Selective β_1-Antagonism with Bisoprolol Is Associated with Fewer Postoperative Strokes than Atenolol or Metoprolol

A Single-center Cohort Study of 44,092 Consecutive Patients

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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.

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What We Already Know about This Topic

- Perioperative β-blockade has been associated in one large study with an increased risk of stroke
- β-blockade might predispose to stroke by attenuating β_2-adrenoceptor-mediated cerebral vasodilation, in which case a β_1-selective agent might reduce this risk

What This Article Tells Us That Is New

- In a propensity-adjusted cohort study on approximately 2,500 patients undergoing noncardiac, nonneurologic surgery with perioperative β-blockade, those receiving the β_1-selective agent, bisoprolol, had a five-fold reduced risk of stroke compared with those receiving nonselective β-blockers
- Randomized controlled trials comparing these agents are needed

ABSTRACT

Background: Perioperative metoprolol increases postoperative stroke. Animal studies indicate that the mechanism may be related to attenuated β_2-adrenoreceptor-mediated cerebral vasodilatation. The authors therefore conducted a cohort to study whether the highly β_1-specific β-blocker (bisoprolol) was associated with a reduced risk of postoperative stroke compared with less selective β-blockers (metoprolol or atenolol).

Methods: The authors conducted a single-center study on 44,092 consecutive patients with age 50 yr or more having noncardiac, nonneurologic surgery. The primary outcome was stroke within 7 days of surgery. The secondary outcome was a composite of all-cause mortality, postoperative myocardial injury, and stroke. A propensity score-matched cohort was

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created to assess the independent association between bisoprolol and less β_1-selective agents metoprolol or atenolol. A secondary analysis using logistic regression, based on previously identified confounders, also compared selective β_1-antagonism.
Results: Twenty-four percent (10,756) of patients were exposed to in-hospital β-blockers. A total of 88 patients (0.2%) suffered a stroke within 7 days of surgery. The matched cohort consisted of 2,462 patients, and the pairs were well matched for all variables. Bisoprolol was associated with fewer postoperative strokes than the less selective agents (odds ratio = 0.20; 95% CI, 0.04–0.91). Multivariable risk-adjustment in the β-blockers-exposed patients comparing bisoprolol with the less selective agents was associated with a similarly reduced stroke rate.
Conclusions: The use of metoprolol and atenolol is associated with increased risks of postoperative stroke, compared with bisoprolol. These findings warrant confirmation in a pragmatic randomized trial.

THE initial enthusiastic use of perioperative β-blockers, which was largely based on two positive trials,[1,2] has been tempered after the publication of the results of the Perioperative Ischemia Evaluation (POISE) trial.[3] POISE trial demonstrated that although metoprolol succinate reduced the risk of perioperative myocardial infarction, it also doubled the incidence of postoperative stroke and increased mortality. This finding was also confirmed by subsequent meta-analyses that showed a similar reduction in myocardial infarction and increase in stroke rates in all perioperative trials that used either formulation of metoprolol (tartate and succinate) or atenolol.[4]

The specific reasons why perioperative β-blockade may cause acute stroke have not been elucidated. A potential mechanism is impairment in normal physiological responses to significant perioperative blood loss, which is also associated with postoperative stroke.[3] Notably, the sequelae of major surgical blood loss, namely acute perioperative anemia, is both common[5] and entails adaptive homeostatic responses that include increases in cardiac output,[6] cerebral blood flow, and cerebrovascular dilatation.[7,8] Less selective β-antagonists have the potential to impair all of these adaptive responses.

To further explore this potential mechanism for perioperative stroke, we undertook a series of animal experiments to investigate the separate roles of β_1- and β_2-adrenergic receptors in mediating the physiologic response to acute anemia. In a rat model of acute anemia, the use of a weakly β_1-selective β-blocker metoprolol (relative β_1/β_2 affinity of 2.3) impaired the cardiac output response and reduced brain tissue P_{O_2}, thereby causing global cerebral hypoxia.[9] In addition, the specific antagonism of the β_2-receptor in the setting of acute anemia attenuated β_2-mediated cerebral vascular dilation[10] and reduced brain P_{O_2}.[11] In comparison, treatment with a low dose of a highly β_1-selective β-blocker, nebivolol, effectively inhibited the cardiac response to anemia without attenuating brain P_{O_2}, possibly by preserving the vascular response to acute anemia.[12]

These experimental data suggest that the relative β_1-selectivity of β-blockers may influence their efficacy in preventing postoperative cardiovascular outcomes, as has been suggested by a recent meta-analysis.[13] Notably, the three most commonly used chronic β-blockers in clinical practice vary with respect to their β-receptor selectivity. Specifically, their relative β_1/β_2 affinities are: 2.3 for metoprolol, 4.7 for atenolol, and 13.5 for bisoprolol.[14,15]

We therefore undertook this retrospective cohort study to evaluate the association of β-blocker selectivity with the risk of postoperative acute stroke. Our primary hypothesis was that a more β_1-selective agent, namely bisoprolol, would be associated with lower adjusted risk of postoperative stroke than the less selective antagonists such as metoprolol or atenolol.

Materials and Methods

Study Setting, Sample, and Data Collection

We conducted a single-center, retrospective cohort study on patients having intermediate- to high-risk noncardiac surgery at the University Health Network in Toronto, Ontario, Canada. The study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The University Health Network, which is a teaching hospital network affiliated to the University of Toronto (Toronto, Ontario, Canada), offers a full range of adult noncardiac surgery performed at three sites. This study was initiated after the approval by the University Health Network Institutional Research Ethics Board (Toronto, Ontario, Canada), which waived the requirement for informed consent for this study.

We evaluated consecutive patients who were aged 50 yr or older, had American Society of Anesthesiologists physical status scores of four or less, underwent noncardiac and nonneurologic surgery from January 2003 to December 2010, and required an overnight admission to hospital. We also excluded patients who underwent solid organ transplantation. To define the timing of each stroke, the first surgery was considered as the index in patients having more than one surgery during the admission.

