Perioperative Metoprolol and Risk of Stroke after Noncardiac Surgery

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ABSTRACT

Background: Numerous risk factors have been identified for perioperative stroke, but there are conflicting data regarding the role of β adrenergic receptor blockade in general and metoprolol in particular.

Methods: The authors retrospectively screened 57,218 consecutive patients for radiologic evidence of stroke within 30 days after noncardiac procedures at a tertiary care university hospital. Incidence of perioperative stroke within 30 days of surgery and associated risk factors were assessed. Patients taking either metoprolol or atenolol were matched based on a number of risk factors for stroke. Parsimonious logistic regression was used to generate a preoperative risk model for perioperative stroke in the unmatched cohort.

Results: The incidence of perioperative stroke was 55 of 57,218 (0.09%). Preoperative metoprolol was associated with an approximately 4.2-fold increase in perioperative stroke ($P < 0.001$; 95% CI, 2.2–8.1). Analysis of matched cohorts revealed a significantly higher incidence of stroke

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What We Already Know about This Topic

- The PeriOperative Ischemic Evaluation trial demonstrated that metoprolol increased the risk of stroke after noncardiac surgery compared with placebo, but the trial was criticized for the use of high doses of β blocker and the lack of dose titration

What This Article Tells Us That Is New

- In this retrospective study, routine use of preoperative and intraoperative metoprolol—but not other β blockers—was associated with an increased risk of stroke after noncardiac surgery
- These data suggest that results of the PeriOperative Ischemic Evaluation trial may have reflected a drug-specific effect of metoprolol in perioperative stroke

in patients taking preoperative metoprolol compared with atenolol ($P = 0.016$). However, preoperative metoprolol was not an independent predictor of stroke in the entire cohort, which included patients who were not taking β blockers. The use of intraoperative metoprolol was associated with a 3.3-fold increase in perioperative stroke ($P = 0.003$; 95% CI, 1.4–7.8); no association was found for intraoperative esmolol or labetalol.

Conclusions: Routine use of preoperative metoprolol, but not atenolol, is associated with stroke after noncardiac surgery, even after adjusting for comorbidities. Intraoperative metoprolol but not esmolol or labetalol, is associated with increased risk of perioperative stroke. Drugs other than metoprolol should be considered during the perioperative period if β blockade is required.

PERIOPERATIVE stroke occurs after both cardiac[1,2] and noncardiac surgeries,[3,4] with an associated increase in mortality. A possible association of β blockade with perioperative stroke has been a subject of controversy.[5–8] The PeriOperative Ischemic Evaluation (POISE) trial demonstrated an increased risk of stroke after noncardiac surgery with the use of perioperative metoprolol compared with placebo.[9] It has been argued, however, that the protocol in this trial did not reflect routine dosing and may have contributed to greater hemodynamic changes than are currently seen in clinical practice.[7] Current guidelines state that routine administration of high-dose β blockers without careful dose titration may be harmful in patients undergoing noncardiac surgery.[10]

After the POISE trial, a retrospective case-control study suggested no increased risk of perioperative stroke with clinically routine doses of β blockers.[11] However, this investigation did not analyze the adverse effects of individual β blockers such as metoprolol, but rather, the class of β-blockade drugs in aggregate. A study on low-dose bisoprolol—but no other β blockers—also concluded that there was no increased risk of perioperative stroke.[12] As a result, it is still unclear whether routine perioperative metoprolol (or its hemodynamic effects)[13] is associated with an increased perioperative stroke risk compared with other β blockers. Given the fact that metoprolol is a widely prescribed β blocker, a more precise understanding of its role in perioperative stroke after noncardiac surgery is critical. Accordingly, the objective of the current study was to assess the incidence and risk factors of perioperative stroke in the noncardiac, nonneurosurgical population, with a focus on the effects of specific β blockers.

Materials and Methods

Study Sample

Institutional Review Board (University of Michigan, Ann Arbor, Michigan) approval was obtained, and written consent was waived because no care interventions were performed, and all protected health information was removed after data abstraction. The standard of care at our institution is to continue routine preoperative β blockade, including the day of surgery. Departmental quality improvement data (not shown) have demonstrated 90–95% compliance with continuation of perioperative β blockade, consistent with U.S. national benchmarks (Surgical Care Improvement Project) for this publicly reported measure. We examined consecutive cases of noncardiac, nonneurologic surgery from July 2003 to June 2009 at the University of Michigan Health System, which were documented in our electronic health record (Centricity®; General Electric Healthcare, Waukesha, WI).

