescription was discontinued during the first week after surgery (cumulative event rate 7.9%).

A propensity score predicting the probability of a patient being prescribed a β-blocker on POD0 was calculated. The area under the receiver operator characteristic curve of the propensity score model was 0.71 (95% CI 0.69–0.73) (table 3). The propensity score for prescription of a β-blocker on POD0 was subdivided into quintiles to enhance interpretation of this propensity score when it was used to risk-adjust the association between

Table 3. Factors Related to β-blocker Prescription on the Day of Surgery (Propensity Score)

Factor	β	Odds Ratio (95% CI)	*P* Value
Age (per year)	0.045	1.05 (1.04–1.06)	< 0.01
Female gender	−0.160	0.85 (0.73–0.99)	0.04
Coronary artery disease	1.223	3.43 (2.47–4.76)	< 0.01
Stroke	1.543	4.68 (2.04–10.7)	< 0.01
Congestive heart failure	0.478	1.61 (1.07–2.44)	< 0.01
Diabetes mellitus	0.332	1.39 (1.07–1.81)	0.03
Chronic renal failure	0.856	2.35 (1.47–3.78)	< 0.01
Postoperative Troponin measurment	0.525	1.69 (1.37–2.09)	< 0.01

The factors reported in this table were used to calculate a propensity score that was used to risk-adjust the association between β-blockade and perioperative myocardial infarction. The area under the receiver operating characteristic curve of this propensity score was 0.71 (95% CI 0.69–0.73).

CI = confidence interval.

Table 4. Association between β-blocker Prescription and Postoperative Myocardial Infarction, Adjusted for the Risk of Being on a β-blocker on the Day of Surgery by Using the Propensity Score

	Odds Ratio (95% CI)	*P* Value
No β-blocker on day of surgery	Reference	
β-blocker discontinued during first week	2.0 (1.1–3.9)	0.04
β-blocker continued for at least 1 week	1.5 (0.9–2.8)	0.15
Propensity score		
0.0–0.20	Reference	
0.20–0.40	43 (5.8–315)	< 0.01
0.40–0.60	174 (23–1316)	< 0.01
0.60–0.80	480 (62–3700)	< 0.01
0.80–1.0	683 (67–7010)	< 0.01
Knee replacement (*vs.* hip)	0.6 (0.3–1.1)	0.11
Preoperative hemoglobin (per 10 g · l^{-1} <)	1.0 (0.8–1.1)	0.57
Postoperative hemoglobin (per 10 g · l^{-1} <)	1.5 (1.2–1.8)	< 0.01

CI = confidence interval.

β-blocker prescription and outcomes (table 4). Discontinuation of β-blocker prescription during the first week was significantly associated with POMI (table 4), whereas continuation was not. For every decrease in postoperative hemoglobin with 10 g · l^{-1}, the risk of POMI increased by 50% (OR 1.5, 95% CI 1.2–1.8). Adjustment for confounding factors included in the RCRI instead of using the propensity scores yielded comparable results (table 5). The area under the receiver operator characteristic curve of the RCRI predicting POMI was 0.77 (95% CI 0.70–0.83).

Discontinuation of β-blocker prescription was associated with death (OR 2.0, 95% CI 1.0–3.9), but continuation showed a nonsignificant trend to improvement

Table 5. Association between β-blocker Prescription and Postoperative Myocardial Infarction, Adjusted for the Risk of Being on a β-blocker on the Day of Surgery by Using the Cardiac Risk Factors as Included in the Revised Cardiac Risk Index