All perioperative data were prospectively collected in linked institutional databases, as has been previously described.[5,16,17] These data included demographics, comorbidities, medications, surgical information, laboratory test results, blood product transfusion, and postoperative events. The accuracy of the database has also been confirmed. In brief, we compared all the relevant electronic data with the paper record in 100 randomly selected patients and found an error rate of less than 2%.[16] The type and dose of β-antagonists were recorded and for the most part reflects chronic longer term use.

β-Blocker Exposure. Data on β-blocker exposure was defined primarily using two separate databases, the electronic preoperative assessment data, which is a surrogate for chronic use but does not include data for emergency surgery or inpatients transferred from other hospitals before elective surgery. Approximately 35% of all surgical patients have no data on preoperative β-blocker exposure. The inpatient pharmacy database shows all inpatient drug use but cannot distinguish

between acute and chronic use or those withdrawn from β-blockers. Previous work from our groups shows that approximately 30% of patients are started on β-blockers between the inpatient visit and surgery, whereas less than 10% are withdrawn from β-blockers, when the preoperative data are compared with the inpatient pharmacy database. Thus the current analysis is based on in-hospital exposure to β-blockers that is predominately chronic in nature. The β-blocker exposure in this analysis reflects data from the inpatient pharmacy database for each of the first six postoperative days, where the day of surgery is considered the day 1. To establish the consistency of the β-blocker dosage and type and dose, we compared the drug administered on the first 2 postoperative days to the rest of the 6 postoperative days and establish the β-blocker crossover rate, in each β-blocker exposed patient. Less than 1% (107 of 10,756) of all patients received different β-blockers between the first and last inpatient days. We included all of these patients in the analysis because this small number of patients was unlikely to influence the outcome. The drug exposure of interest was considered to be the first β-blocker administered in all cases.

Outcome

The primary outcome was postoperative stroke within 7 days of surgery, and this definition was defined *a priori* because POISE trial showed the increase in the number of strokes in patients receiving metoprolol, compared with the control group occurred in this time frame.[3] Identification of patients with stroke was defined in a multiple step process. First, we surveyed the discharge abstract database of 10th version of the International Classification of Diseases-10 (ICD-10) codes for cerebral ischemia and stroke (appendix). We then cross-referenced these results with the medical imaging database for patients having computed tomography or magnetic resonance imaging of the brain within 7 days of surgery. After reviewing the medical and radiological reports of this cohort, two investigators (Drs. Judelman and Ashes) adjudicated the presence of postoperative strokes based on the presence of confirmatory clinical or radiological evidence. The stroke timing and adjudication occurred without knowledge of medication history or hematologic status. Finally, we surveyed all patients who died within 7 days of surgery to reduce the number of missed strokes in patients who died before diagnosis. All disagreements were resolved through consensus or involvement of a third reviewer (Dr. Beattie).

The secondary outcome was a composite comprising in-hospital death within 30 days of surgery, stroke, and postoperative myocardial injury, which was defined as a peak troponin I of greater than 0.7 μg/l. Myocardial injury was assessed using troponin I, using the Dade Behring Dimension assay (detection limit 0.07 μg/ml; Siemens Healthcare Diagnostics, Deerfield, IL). In May 2008, the institution changed to the Abbott Architect i2000 analyzer (Abbott Diagnostics, Abbott Park, IL). Internal correlation studies showed a 1-to-1 correlation to the Dade Behring assay and the change in assay method does not affect the interpretation of the results presented here.

Statistical Analysis

We compared the demographic, surgical, comorbid, and pharmacologic characteristics of the patients taking the different β-blockers with patients who were not exposed to in-hospital β-blockers. We then assessed the unadjusted relationship between nadir hemoglobin†† and postoperative stroke by constructing a restricted cubic spline curve for each of metoprolol, atenolol, and bisoprolol. Because the number of strokes limited the number of confounding variables that could be reliably entered into logistic regression analysis, the primary analysis consisted of a propensity score-matched pairs analysis comparing bisoprolol with the combination of metoprolol or atenolol. A propensity score estimating the probability of being exposed to bisoprolol was generated using a nonparsimonious multivariable logistic regression model that included all measured covariates.‡‡ Individuals receiving bisoprolol were then matched to individuals receiving metoprolol or atenolol, on a 1-to-1 basis. In this analysis, two cohorts with similar characteristics were created using a 5 to >1 computerized greedy-matching algorithm. Covariate balance between the matched pairs was then evaluated using standardized difference. This process was repeated iteratively, blinded to the outcomes, until good covariate balance (standardized difference <10%, in every confounding variable) was achieved. We used conditional logistic regression to compare rates of the primary outcome and secondary outcome, in the matched pairs.

A second analysis was then conducted using multivariable logistic regression analysis. The candidate variables in this model included the predictors of stroke identified in the POISE trial and two potential predictors of stroke that were identified based on our animal experiments: a nadir hemoglobin under 9 gm/dl and β-blocker type. In this analysis, β-blockers type compared bisoprolol with the two agents, metoprolol or atenolol. Model calibration was evaluated by the Hosmer–Lemeshow test, whereas discrimination was assessed using the c-statistic. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC)

Results

The final cohort consisted of 44,092 consecutive patients having in-hospital procedures. The details of the assembly of this cohort are presented in figure 1, whereas the characteristics of the study sample are presented in table 1. Eighty-eight patients (0.2%) experienced acute stroke within 7 days of surgery. Among patients with a Revised Cardiac Risk Index of 1 or more, the risk of stroke was 0.4%. The peak incidence of stroke was on the first postoperative day, and approximately two thirds of strokes occurring within 48 h of surgery

†† Since there was no routine protocol for postoperative measurement of hemoglobin, nadir hemoglobin was defined as the lowest level in the first 3 days after surgery.

‡‡ In the initial submission, our primary analysis used a logistic regression and the secondary analysis compared Bisoprolol to Metoprolol in a propensity matched cohort. The present analysis was suggested during the review process.