Exclusion Criteria

Cases across various surgical subspecialties were excluded on the basis of intrinsic procedural risk of intraoperative and perioperative stroke or neurologic deficit. Exclusion was conducted both manually, and by an automated technique using case codes. All intracranial neurosurgical cases were excluded. The following cardiac and vascular procedures, known to have a high stroke risk, were also excluded: any procedure involving cardiopulmonary bypass, carotid endarterectomies, major vascular cases for vessels above the diaphragm, implantable cardiac defibrillator cases, cardiac dysrhythmia ablation procedures, cases requiring cardioversion, and tamponade evacuations. Otolaryngology cases involving skull base surgery as well as carotid body tumor resections were excluded. Oral-maxillofacial cases, involving penetrating trauma and gunshot wounds to the face and skull, were excluded. All trauma cases involving multiple organ injury, traumatic brain injury, closed head injuries, and penetrating trauma to the neck were excluded. Finally, organ procurement cases were excluded.

Outcome Measures

The primary outcome was perioperative stroke, defined as any new-onset cerebrovascular ischemic event (due to hypoperfusion, thromboembolism, or hemorrhage) established by neuroimaging and supporting medical record documentation within the first 30 days after surgery. The study sample was automatically screened for patients who had either brain computed tomography, or magnetic resonance imaging within 30 days after surgery at our institution. This approach is justified because automated identification of postoperative complications using electronic health record data has recently been found to be more sensitive than methods based on discharge coding.[14] Cases that screened positively for stroke by neuroimaging within 30 days after surgery were then manually reviewed for accuracy; the medical records of patients were assessed to identify diagnoses of stroke by the care teams treating the patient (case review by Drs. Vlisides, Matlen, Merte, and Freundlich). Diagnoses of stroke were confirmed by a blinded, clinically experienced investigator (Dr. Mashour). For patients who had multiple surgeries, the first surgery of the admission was deemed the index case for the purposes of defining perioperative stroke. Secondary outcomes collected for the entire cohort were 30-day and 1-yr all-cause mortality using a combination of hospital vital statistics and the social security death master file. Social security death master file data were censored with the August 2012 update. Patients were matched by an exact social security number match or name and date of birth match.

Variables Analyzed

Preoperative data were collected per normal standard of care using clinical documentation entered by anesthesia care providers into our electronic health record. This documentation included a structured electronic history and physical examination on every patient; each clinical element is stored as a discrete database element, which can be queried for research purposes. In order to screen for artifact, data elements for all patients in the current study were manually reviewed by investigators blinded to perioperative β blockade use (Drs. Sharifpour, Mashour, and Weightman). Preoperative medication data were collected using a selection list of common home medications and included both trade and generic names. A surgery was defined as emergent if the anesthesiologist indicated an emergent code as part of the American Society of Anesthesiologists physical status classification.

Intraoperative hemodynamic monitoring data were acquired *via* an automated, validated electronic interface from the physiologic monitors (Solar 9500®; General Electric Healthcare). The interface records one invasive arterial catheter blood pressure measurement each minute and all noninvasive blood pressure measurements. Noninvasive

blood pressure measurements are obtained every 3–5 min when invasive arterial catheters are not used. Each intraoperative anesthetic record was divided into 10-min epochs. The median systolic blood pressure and median mean arterial blood pressure for each 10-min epoch were calculated. The use of a median value of 10 min decreases the impact of monitoring artifacts and identifies sustained hemodynamic values.[15] We tabulated the number of epochs in which the median intraoperative mean arterial or systolic blood pressure was less than 20, 30, or 40% of the preoperative baseline.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 19 (IBM Corp., Somers, NY). Perioperative stroke within 30 days of surgery was considered the primary outcome variable. Preoperative and intraoperative characteristics for patients with and without 30-day stroke were compared using univariate statistical tests, like Pearson chi-square, Fisher exact test, or Mann–Whitney U tests wherever appropriate. All-cause 30-day and 1-yr mortality associations were evaluated using a Pearson chi-square test. A *P* value of less than 0.05 was considered statistically significant.