	Odds Ratio (95% CI)	*P* Value
No β-blocker on day of surgery	Reference	
β-blocker discontinued during first week	2.3 (1.2–4.7)	0.02
β-blocker continued for at least 1 week	2.0 (1.1–3.7)	0.02
Age (per 10 yrs >)	2.0 (1.5–2.6)	< 0.01
Female gender	0.5 (0.3–0.9)	0.02
Coronary artery disease	4.3 (2.4–7.9)	< 0.01
Stroke	0.9 (0.1–7.5)	0.94
Congestive heart failure	4.4 (2.3–8.5)	< 0.01
Diabetes mellitus	1.1 (0.5–2.4)	0.78
Chronic renal failure	2.6 (1.2–6.0)	0.02
Knee replacement (*vs.* hip)	0.6 (0.3–1.1)	0.12
Preoperative hemoglobin (per 10 g · l^{-1} <)	1.1 (0.9–1.3)	0.36
Postoperative hemoglobin (per 10 g · l^{-1} <)	1.4 (1.1–2.0)	< 0.01

CI = confidence interval.

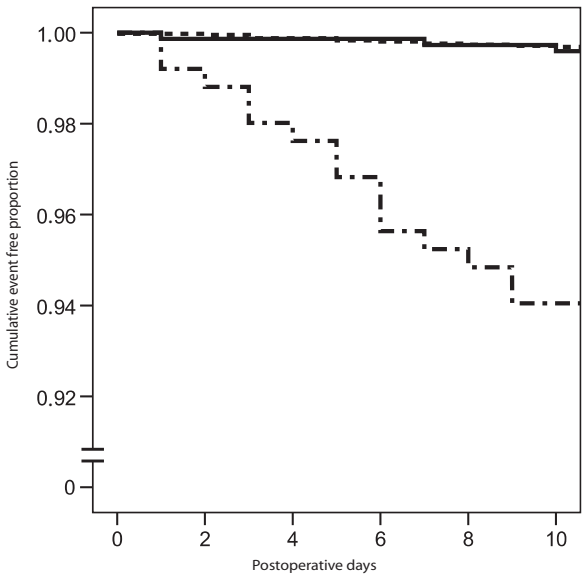

Fig. 3. Kaplan-Meier curve showing the cumulative event-free proportion (death did not occur) during the first 10 postoperative days. The *dotted line* represents patients who were not prescribed a β-blocker on the day of surgery (cumulative event rate 0.7%). The *solid line* represents those patients who were prescribed a β-blocker on the day of surgery and in whom this prescription was continued for at least 1 week or until hospital discharge, whichever came first (cumulative event rate 0.9%). The *dashed - dotted line* represents those who were prescribed a β-blocker on the day of surgery and in whom this prescription was discontinued during the first week after surgery (cumulative event rate 7.5%).

(OR 0.5, 95% CI 0.2–1.2) (fig. 3). Other variables significantly associated to death were knee replacement (OR 0.2, 95% CI 0.1–0.6) and the propensity score (model not shown).

Figure 4 graphically shows the incidence of POMI stratified across RCRI class, β-blocker prescription status, and postoperative hemoglobin. In both postoperative hemoglobin categories (fig. 4A postoperative hemoglobin greater than 100 g · l^{-1} and fig. 4B postoperative hemoglobin less than 100 g · l^{-1}), discontinuation of β-blocker prescription was associated with an increased risk of POMI, especially in lower-risk patients (RCRI I and II).

Finally, a comparable regression analysis including all POMI (*i.e.*, including those occurring on POD0 and after POD10) was conducted. This analysis did not change the direction of our findings.

Discussion

The results of this observational study indicate that discontinuation of β-blocker prescription during the first week after surgery in patients undergoing hip and knee arthroplasty was significantly associated with POMI (OR 2.0, 95% CI 1.1–3.9) and death (OR 2.0, 95% CI 1.0–3.9). A lower postoperative hemoglobin level independently contributed to this risk. The association between