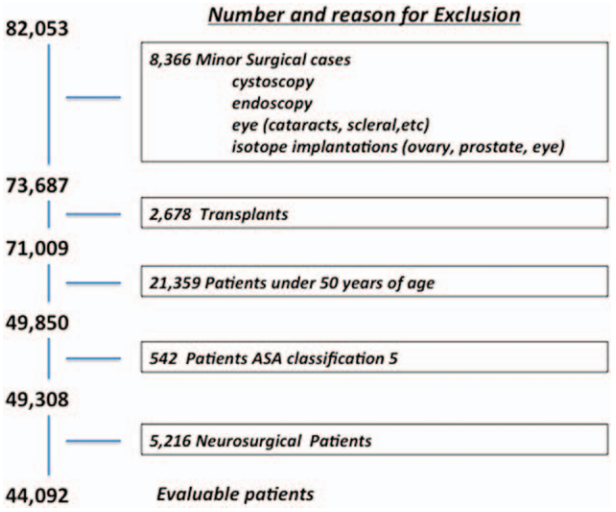

Fig. 1. Make up of the study population. Each step of this diagram depicts the number of exclusions and reasons for the exclusion, leading to the final population evaluated. ASA = American Society of Anesthesiologists.

(fig. 2). Of the 88 patients who suffered postoperative strokes, 17 (19.3%) died in hospital within 30 days of surgery. The median length-of-stay of the surviving stroke patients was 27 days (intraquartile range 14–47), contrast to 4 days (intraquartile range 2–8) for those patients who survived without having a stroke. Of the surviving stroke patients, 57 (80%) required long-term care, rehabilitation facilities, or some form of extra care on hospital discharge. In comparison, this proportion was 33% among surviving nonstroke patients.

Twenty-four percent (n = 10,756) of the patients in this study sample were taking β-blockers during the hospital stay. The patient characteristics, including demographics and comorbidities, the median dosage and range of each of the β-blockers of interest, surgical details and transfusion requirements, and concomitant cardiovascular medications are seen in table 1. It is important to note that patients taking atenolol had fewer risk factors associated with stroke than patients receiving bisoprolol or metoprolol. Specifically, patients receiving atenolol had less cerebral vascular disease, chronic renal failure, and diabetes. The patients exposed to atenolol were being predominately treated for hypertension (57%).

The relationship between nadir hemoglobin and stroke is displayed in figure 3. There is a difference in the baseline risk of stroke between metoprolol and the other two agents. Second, there is a sharp increase in the incidence of stroke when hemoglobin levels decrease to below a level of 9 gm/dl.

The matched cohort consisted of 2,462 patients; half receiving bisoprolol and the remainder receiving either metoprolol or atenolol. The pairs were well matched for all variables. The mean standardized difference for the 50 known variables was −0.008 and ranged from −0.098 to 0.045 (table 2). In the matched cohort analysis, two patients taking bisoprolol and 10 patients taking less selective β-antagonists experienced postoperative stroke (odds ratio, 0.20; 95% CI, 0.04–0.91). The components of the composite secondary outcomes showed less acute myocardial injury as judged by increased troponin after surgery, and no difference in mortality.

The result of the restricted logistic regression analysis comparing bisoprolol with atenolol and metoprolol is seen in table 3. Bisoprolol is associated with fewer postoperative strokes than the less selective β-blockers (0.20, 95% CI, 0.04–0.99). In addition, factors associated with cerebral hypoxia and stroke from earlier animal experiments and clinical studies were retained in the current study. Acute anemia was associated with stroke in a manner that was dependent on the magnitude of the decrease in hemoglobin concentration. The most significant predictor of stroke was a history of cerebral vascular disease. New onset of atrial fibrillation (AF), an important factor in POISE trial, was not significant in our analysis (odds ratio, 0.72; 95% CI, 0.1–5.3). This model has good discrimination (c-statistic, 0.788) and good calibration (P = 0.712).

Discussion

In this single-institution retrospective cohort study, postoperative stroke was a rare but devastating complication of major noncardiac surgery. The highly selective β_1-antagonist bisoprolol was associated with decreased stroke rate compared with the less β_1-selective agents metoprolol or atenolol. The increase in stroke rate observed was also associated with an increase in other severe adverse clinical outcomes suggesting that the impact of the less selective agents have broad clinical effects on patient outcomes. This analysis also demonstrates that there is an increase in adverse cardiac outcomes when β-blocked patients experience acute anemia (hemoglobin <9 gm/dl).

Our results warrant comparison with the POISE trial[3] and our animal experiments[9–12]. Similar to the POISE trial, cerebral vascular disease was a major risk factor for postoperative stroke. A history of cerebral vascular disease or stroke is the most consistent predictor of postoperative stroke and has been seen in several recent large observational trials.[17–19] In addition, transfusion was associated with stroke in a dose-dependent manner, which has been previously demonstrated.[20] In that analysis, 4 units of transfusion were used to define major blood loss as compared with 2 units in POISE trial. Our analysis, which is composed of predominantly of patients with chronically administered β-antagonists, also demonstrates that metoprolol is associated with an increased incidence of postoperative stroke, as has recently been observed in two other retrospective cohort studies.[21,22] In those investigations, metoprolol was compared with atenolol, however, we find these two drugs were essentially equivalent in increasing the stroke rate compared with unexposed patients (analysis not shown). The differences between metoprolol and atenolol in those analyses[5,22] could result from confounding by indication as was discussed.[21] Our data supports this supposition given that, in our study, atenolol-exposed patients had much lower risk of stroke. The baseline risk factors for stroke in patients administered metoprolol and bisoprolol were similar limiting the risk of confounding by indication.