Patients taking preoperative metoprolol and atenolol were matched on the basis of the following comorbidities: coronary artery disease, atrial fibrillation, myocardial infarction, valvular disease, renal failure or insufficiency, stroke or transient ischemic attacks, and age by decades. To create the matched cohort, the data were coded to create a new variable for only those patients who were taking preoperative metoprolol or atenolol. We then developed a propensity score, using a logistic regression model where the dependent variable was the newly created preoperative dichotomous β-blocker variable, and the remaining covariates listed above were entered into the model. This created a propensity score for each patient. Patients, who were taking either preoperative metoprolol or preoperative atenolol, were randomly matched on the basis of the propensity score (using 3 digits). After the matching was completed, we examined the data to ensure that there were no significant postmatch differences between the patients who were taking preoperative metoprolol or atenolol, and the previously listed comorbidities. Matching was accomplished using author-generated algorithms within IBM SPSS Statistics version 19 (IBM Corp.) Within the matched cohort, a Fisher exact test was performed to determine if there was an increased incidence of strokes in patients taking preoperative metoprolol *versus* preoperative atenolol.

We next sought to determine if the use of preoperative metoprolol or atenolol is an independent predictor of postoperative stroke using a parsimonious logistic regression

‡‡ RMS library package designed for R statistical package 2.12. Available at: http://cran.r-project.org/web/packages/rms/rms.pdf. Accessed March 6, 2013.

model for patients aged 40 yr and more; age was not included as a variable in order to conserve parameter space. The dichotomous outcome was perioperative stroke, and the covariates that were entered into the model were preoperative metoprolol use, preoperative atenolol use, history of coronary artery disease, preoperative hypertension, history of atrial fibrillation, history of renal insufficiency or failure, and history of stroke or transient ischemic attack. Colinearity diagnostics and Pearson correlations were evaluated for all covariates before entering them into a backward stepwise Wald logistic regression model. Preoperative renal failure was defined using the Cockcroft–Gault Formula to calculate glomerular filtration rate. A glomerular filtration rate of 80 or more was considered normal, a glomerular filtration rate more than 20 but less than 80 was considered renal insufficiency, and a glomerular filtration rate of 20 or lesser was considered renal failure. Any variable with a *P* value of less than 0.05 was considered an independent predictor. Goodness of fit was assessed using both the Omnibus Tests of Model Coefficients and the Hosmer and Lemeshow Test. The risk model was evaluated using the c-statistic. Effect size for each independent predictor was evaluated using an adjusted odds ratio with 95% CIs. Due to concerns of overfitting the logistic regression model, we validated the model using bootstrapping in the rms library package within R statistical package 2.12.‡‡ Briefly, bootstrapping generates a set number of samples with replacement and estimates the original model within each new sample. The new estimates of the models are then compared against the original data set. The difference between the two is the optimism score, also referred to as the bias due to overfitting the model.[16,17] A bias-corrected value based on overfitting of the model can then be calculated.[17] One way to assess the bootstrapped model is with Somers Dxy rank correlation, which is a concordance index.[17] Somers Dxy of zero indicates the model is making random predictions, whereas a Somers Dxy of one indicates perfect discrimination.[17]

Results

Incidence of Perioperative Stroke and Univariate Associations

A total of 57,218 patients undergoing noncardiac and nonneurologic surgeries met the inclusion criteria. Of these, 55 patients had perioperative stroke, for an incidence of 0.09%; two of the 55 patients had subarachnoid hemorrhage. The distribution of strokes in the 30-day postoperative period is shown in figures 1 and 2. Preoperative univariate associations with stroke included age, body mass index, emergent surgery, atrial fibrillation, hypertension, history of myocardial infarction or coronary artery disease, valvular disease, renal insufficiency or failure, and history of stroke or transient ischemic attack (table 1). Notably, diabetes and tobacco use were not associated with perioperative stroke in this cohort. Preoperative metoprolol

was associated with a 4.2-fold increased risk of perioperative stroke ($P < 0.001$; 95% CI, 2.2–8.1). Preoperative atenolol, bisoprolol, carvedilol, nadolol, propranolol, or sotalol did not have a statistically significant association with stroke, but the number of patients who were prescribed some of these β blockers were low, which mitigated any definitive conclusions.