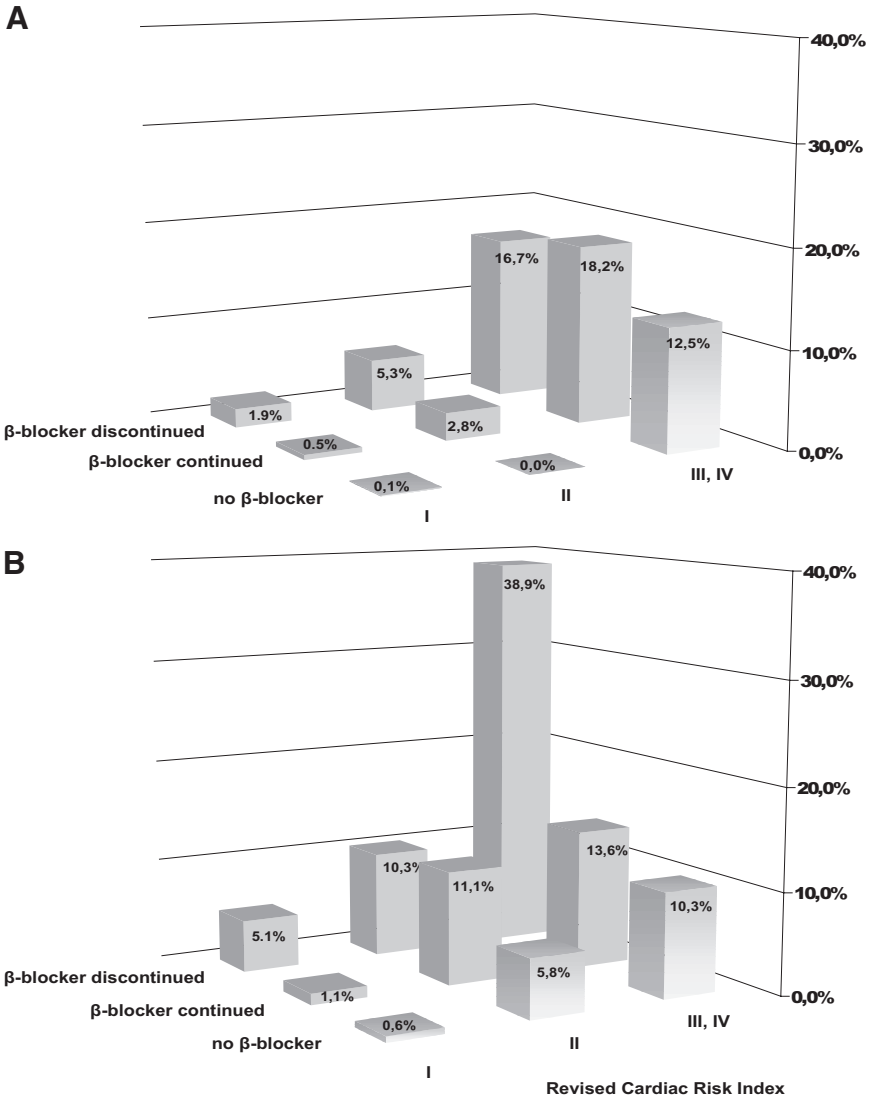

Fig. 4. The incidence of postoperative myocardial infarction, stratified across Revised Cardiac Risk Index classes, β-blocker prescription status, and postoperative hemoglobin (*A*) greater than 100 g · l^{-1} and (*B*) less than 100 g · l^{-1}.

β-blocker discontinuation and POMI persisted after adjustment for factors predicting the use of a β-blocker and risk factors known to predict adverse cardiac events.

Our results showed a significant association with POMI and mortality in those patients in whom β-blocker prescription was discontinued. These results seem to support and might explain Lindenauer's findings that use of β-blockers in low-risk populations did not yield an improvement in perioperative mortality.[9] In this study of more than 650,000 patients undergoing elective noncardiac surgery, more than 120,000 (18%) received a β-blocker during the first two postoperative days. The vast majority (86%) of the patients in this large administrative data set had no more than one cardiac risk factor (RCRI class I and II). Among these patients at low cardiovascular risk, β-blocker treatment was associated with no benefit and possible harm with an OR for mortality of 1.4 (95% CI 1.3–1.6) and 1.1 (95% CI 1.0–1.3) in patients classified as RCRI I and II, respectively. A reduction in mortality with β-blockade was noted only among the minority (2.6%) of patients with at least three cardiac risk factors. However, although this was a carefully designed study, its results must be interpreted with caution because the timing of β-blocker prescription and outcome could not be determined in the administrative database used.