Table 1. Patient Characteristics *versus* Type of β-Blocker

	No β-Antagonist n = 33,285	Metoprolol n = 5,995	Atenolol n = 2,541	Bisoprolol n = 1,246
Dose (daily mg)		100 (50–100) 400	50 (25–50) 100	5 (2.5–5) 15
Age 65–75	9,918 (29.1)	2,088 (34.8)	922 (36.3)	406 (32.6)
Age >75	6,983 (20.5)	2,358 (39.3)	849 (33.4)	478 (38.4)
Sex (male)		3,510 (58.6)	1,351 (53.2)	754 (60.5)
Year of surgery				
2003	3,549 (8.1)	770 (1.8)	326 (0.7)	44 (0.1)
2004	3,738 (8.5)	804 (1.8)	311 (0.7)	72 (0.2)
2005	3,961 (9.0)	864 (1.9)	334 (0.8)	107 (0.3)
2006	4,136 (9.4)	757 (1.7)	335 (0.8)	142 (0.3)
2007	4,565 (10.4)	755 (1.7)	338 (0.8)	239 (0.5)
2008	4,476 (10.2)	687 (1.6)	304 (0.7)	189 (0.4)
2009	4,361 (9.9)	655 (1.5)	304 (0.7)	209 (0.5)
2010	4,499 (10.2)	703 (1.6)	289 (0.6)	244 (0.6)
Surgical type				
Ear, nose, throat	3,876 (80.1)	440 (9.2)	266 (5.6)	111 (2.3)
Urology	9,408 (75.2)	1,660 (13.3)	802 (6.4)	323 (2.6)
Vascular	1,330 (41.1)	1,207 (37.6)	297 (9.3)	237 (7.4)
Orthopedic	2,345 (80.1)	263 (9.1)	162 (5.6)	76 (2.6)
General	6,217 (75.9)	1,136 (13.9)	432 (5.3)	211 (2.6)
Thoracic	3,297 (77.8)	565 (13.3)	167 (3.9)	116 (2.7)
Plastic	1,438 (85.5)	123 (7.3)	56 (3.3)	27 (1.6)
Gynecology	5,374 (81.5)	601 (9.1)	359 (5.5)	145 (2.2)
Emergent	6,001 (17.6)	1,938 (32.3)	477 (18.8)	250 (20.1)
Duration (min)	140 (119)	151.7 (125)	145 (114)	153 (125)
Comorbid states				
CAD	534 (1.6)	561 (9.4)	156 (6.1)	138 (11.1)
CHF	435 (1.3)	365 (6.1)	74 (2.9)	99 (8.0)
CVD	800 (2.4)	358 (6.0)	102 (4.0)	69 (5.5)
Diabetes mellitus	907 (2.7)	812 (13.5)	150 (5.9)	177 (14.2)
CRF	824 (2.4)	570 (9.5)	107 (4.2)	96 (7.7)
Anemia	6,077 (17.8)	1,980 (33.0)	603 (23.7)	334 (26.8)
Cancer	12,702 (37.3)	1,862 (31.1)	878 (34.6)	452 (36.3)
Metastatic cancer	4,600 (13.5)	682 (11.4)	311 (12.2)	150 (12.0)
Hypertension	6,125 (17.9)	2,298 (38.3)	1,402 (56.2)	489 (39.2)
Coagulopathy	540 (1.62)	353 (5.9)	86 (3.4)	63 (5.1)
Risk indices				
ASA class 2	13,370 (40.2)	754 (12.6)	618 (24.3)	161 (12.9)
ASA class 3	15,300 (46.0)	2,486 (58.2)	1,536 (60.5)	739 (59.3)
ASA class 4	2,968 (8.9)	1,733 (28.9)	378 (14.9)	341 (27.4)
RCRI = 1	7,293 (21.4)	2,150 (35.9)	728 (28.7)	406 (32.6)
RCRI = 2	1,715 (5.0)	1,536 (25.6)	388 (15.3)	339 (27.2)
RCRI ≥3	362 (1.1)	436 (7.3)	110 (4.3)	125 (10.3)
Concomitant cardiac medications				
Statins	5,189 (15.2)	2,452 (40.9)	987 (38.8)	552 (44.3)
CCBs	4,000 (11.7)	1,417 (23.6)	701 (27.6)	312 (25.0)
ACE inhibitors	4,689 (13.8)	1,895 (31.6)	816 (32.1)	423 (33.9)
Aspirin	2,041 (6.1)	1,561 (27.5)	474 (18.7)	319 (26.6)
Hematology				
Preop hemoglobin	13.3 (1.8)	12.6 (2.0)	13.0 (1.8)	12.9 (1.8)
Postop hemoglobin	10.3 (1.8)	9.9 (1.7)	10.3 (1.7)	10.2 (1.7)
Nadir	7,459 (21.9)	2,180 (36.4)	686 (27.0)	366 (29.4)
No transfusion	32,019 (96.2)	5,436 (90.6)	2,421 (95.3)	1,150 (92.3)
1–4 UE	1,210 (3.6)	538 (9.0)	118 (4.6)	92 (7.4)
More than four UE	66 (0.4)	21 (0.4)	2 (0.3)	2 (0.5)

(*continued*)

Table 1. (*Continued*)

	No β-Antagonist n = 33,285	Metoprolol n = 5,995	Atenolol n = 2,541	Bisoprolol n = 1,246
Postoperative disposition				
PACU	32,395 (97.3)	5,571 (92.3)	2,465 (97.0)	1,187 (95.3)
New AF	114 (0.3)	207 (0.5)	18 (0.1)	13 (0.03)
In-hospital 30-day mortality	430 (1.26)	199 (3.32)	34 (1.34)	25 (2.01)
Stroke (7 days)	40 (0.1)	37 (0.62)	9 (0.35)	2 (0.16)
Composite outcome	733 (2.15)	713 (11.9)	103 (4.01)	77 (6.2)

Two hundred ten patients with other β-antagonists (sotalol, carvediolol, nadolol, and labetolol) are not displayed. There were no strokes in these patients. Daily dosages are on hospital admission and from the Preoperative Assessment and are expressed in milligram. The doses are expressed as median (25th to 75th percentile) and maximum dose. The median dose found in this analysis, metoprolol, atenolol, and bisoprolol is the recommended daily dose for both angina and hypertension. Three percent of the metoprolol population was taking the succinate formulation, however, the daily doses are equal. The composite outcome is defined as any or all of stroke within 7 days of surgery, postoperative myocardial injury (troponin I increase >0.7 μg/l), and in-hospital death within 30 days of surgery.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; Anemia = the World Health organization definition adjusted for sex; ASA class = the American Society of Anesthesiologists' classification; CAD = coronary artery disease; CCBs = calcium channel blockers; CHF = congestive heart failure; CRF = chronic renal failure; CVD = cerebral vascular disease; Nadir = the number and percent of patients with the lowest postop hemoglobin <9.0 mg/dl; PACU = postanesthesia care unit; RCRI = revised cardiac risk index; UE = units of erythrocytes transfused.