In terms of intraoperative factors (table 1), we found no difference in stroke risk between general and regional anesthesia. Within the population undergoing general anesthesia, there was no increased risk with the use of nitrous oxide. Relative mean or systolic arterial pressures less than 20, 30, and 40% were associated with perioperative stroke; there was no colinearity between intraoperative hypotension and preoperative metoprolol use. Intraoperative intravenous metoprolol tartrate was associated with a 3.3-fold increased risk of perioperative stroke ($P = 0.003$; 95% CI, 1.4–7.8), whereas use of intraoperative intravenous esmolol or labetalol had no association with stroke.

Animal studies have suggested that metoprolol reduces cerebral tissue oxygenation in the setting of hemodilution;[18] we therefore assessed estimated blood loss in patients taking metoprolol with or without strokes. The median estimated blood loss in patients who took metoprolol and had a postoperative stroke was 300 cc (interquartile range, 100–2,200 cc) compared with 125 cc (30–400 cc) in patients who took metoprolol and did not have a stroke ($P = 0.18$).

Perioperative stroke was associated with a 17.8-fold increase in 30-day mortality ($P < 0.001$; 95% CI, 7.6–41.9) and a 10.8-fold increase in 1-yr mortality ($P < 0.001$; 95% CI, 2.7–10.8; table 1).

Comparison of Stroke Incidence in Matched Cohorts Taking Metoprolol or Atenolol

The cohorts taking preoperative metoprolol or atenolol were matched successfully, with 2,066 patients per group (table 2). In the matched groups, seven patients (0.3%) taking preoperative metoprolol experienced a postoperative stroke compared with zero stroke events in patients taking preoperative atenolol ($P = 0.016$).
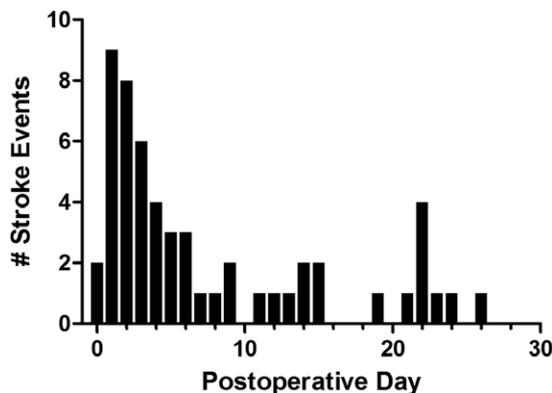
Fig. 1. Distribution of strokes after noncardiac surgery for all patients.
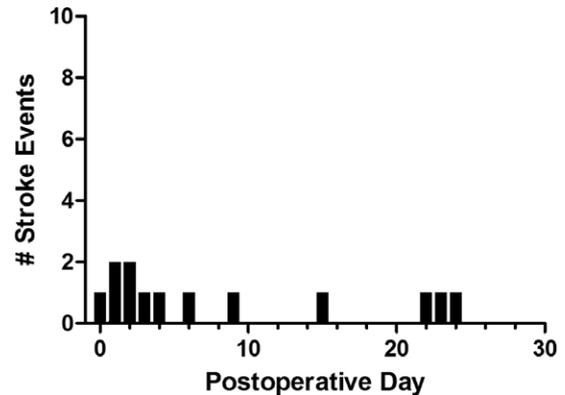
Fig. 2. Distribution of strokes after noncardiac surgery for patients taking β blockers.