Some remarks about the three perioperative β-blocker groups should be made. First, in the group in which β-blocker prescription was discontinued, the reasons for discontinuation were not known, and these patients had higher baseline risk for the occurrence of the outcome (table 1). Cessation of β-blocker prescription could be in response to an acute event that preceded POMI or death. Furthermore, the group that was never prescribed a β-blocker (our control group) may have included patients who were on a β-blocker at home but in whom a β-blocker was not started on admission. In fact, such patients were withdrawn, which may have increased the number of events in the control group, resulting in a weakening of the association between discontinuation

of β-blocker prescription and POMI (*i.e.*, the reported OR of 2.0 is underestimated). Finally, a β-blocker prescribed on the day of surgery and afterwards for at least 1 week seemed to fail to improve outcomes in low-risk patients (RCRI class I and II) (table 4). It should be noted, however, that we were not able to distinguish between patients who were on chronic β-blockade and those who were prescribed β-blockers perioperatively, which is an important limitation. Although multivariable regression techniques were used to adjust for factors associated with β-blocker prescription and conditions known to be associated with postoperative cardiac morbidity, it remains possible that β-blockade represents a surrogate for risk factors not assessed or adjusted for in our models. On the other hand, results from randomized trials of perioperative β-blockade do suggest that lower-risk populations may not benefit from prophylaxis. Two trials of perioperative β-blockade, the Diabetic Postoperative Mortality and Morbidity[4] and Metoprolol after Vascular Surgery[5] trials, recruited patients from relatively unselected groups of patients perceived to be at risk of perioperative cardiac events. The Diabetic Postoperative Mortality and Morbidity trial enrolled 961 patients with a single cardiac risk factor (diabetes mellitus) and found no reduction in risk with perioperative metoprolol therapy (hazard ratio 1.1; 95% CI 0.8–1.4).[4] Similarly, metoprolol prophylaxis failed to significantly reduce the relative risk of cardiac events (relative risk reduction 15%; 95% CI −38% to 48%) in a population of 494 patients undergoing vascular surgery in whom 297 (60%) had only a single risk factor.[5] In contrast, the large-sized Perioperative Ischemic Evaluation Study included intermediate risk patients and found significant reductions in perioperative cardiac morbidity in all RCRI subgroups of patients, but at the cost of an increased overall mortality and stroke rate.[8] It should be mentioned that the dosing of metoprolol in this trial was higher than the generally recommended starting dose of metoprolol.[11,12] It might be argued that this high dose contributed to the increased incidence of side effects (mortality and stroke). However, a recent meta-analysis showed that the incidence of cerebrovascular accidents and hypotension was uniform in all studies included.[13]

Perioperative physicians have long assumed that blunting of the adrenergic response to anesthesia and surgery with β-blockers would favor oxygen supply-demand relationships and reduce myocardial ischemia and infarction in high-risk patients.[14] Nothing in this pathophysiological model would suggest that lower-risk patients would fail to benefit from reduced myocardial oxygen demand, and yet a variety of studies suggest that such do not benefit from β-blockers. Why should this be the case? Previous randomized trials have reported that β-blocked patients more frequently show clinically significant bradycardia (relative risk 2.3; 95% CI 1.5–3.4) and hypotension (relative risk 1.3; 95% CI 1.0–1.6).[7] *Post hoc* analyses reported in the Perioperative Ischemic Evaluation Study suggest that the hemodynamic effects of β-blockade may adversely influence the response to sepsis and may result in stroke.[8] It is of interest that hemodynamic control with β-blockers after stroke is associated with an increased risk of early fatality (OR 1.8; 95% CI 1.1 to 3.0).[15] Indeed, β-blockers are no longer recommended as first line therapy for hypertension because of a negligible effect on mortality when compared to placebo and a significant increase in the risk of stroke when compared to calcium channel blockers or renin-angiotensin system inhibitors.[16] It is possible that a decrease in perfusion and/or oxygen delivery to other organs associated with β-blockade outweighs the benefit to heart rate control in low-risk individuals.