These findings that bisoprolol may be a safer alternative in β-blocked patients clearly warrants further investigation in a controlled clinical trial.

Our experimental findings suggested that the risk of stroke associated with less selective agents results from inhibition of β_2-mediated cerebral vasodilation. Animal studies show that all the β-blockers evaluated would be expected to have a comparable effect on limiting the cardiac output responsiveness through comparable antagonism of β_1-receptors.[9–12] The compensatory increase in cardiac output becomes predominantly heart rate dependent at a hemoglobin level between 9 and 10 gm/dl.[6] Below this hemoglobin level, all of the β-blockers that we studied were associated with increasing stroke rates (fig. 3). However, as previously described, the impact of β_2-inhibition by less selective β-blockers may impair cerebral vasodilation independent of hemoglobin level; possibly explaining the difference seen between metoprolol and bisoprolol at nadir hemoglobin levels greater than 9 gm/dl (fig. 3) because nonselective β-blockers may impair cerebral vasodilation (β_2-mediated effect) across all levels of blood loss. Our animal data support this argument by demonstrating that metoprolol increased systemic vascular resistance and reduced brain tissue P_{O_2} *in vivo*, at normal hemoglobin levels.[10] In addition, metoprolol

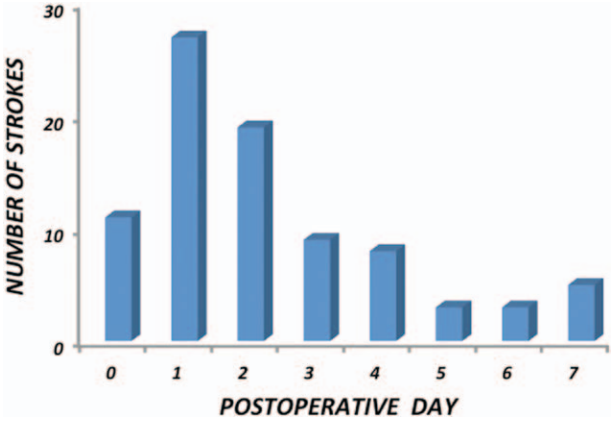

Fig. 2. The temporal relationship between surgery and postoperative stroke. The peak incidence of stroke was seen on the first postoperative day. Day 0 depicts the day of surgery. The peak incidence is on the day after surgery, whereas two thirds of the strokes occur within the first 72 h.

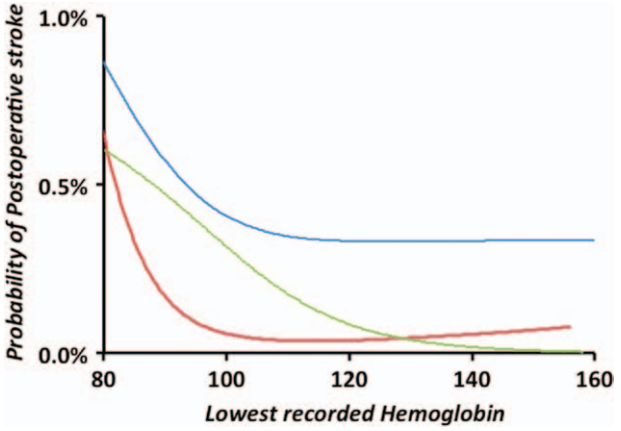

Fig. 3. Comparison of the effect of lowest recorded hemoglobin on postoperative stroke. The figure illustrates the restricted cubic spline relationship between nadir hemoglobin (defined as the lowest recorded hemoglobin in the first 72 h after surgery) and the probability of postoperative stroke. The relationship is shown for the three most common β-adrenergic antagonists in this population. Metoprolol (β_1/β_2 = 2.3) is shown in *blue*; atenolol (β_1/β_2 = 4.7) is shown in *green*, and bisoprolol (β_1/β_2 = 13.5) is shown in *red*. The relationship shows that metoprolol has a higher baseline risk of stroke, whereas atenolol has a baseline stroke risk similar to bisoprolol. The risk of stroke increases for all β-blockers at a postoperative hemoglobin level of 9 gm/dl. A spline curve refers to a smoothing process. The process involves a third-order polynomial function that in this case presents the probability of stroke for the level of nadir hemoglobin.

Table 2. Patient Characteristics before and after Propensity Score Matching: An Analysis Comparing Highly Selective β-Blockade (Bisoprolol) to Less Selective Agents (Atenolol and Metoprolol)