Independent Predictors of Perioperative Stroke

In the overall (unmatched) patient population, logistic regression analysis demonstrated history of atrial fibrillation (adjusted odds ratio 3.9; 95% CI, 1.9–7.8) and history of stroke or transient ischemic attacks (adjusted odds ratio 5.2; 95% CI, 2.6–10.3) as independent predictors of stroke in patients aged 40 yr or more (table 3). Neither preoperative metoprolol nor atenolol were independent predictors of stroke (table 3). The Omnibus Tests of Model Coefficients demonstrated a chi-square of 38.254, three degrees of freedom, and a P value of less than 0.001. The Hosmer and Lemeshow Test demonstrated a chi-square of 0.369, one degree of freedom, and a P value of 0.543. The c-statistic for this model was 0.68 (95% CI, 0.59–0.77). The two independent predictors were validated using the bootstrapping method to test for overestimating the model using 1,000 samples with replacement. Somers Dxy was 0.4247 for the original data set, 0.4591 for the training set, and 0.3907 for the test set. The optimism was 0.0684 and the bias-corrected Somers Dxy was 0.3563. A separate regression was run eliminating (1) any patient from the cohort taking intraoperative β blockers or (2) those taking preoperative β blockers other than metoprolol or atenolol. The independent predictors of atrial fibrillation and history of stroke or transient ischemic attack remained, and no other variables were significant.

Discussion

This retrospective observational study of 57,218 patients undergoing noncardiac surgery demonstrates that the routine use of preoperative metoprolol is associated with increased risk of perioperative stroke compared with atenolol in a matched cohort. Furthermore, intraoperative metoprolol is associated with increased risk of perioperative stroke, whereas labetolol and esmolol are not. These findings support the findings of the POISE trial in that patients with cardiovascular risk factors undergoing noncardiac surgery had an increased risk of stroke that appeared specific to metoprolol, even in routine clinical use.[9] However, metoprolol

Table 1. Patient Characteristics, Variables, and Univariate Associations with Perioperative Stroke

| | 30-d Perioperative | | | |
	Stroke—No (N = 57,163)	Stroke—Yes (N = 55)	P Value	Odds Ratio (95% CI)
Patient Characteristics				
Age ≥56 (yr)	26,394 (46%)	46 (84%)	<0.001	6.0 (2.9–12.2)
Body mass index				
Normal	16,835 (30%)	19 (37%)	0.012	N/A
Underweight	1,327 (2.4%)	2 (3.9%)		
Overweight	18,128 (32%)	23 (45%)		
Obese	19,991 (36%)	7 (14%)		
Male sex	27,041 (47%)	27 (49%)	0.791	1.1 (0.6–1.8)
Emergent operation	3,389 (5.9%)	10 (18%)	<0.001	3.5 (1.8–7.0)
Preoperative variables				
Current smoker	8,599 (15%)	11 (20%)	0.309	1.4 (0.7–2.7)
Former smoker	12,925 (23%)	16 (29%)	0.256	1.4 (0.8–2.5)
Diabetes type I	3,588 (6.3%)	3 (5.5%)	1.000	0.9 (0.3–2.7)
Diabetes type II	7,857 (14%)	11 (20%)	0.182	1.6 (0.8–3.0)
History of atrial fibrillation	2,161 (3.8%)	11 (20%)	<0.001	6.4 (3.3–12.3)
History of hypertension	20,021 (35%)	33 (60%)	<0.001	2.8 (1.6–4.8)
History of MI	3,539 (6.2%)	10 (18%)	<0.001	3.4 (1.7–6.7)
Coronary artery disease	6,663 (12%)	12 (22%)	0.020	2.1 (1.1–4.0)
Acute-on-chronic heart failure	154 (0.3%)	1 (1.8%)	0.139	6.8 (0.9–49.7)
History of carotid vertebral disease	545 (1.0%)	0 (0%)	1.000	1.0 (1.0–1.0)
History of valvular disease	2,363 (4.1%)	6 (11%)	0.012	2.8 (1.2–6.6)
History of PVOD/claudication	1,762 (3.1%)	4 (7.3%)	0.090	2.5 (0.9–6.8)
Renal insufficiency or failure	15,313 (38%)	29 (58%)	0.003	2.3 (1.3–4.0)
History of stroke	1,264 (2.2%)	8 (15%)	<0.001	7.5 (3.6–16)
History of TIA	900 (1.6%)	4 (7.3%)	0.011	4.9 (1.8–13.6)
Preoperative β blockers				
Metoprolol	3,213 (5.6%)	11 (20%)	<0.001	4.2 (2.2–8.1)
Atenolol	2,666 (4.7%)	2 (3.6%)	1.000	0.8 (0.2–3.2)
Propranolol	566 (1.0%)	0 (0%)	1.000	1.0 (1.0–1.0)
Nadolol	221 (0.4%)	1 (1.8%)	0.193	4.8 (0.7–34.6)
Sotalol	116 (0.2%)	0 (0%)	1.000	1.0 (1.0–1.0)
Bisoprolol	305 (0.5%)	0 (0%)	1.000	1.0 (1.0–1.0)
Carvedilol	1,027 (1.8%)	1 (1.8%)	1.000	1.0 (0.1–7.3)
Intraoperative variables				
Length of surgery, min*	144 [89–217]	193 [120–342]	0.003	N/A
General anesthesia	50,583 (89%)	51 (93%)	0.403	1.7 (0.6–4.6)
Nitrous oxide used	18,153 (32%)	13 (24%)	0.196	0.7 (0.4–1.2)
Episodes of hypotension <20% baseline SBP*	5 [1–10]	9 [2–19]	0.003	
Episodes of hypotension <30% baseline SBP*	1 [0–5]	4 [0–11]	0.001	
Episodes of hypotension <40% baseline SBP*	0 [0–1]	1 [0–5]	<0.001	
Episodes of hypotension <20% baseline MAP*	4 [1–9]	8 [3–17]	<0.001	
Episodes of hypotension <30% baseline MAP*	1 [0–4]	4 [0–14]	<0.001	
Episodes of hypotension <40% baseline MAP*	0 [0–1]	1 [0–6]	<0.001	
Intraoperative β blockers				
Metoprolol given	2,030 (3.6%)	6 (11%)	0.003	3.3 (1.4–7.8)
Labetalol given	1,956 (3.4%)	4 (7.3%)	0.120	2.2 (0.8–6.1)
Esmolol given	1,356 (2.4%)	2 (3.6%)	0.376	1.6 (0.4–6.4)
Postoperative outcomes				
30-d postoperative death	390 (0.7%)	6 (11%)	<0.001	17.8 (7.6–41.9)
1-yr postoperative death	2,253 (3.9%)	10 (18%)	<0.001	5.4 (2.7–10.8)