Our study has several other limitations. First, perioperative care, including Troponin T and electrocardiogram testing, was left to the discretion of the attending physician. It is likely that patients with increased comorbidity or side effects related to β-blockade may have received more frequent testing. As the majority of POMI are silent, any increased testing among patients taking β-blockers could result in unbalanced identification of events in this cohort.[14] Furthermore, as electrocardiogram results were not available electronically in our data warehouse, we were not able to include these electrocardiogram results into the definition of the primary outcome. However, we included the Troponin T measurement in the propensity score analysis to adjust for the possibility of selectively increased testing among more diseased patients. As far as we know, using postoperative Troponin T measurements to adjust for "confounding by indication" has never been done before. Second, patients taking β-blockers in this cohort were undoubtedly older and more likely to suffer from comorbid conditions than their control group. Third, we showed that postoperative hemoglobin level as a proxy for perioperative blood loss was associated with POMI. This suggests that perioperative blood loss or allogenic transfusion might be associated with POMI. As we unfortunately were unable to accurately determine blood loss or transfusion from the dataset, we cannot be sure that the association between postoperative anemia and POMI result from anemia, blood loss, transfusion, or an interaction among these factors. Finally, we have chosen to limit our analysis to myocardial infarctions occurring on POD1 to POD10 to ensure that we could reliably identify that β-blocker prescription preceded POMI and that all events were related to the perioperative period. However, the analysis including all POMI did not change the direction of our findings.

Estimates suggest that approximately 750,000 hip and knee replacements are performed in North America annually, a number expected to grow as the population ages.[17] Patients undergoing hip and knee arthroplasty face a risk of POMI between 0.8 and 1.8% and are

considered to be at low to intermediate risk of cardiac death and nonfatal myocardial infarction.[1,18] As a result of their advanced age and poor functional capacity, patients awaiting joint replacement represent a relatively large group of patients in whom the perioperative use of β-blockers may be considered. However, before initiating β-blocker prophylaxis, both the risks of perioperative cardiac events and the risks and benefit of β-blockade should be taken into account. To date, there still have been relatively few patients enrolled in trials of perioperative β-blockade. A systematic review that included Perioperative Ischemic Evaluation Study results identified slightly more than 10,000 subjects suffering 295 all-cause deaths and 434 nonfatal POMI in randomized trials of β-blockers in noncardiac surgery.[8] A more recently published meta-analysis including 12,306 patients from 33 trials reported a decrease in the incidence of nonfatal myocardial infarction and myocardial ischemia at the expense of an increase in nonfatal strokes.[13] It concluded that evidence does not support the use of β-blocker therapy for the prevention of perioperative clinical outcomes in patients having noncardiac surgery. It should be noted, however, that about 70% of the patients included in this meta-analysis were form the Perioperative Ischemic Evaluation Study.

Most foregoing trials have focused on higher risk patients, leaving the question of risk reduction in low-risk populations unanswered. The results of the current study identified that nearly 78% of POMIs occurred in patients with no more than one cardiac risk factor (RCRI I and II), suggesting that efforts to reduce the incidence of POMI should not be limited to high-risk patients. Our results confirm the American College of Cardiology/American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery, which recommend not to withdraw β-blocker therapy.[1]

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