	Unadjusted			After Propensity Score Matching		
	Bisoprolol n = 1,246	Others n = 9,550	Standardized Difference	Bisoprolol n = 1,231	Atenolol or Metoprolol n = 1,231	Standardized Difference
Demographics						
Sex (male)	754 (60.5)	5,458 (57.1)	0.07	744 (30.2)	723 (29.4)	0.000
Age (years)	70.9 (10)	70.6 (9.5)	0.031	70.6 ± 9.5	69.9 ± 9.9	−0.002
Year of surgery						
2003	44 (0.3)	1,220 (12.8)	0.429	44 (2.0)	48 (1.8)	0.015
2004	72 (5.8)	1,231 (12.9)	−0.246	72 (2.6)	63 (2.9)	−0.018
2005	107 (7.5)	1,317 (13.8)	−0.205	107 (4.4)	107 (4.4)	0.000
2006	142 (12.0)	1,207 (12.6)	−0.018	142 (5.8)	170 (6.9)	0.045
2007	239 (14.6)	1,230 (12.9)	0.101	239 (9.8)	172 (7.0)	−0.098
2008	189 (15.4)	1,103 (11.5)	0.144	189 (7.7)	203 (8.3)	0.022
2009	209 (16.0)	1,100 (11.5)	0.131	203 (8.3)	215 (8.7)	0.014
2010	244 (19.6)	1,153 (12.1)	0.206	235 (9.6)	253 (10.3)	0.023
Surgical type						
Ear, nose, throat	111 (8.4)	805 (8.4)	0	108 (4.4)	107 (4.4)	−0.003
Urology	323 (26)	2,784 (29)	−0.067	321 (26)	318 (25.8)	−0.005
Vascular	237 (19)	1,639 (17)	0.05	233 (19.0)	238 (19.2)	0.005
Orthopedic	76 (6.1)	472 (5)	0.048	75 (6.2)	74 (6.1)	0.004
General	211 (18)	1,759 (18)	0	209 (17.0)	207 (16.9)	0.003
Thoracic	116 (9)	817 (9)	0	115 (9.4)	114 (9.3)	0.003
Plastic	27 (2)	216 (2)	0	27 (1.1)	25 (1.0)	−0.005
Gynecology	145 (12)	1,026 (11)	0.031	145 (5.9)	146 (5.9)	0.003
Duration (min)	153 (119)	148 (119)	0.042	152 ± 124	154 ± 127	0.066
Emergent surgery	250 (20.1)	2,415 (25.4)	−0.127	246 (20.0)	246 (20.0)	0.000
Comorbidities						
CAD	138 (11.0)	799 (8.4)	0.088	133 (10.8)	134 (10.85)	−0.003
CVD	69 (5.5)	515 (5.4)	0.04	68 (2.8)	67 (2.8)	0.000
CHF	99 (8.0)	531 (5.6)	0.095	89 (3.6)	105 (3.9)	−0.016
Diabetes mellitus	177 (14.2)	1,075 (11.2)	0.091	173 (7.0)	180 (7.3)	−0.012
CRF	76 (6.1)	641 (6.7)	−0.025	73 (5.9)	82 (6.6)	−0.029
Anemia	334 (26.8)	2,865 (30.0)	−0.071	330 (13.4)	344 (14.0)	−0.017
COPD	115 (9.2)	591 (6.2)	0.016	102 (4.1)	105 (4.4)	−0.014
Metastatic	150 (12.0)	1,095 (11.5)	0.113	149 (6.1)	153 (6.2)	−0.004
Hypertension	489 (39.2)	3,700 (44.0)	−0.097	484 (35.7)	484 (35.7)	0.000
Coagulopathy	63 (5.1)	520 (5.4)	−0.013	60 (2.4)	65 (2.6)	−0.013
Risk indices						
ASA class 2	161 (1.5)	1,561 (14.4)	−0.491	173 (14.1)	160 (13.0)	−0.011
ASA class 3	739 (59.4)	5,599 (58.6)	0.016	716 (58.2)	734 (59.3)	0.002
ASA class 4	341 (27.4)	2,363 (24.7)	0.062	339 (27.6)	332 (27.0)	0.006
RCRI = 1	406 (32.6)	3,199 (33.5)	−0.019	404 (16.4)	424 (17.2)	0.008
RCRI = 2	214 (17.2)	1,492 (15.6)	0.043	210 (8.5)	212 (8.6)	0.002
RCRI ≥3	125 (10.0)	621 (6.5)	0.127	116 (4.7)	122 (5.0)	−0.011
Hematologic factors						
Preop hemoglobin	12.9 (1.8)	12.8 (1.9)	0.052	12.9 (1.9)	12.8 (2.0)	0.050
Postop hemoglobin	10.2 (1.6)	10.0 (1.7)	0.12	10.2 (1.7)	10.1 (1.7)	0.057
Nadir	29.3	28.8	0.011	389 (15.2)	372 (14.5)	0.019

(*continued*)

Table 2. (*Continued*)

	Unadjusted			After Propensity Score Matching		
	Bisoprolol n = 1,246	Others n = 9,550	Standardized Difference	Bisoprolol n = 1,231	Atenolol or Metoprolol n = 1,231	Standardized Difference
No transfusion	1,089 (87)	8,162 (85)	–0.058	1,077 (87.6)	1,051 (85.4)	0.058
1–4 UE	135 (11)	1,124 (13)	–0.33	132 (10.8)	141 (11.4)	–0.003
More than four UE	36 (2)	275 (2)	0.049	22 (1.6)	39 (3.2)	–0.008
Chronically administered medications						
Statins	552 (44.3)	3,802 (40.0)	0.87	545 (44.2)	543 (44.2)	0.003
Aspirin	319 (25.6)	2,304 (24.1)	0.035	313 (12.7)	317 (12.9)	–0.009
CCBs	312 (25.0)	2,357 (24.7)	0.007	311 (25.2)	294 (23.8)	0.003
ACE inhibitor	423 (33.9)	2,711 (31.8)	0.032	422 (31.7)	422 (31.7)	0.000
Postoperative events						
PACU	1,187 (95.5)	9,000 (94.3)	0.055	1,173 (95.3)	1,160 (94.2)	0.046
New AF	11 (0.5)	253 (2.6)	–0.171	11 (0.5)	6 (0.3)	0.032
Primary outcome						
Stroke	2 (0.01)	49 (0.5)		2 (0.01)	10 (0.1)	
Secondary outcomes						
POM.I	68 (5.5)	686 (7.2)		65 (5.3)	105 (8.5)	
In-hospital mortality	25 (2.0)	265 (2.8)		25 (2.0)	31 (2.5)	
Comp out.	77 (6.2)	890 (9.3)		74 (6.0)	133 (10.8)	
Relative risk of stroke (bisoprolol *vs*. metoprolol or atenolol)					0.20 (95% CI, 0.04–0.91)	
Relative risk of composite (bisoprolol *vs*. metoprolol or atenolol)					0.56 (95% CI, 0.42–0.73)	