* Nonparametric data assessed using Mann–Whitney U test and results reported as median [25th percentile to 75th percentile].

MAP = mean arterial blood pressure; MI = myocardial infarction; N/A = not applicable; PVOD = peripheral vascular occlusive disease; SBP = systolic blood pressure; TIA = transient ischemic attack.

Table 2. Matched Cohorts Taking either Atenolol or Metoprolol

	Atenolol (N = 2,066)	Metoprolol (N = 2,066)	P Value	Odds Ratio (95% CI)
Age, yr				
18–30	47 (2%)	47 (2%)		
31–40	84 (4%)	84 (4%)		
41–50	212 (10%)	212 (10%)		
51–60	452 (22%)	453 (22%)	1.00	N/A
61–70	556 (27%)	555 (27%)		
71–80	496 (24%)	497 (24%)		
81 plus	219 (11%)	218 (11%)		
Coronary artery disease	609 (29%)	610 (30%)	0.95	1.01 (0.88–1.15)
History of atrial fibrillation	120 (5.8%)	120 (5.8%)	1.00	1.00 (0.77–1.30)
History of hypertension	1,565 (76%)	1,565 (76%)	1.00	1.00 (0.87–1.15)
History of valvular disease	82 (4.0%)	82 (4.0%)	1.00	1.00 (0.73–1.37)
History of stroke/TIA	95 (4.6%)	95 (4.6%)	1.00	1.00 (0.75–1.34)
Renal insufficiency or failure	997 (57%)	997 (57%)	1.00	1.00 (0.88–1.14)

N/A = not applicable; TIA = transient ischemic attack.

was not an independent predictor in the overall cohort, which included a broad range of patients with or without β blockade.

The current study also clarifies perceived inconsistencies among studies on β blockade and stroke subsequent to the POISE trial. van Lier et al.[11] found no association of β blockade and stroke, but this is likely because the authors assessed β blockers in aggregate rather than individually. Our data are also consistent with the study of van Lier et al.[12] showing no increase of perioperative stroke with low-dose bisoprolol; the routine preoperative use of bisoprolol was not associated with stroke in our study. Thus, the current investigation reconciles data on perioperative stroke and β blockade that previously seemed inconsistent.

The POISE trial identified "clinically significant hypotension" as a predictor of stroke.[9] Our data support this in the intraoperative setting by demonstrating that a 10-min epoch of a median decrease of less than 20, 30, or 40% in mean arterial or systolic blood pressure is associated with stroke, a finding consistent with a recent study of intraoperative hypotension and postoperative stroke.[19] However, there was no colinearity between metoprolol use and hypotension. Further work is required on the role of postoperative hypotension or bradycardia in perioperative stroke, as well as the mechanism by which metoprolol increases risk for stroke. Comparison of estimated blood loss in patients taking metoprolol with or without stroke revealed no difference; however, this finding should be explored in a larger patient cohort. Importantly, a recent investigation identified major perioperative hemorrhage itself as a risk factor of stroke after noncardiac, nonneurologic surgery.[20]

There are a number of limitations to this study. First, there was a relatively low event frequency of perioperative stroke in this single-center study, which creates the potential for overfitting of the logistic regression risk model. However, analysis

using bootstrapping suggested that overfitting was fair because the bias-corrected Somers Dxy was 0.3563.[17] Second, precise dosing and drug formulation data were not available, which precluded the analysis of drug–dose–response relationships. Third, we were not able to assess patient-specific compliance with preoperative β blockade, an important point, given the risks of withdrawal.[15] However, there is no reason to believe that compliance with metoprolol would be systematically different from compliance with atenolol, bisoprolol, carvedilol, nadolol, propranolol, or sotalol, none of which had associations with stroke. Importantly, intraoperative administration of metoprolol tartrate was also associated with stroke, a finding that is not subject to the potential confound of compliance. Fourth, there was relatively low use of β blockers in this surgical population, which might increase the risk for spurious associations. Fifth, indication bias is a potential confound that mitigates our conclusions, but we have attempted to control for this possibility by comparing a comorbidity-matched cohort receiving atenolol. Finally, we are potentially underestimating the incidence of perioperative stroke in this cohort, as some patients could have had follow-up

Table 3. Independent Predictors of Perioperative Stroke for Age ≥40 Years

Covariate	P Value	Adjusted Odds Ratio (95% CI)
History of stroke/TIA	<0.001	5.0 (2.5–10.1)
History of atrial fibrillation	<0.001	3.7 (1.8–7.6)
Preoperative metoprolol	0.13	1.8 (0.8–3.9)
Preoperative hypertension	0.24	1.4 (0.8–2.7)
Renal insufficiency or failure	0.46	1.3 (0.7–2.4)
Coronary artery disease	0.42	0.7 (0.3–1.5)
Preoperative atenolol	0.24	0.3 (0.1–2.2)

TIA = transient ischemic attack.

care at hospitals outside of our health system. The current incidence of 0.09% is nonetheless consistent with our earlier study that found an incidence of 0.1% in a broad noncardiac surgical population, using prospectively gathered data.[4] It is noteworthy that both our current and past studies, as well as numerous other investigations,[21] have consistently identified a history of stroke or transient ischemic attack as independent predictors of perioperative stroke.

Despite the limitations, our investigation provides insight into perioperative stroke and the routine clinical use of metoprolol. One of the main findings of this study is that metoprolol alone, rather than the class of β blockers as a whole, is associated with increased stroke risk. This finding is consistent with a recent report showing that metoprolol, but not bisoprolol, was associated with an increased risk of perioperative stroke.[22] With further validation in larger studies, the current data suggest that alternative β blockers may be safer in the perioperative period with respect to stroke risk. This interpretation is supported by the finding that metoprolol is associated with a higher perioperative mortality compared with atenolol.[23] In terms of intraoperative β blockade, intravenous drugs such as esmolol, which has been analyzed for perioperative safety,[24] or labetalol may be preferable until further research clarifies the role of intraoperative metoprolol in postoperative stroke. We must emphasize, however, that we are not recommending the discontinuation of metoprolol in the immediate preoperative period for those patients who already taking it.

In conclusion, the routine use of both preoperative and intraoperative metoprolol is associated with increased risk of perioperative stroke after noncardiac surgery. These data support the findings of the POISE trial[9] and also reconcile apparent inconsistencies with subsequent studies of perioperative β blockade and stroke.[9,11] Further studies are required to assess the safety of individual β blockers with respect to perioperative stroke risk and how such risk is balanced by the reduction of adverse cardiac events.

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