ACE = angiotensin-converting enzyme; Anemia = the World Health organization definition adjusted for sex; ASA Class = the American Society of Anesthesiologists' classification; CAD = coronary artery disease; CCB = calcium channel blockers; CHF = congestive heart failure; Comp out. = the composite outcome defined as any or all of postoperative stroke, postoperative myocardial injury (troponin >0.07 μg/ml) and in-hospital 30-day mortality; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVD = cerebral vascular disease; New AF = the new onset of postoperative atrial fibrillation; Nadir = the number and percentage of patient with a postoperative hemoglobin <9 gm/dl; PACU = postanesthesia care unit; Preop hemoglobin = the hemoglobin levels before surgery in gm/dl; POMI = postoperative myocardial injury; Postop hemoglobin = the lowest hemoglobin level postoperatively in gm/dl; RCRI = revised cardiac risk index; UE = units of erythrocytes transfused.

clearly impaired β_2-adrenergic vasodilation of cerebral arteries *in vitro*.[10] Finally, systemic β-blockers administered to anemic animals, at doses that can interact with β_2 receptors, showed acute reduction in brain tissue P_{O_2} and increased expression of biological markers of cerebral hypoxia.[8–10]

Kamel *et al.* first noted an association between acute anemia and postoperative strokes. Using the National Surgical Quality Improvement Project database, they found that transfusion of more than 4 units doubled the stroke rate. Two additional, and independent, studies document that the interaction between β-blockade and acute surgical anemia is associated with an increased risk of postoperative coronary morbidity and multiorgan failure.[5,23] Because selective β_1-antagonists preserve peripheral circulation, it follows that highly cardioselective agents favor vital organ perfusion during conditions of acute blood loss and fluid resuscitation. This is a possible explanation for the finding that chronically administered metoprolol was associated with a greater risk of death after surgery compared with more selective β-antagonists.[24]

The overall stroke rate in the current study was 0.2%. In comparison, in studies where the National Surgical Quality Improvement Project database was used to study acute postoperative stroke, a range of stroke incidence from 0.1 to 0.4% was observed. Although our incidence of stroke falls within this range, it is difficult to explain a four-fold variation in stroke rate, in studies using the National Surgical Quality Improvement Project database but may be due to different study populations. In the subgroup analysis of our sample, patients with at least one cardiac risk factor had an incidence of 0.4%, doubling the overall stroke incidence.

Previous studies have identified numerous risk factors for perioperative stroke which have included age, sex, AF, congestive heart failure, renal disease and cardiovascular disease,[17] chronic obstructive pulmonary disease, left ventricular systolic dysfunction, duration of surgery, and hyperglycemia. Our study did not have the sample size or the power to assess these factors. However, they are unlikely to influence our results because they were well matched in our propensity score. Studies that identified these variables had on average more than 1,000 outcomes and more than 250,000 subjects.

β-Antagonism is known to decrease postoperative AF as demonstrated by the POISE study. Paradoxically, metoprolol doubled the stroke rate in POISE trial. These divergent data suggest that the postoperative strokes associated with

Table 3. The Association between of β_1-Selective Blockade and Stroke: Candidate Variables Based on POISE and Animal Experiments

	Odds Ratio (95% CI)
Cerebral vascular disease	6.13 (3.5–10.9)
Bisoprolol (compared with atenolol or metoprolol)	0.20 (0.04–0.99)
Atenolol or metoprolol (compared with no β-exposure)	5.14 (2.0–13.5)
Emergent surgery	2.47 (1.5–4.0)
Transfusion (per unit of erythrocyte)	1.1 (1.03–1.2)
Postoperative hemoglobin	0.975 (0.96–0.98)
New onset of postoperative atrial fibrillation	0.72 (0.1–5.3)

c-Statistic = 0.774; Hosmer–Lemeshow, P = 0.318. Candidate variables from POISE trial[3]: (1) cerebral vascular disease (or Rx for TIA), (2) major blood loss, and (3) new onset of atrial fibrillation. Note that the definition of major blood loss was dichotomous (two or more units of erythrocytes in POISE trial, the current analysis uses transfusion as continuous variable. Candidate variables form animal experiments[9–12]: (1) β_1-selective agent *vs*. less selective, (2) acute anemia. Note that we defined anemia as a continuous variable based on increasing hemoglobin levels.

POISE = Perioperative Ischemia Evaluation; Rx = therapy; TIA = transient ischemic attack.

β-blockade are unlikely to be related to new onset AF. Furthermore, the incidence of new onset postoperative AF in our study was comparable with POISE trial. However, we did not find that AF was associated with stroke. The potential explanations for this include: (1) AF may have been underestimated or AF may not have been coded properly in the discharge abstract database if it was of short duration or did not require special therapy; (2) previous associations between AF and postoperative stroke were derived on the basis of a history of preoperative AF,[18,19]which is distinct from our study and POISE trial, which found that new onset of AF was associated with postoperative stroke; (3) the American Heart Association guidelines for the management of AF suggest the use of β-blocker alone or in combination with other drugs.[25] This guideline may have contributed to the previous associations between AF and stroke because over 60% of patients with new onset AF reportedly receive metoprolol.[26] Unfortunately, studies finding that preoperative AF was associated with postoperative stroke did not record details of β-blockers use and they did not adjust for the influence of other chronic medication. Thus, the degree to which previous β-adrenergic antagonism confounds these results remains unknown because no difference in AF prophylactic effects were identified when different β-antagonists were prescribed.[27]

Limitations

The retrospective observational nature of this study can be influenced by potential unmeasured confounders and the two factors, β-adrenergic antagonism and acute anemia may identify patients who are "sicker," having procedures with increased complexity. Nonetheless, using a propensity score-matched cohort, we were able to balance all known confounders and show a reduction in the stroke rate with highly selective β_1-antagonism. Cautious interpretation is also warranted because there were less than 90 strokes, rendering the results statistically fragile. However, the odds ratios found by our targeted logistic regression and propensity-matched cohorts are similar. In our opinion, our results are strengthened by the fact that two methods of risk adjustment, using different assumptions, yield similar results.

The use of International Classification of Diseases-10 coding to identify postoperative stroke may have introduced some errors, as other neurological pathology is included in the acute stroke coding.[28,29] The strokes we have identified in this analysis were independently verified by two observers, blinded to β-blocker exposure, using both clinical and radiological evidence. We are unable to comment on the clinically important incidence of perioperative hypotension[3,30] because intraoperative hemodynamic data on all patients were not available. Acute anemia is strongly associated with hypotension. The Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair trial showed that a transfusion trigger of 8 gm/dl was associated with a three-fold increase in serious hypotension, tachycardia, and congestive failure compared with the cohort with a higher transfusion trigger.[31]

We cannot be sure that we have accurately defined all β-blocker exposures; in urgent and emergent procedures data are based solely on inpatient pharmacy data. This limits us because there is the potential to label a patient who had β-blockers withdrawn, as not being exposed or alternatively drug newly started, as a result of some event, could be labeled as chronic use. Both of these scenarios carry different risks.[32] Finally, the use of bisoprolol increased substantially over the period of our study. Although we have balanced the number of patients by year in the propensity analysis, we cannot adjust for other factors that may have influenced the decision to use bisoprolol over this time period.

Conclusions

Postoperative stroke is a rare but devastating event that is associated with the use of the nonselective β-blockers and acute anemia. The analysis further identifies two potentially modifiable risk factors, the type of β-blocker and anemia. Consideration of these factors in the management of at-risk patients may alter the safety profile of perioperative β-adrenergic antagonism which offers irrefutable perioperative cardioprotection. All studies to date show that patients with significant cerebral vascular disease are at risk of stroke and treatment with β-antagonists, of any kind, should be carefully considered. Patients needing β-antagonist-mediated cardioprotection during surgery may benefit from the use of highly selective β_1-agents. We are in the process evaluating these findings prospectively.

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Appendix. ICD 10 Codes

ICD 10 code used in determining preoperative RCRI	
Comorbidity	ICD 10 code
CHF	I42.6,I42.7, I43.8, I42.9, I50.0, I42.0, I42.4, I50.9, I50.1, I42.1, I42.8, I42.2,I42.5, J81. I11.0, I13.0, I13.2
Cardiac ischemia	I24.9,I21.9, I21.4,I21.40, I21.41,I21.42, I21.49, I21.0, I21.1, I21.2, I21.3, I20.1, I20.9, I25.11, I25.10, I25.13, I25.19, I25.14, I20.80, I25.9 I24.0, R94.30, I25.5, I25.2, I24.8 I20.88, I25.8, I23.82, Z95.1,Z95.5, I25.6,I22.0,I22.1,I22.9, I20.0
Cerebral vascular disease	I63.4, I63.9, I63.1, I63.0, I63.3,I63.5, I63.2, I65.1,I65.2,I66.0, I65.3, I66.4, I65.8 I66.8, I66.9, I65.0, I64., G45.9, I67.2, I67.9
Diabetes	H28.0G59.0G63.2H36.0E23.2E10.42E10.30E10.52E10.35E10.22E10.21 E10.23E10.70E10.63E10.20E10.10E10.78E10.60E10.33E10.28E10.38E10.50E10 .4E10.64E10.31E10.32E10.9E11.36E11.42E11.30E11.52E11.0E11.35E11.22E1 1.21E11.23E11.71E11.70E11.63E11.20E11.10 E11.40, E11.78, E11.60, E11.33, E11.68, E11.28, E11.38, E11.50 E11.51, E11.41, E11.64, E11.31, E11.32, E11.9, E13.42, E13.52, E13.35, E13.22 E13.63, E13.1, E13.78, E13.60, E13.33, E13.68, E13.28, E13.41, E13.64, E13.9 E14.30, E14.52, E14.35, E14.22, E14.21, E14.23, E14.71, E14.20, E14.10, E14.11 E14.78, E14.33, E14.41, E14.31, E14.32, E14.61,E14.9E11.500E11.501E11.509E1 1.511E11.513E11.519E11.900E11.901E11.903E11.909E13.229E13.589E13.599 E13.689E13.900E13.909E14.300E14.301E14.309E14.320E14.321E14.329E14.3 30E14.349E14.350E14.351E14.354E14.380E14.390E14.429E14.700E14.781E1 4.789E14.901E14.904E14.909
Renal	Preoperative laboratory value (Creatinine >176 mM)
ICD 10 coding for the postoperative outcomes	
Morbidity	ICD 10 code
Myocardial ischemia	I24.9,I21.9,I21.4,I21.40,I21.41,I21.42,I21.49,I21.1,I21.2,I21.3,I20.1,I20.9,I20.80,I24 .0,R94.30,I25.5,I24.8,I20.88,I23.82,I25.6,I22.0,I22.1,I22.9,I20.0,I24.1
Cerebral ischemia	I63.4,I63.9,I63.1,I63.0,I63.3,I63.5,I63.2,I65.1,I65.2,I66.0,I65.3,I66.4,I65.8,I66.8,I66 .9,I65.0,I64.,G45.9
Acute renal failure	N17.0,N17.8,N17.9,N19.N28.0,N99.0,Z99.2
Pulmonary embolism	I26.9, I26.0
Cardiac arrest	I46.0,I46.1,I46.9,I49.00
Atrial fibrillation	I48.0, I48.1
Myocardial infarction	I24.9,I21.4,I21.40,I21.41,I21.42,I21.49,I21.0,I21.1,I21.2,I21.3,R94.30,I25.5,I24. 8,I23.8, I25.6,I22.0,I22.1,I22.9,I24.1
Congestive heart failure	I50, I 50.1,I50.20,i50.21, I50.23,I50.4,I50.41, I50.43, I50.9

CHF = congestive heart failure; ICD = international classification of diseases; RCRI = revised cardiac risk index.