ANESTHESIOLOGY

Preoperative β-Blocker Therapy and Stroke or Major Adverse Cardiac Events in Major Abdominal Surgery: A Retrospective Cohort Study

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Anesthesiology 2023; 138:42–55

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Controversy surrounds the initiation of perioperative β-blockade to reduce the risk of major adverse cardiac events for patients undergoing major noncardiac surgery
- Clinicians are unclear whether the cardiovascular benefit of β-blockade observed in clinical trials is counterbalanced by an increased risk of stroke

What This Article Tells Us That Is New

- Using national administrative claims data for adults undergoing elective major abdominal surgery, patients initiating β-blocker therapy within 60 days before surgery were compared to patients on chronic β-blocker therapy and β-blocker–naïve patients
- Postoperative stroke was rare: 0.4% (17 of 4,026) of patients initiating a β-blocker, 0.4% (171 of 45,424) on chronic β-blockers, and 0.2% (235 of 155,531) of β-blocker–naïve patients
- After propensity score weighting, patients initiated on a β-blocker (odds ratio, 0.90; 95% CI, 0.31 to 2.04) or on chronic β-blocker therapy (odds ratio, 0.86; 95% CI, 0.65 to 1.15) demonstrated stroke risk similar to β-blocker–naïve patients

ABSTRACT

Background: Perioperative β-blocker therapy has been associated with increased risk of stroke. However, the association between β-blocker initiation before the day of surgery and the risk of stroke is unknown. The authors hypothesized there would be no association between preoperative β-blocker initiation within 60 days of surgery or chronic β-blockade (more than 60 days) and the risk of stroke in patients undergoing major abdominal surgery.

Methods: Data on elective major abdominal surgery were obtained from the IBM (USA) Truven Health MarketScan 2005 to 2015 Commercial and Medicare Supplemental Databases. Patients were stratified by β-blocker dispensing exposure: (1) β-blocker–naïve, (2) preoperative β-blocker initiation within 60 days of surgery, and (3) chronic β-blocker dispensing (more than 60 days). The authors compared in-hospital stroke and major adverse cardiac events between the different β-blocker therapy exposures.

Results: There were 204,981 patients who underwent major abdominal surgery. β-Blocker exposure was as follows: perioperative initiation within 60 days of surgery for 4,026 (2.0%) patients, chronic β-blocker therapy for 45,424 (22.2%) patients, and β-blocker–naïve for 155,531 (75.9%) patients. The unadjusted frequency of stroke for patients with β-blocker initiation (0.4%, 17 of 4,026) and chronic β-blocker therapy (0.4%, 171 of 45,424) was greater than in β-blocker–naïve patients (0.2%, 235 of 155,531; $P < 0.001$). After propensity score weighting, patients initiated on a β-blocker within 60 days of surgery (odds ratio, 0.90; 95% CI, 0.31 to 2.04; $P = 0.757$) or on chronic β-blocker therapy (odds ratio, 0.86; 95% CI, 0.65 to 1.15; $P = 0.901$) demonstrated similar stroke risk compared to β-blocker–naïve patients. Patients on chronic β-blocker therapy demonstrated lower adjusted risk of major adverse cardiac events compared to β-blocker–naïve patients (odds ratio, 0.81; 95% CI, 0.72 to 0.91; $P = 0.007$), despite higher unadjusted absolute event rate (2.6% [1,173 of 45,424] *vs.* 0.6% [872 of 155,531]).

Conclusions: Among patients undergoing elective major abdominal surgery, the authors observed no association between preoperative β-blocker initiation within 60 days of surgery or chronic β-blocker therapy and stroke.

(ANESTHESIOLOGY 2023; 138:42–55)

Major adverse cardiac events after major noncardiac surgery are a significant cause of perioperative morbidity and mortality. Recent estimates of major adverse cardiac events suggest a frequency between 1.4 and 3.9%, with an associated in-hospital mortality between 10 and 65%.[1,2] Few preventative measures have proven effective to reduce the risk of these perioperative major adverse cardiac events.

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 7. This article has a related Infographic on p. A17. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version.

Submitted for publication August 30, 2021. Accepted for publication September 27, 2022. Published online first on October 13, 2022.

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 Anesthesiology 2023; 138:42–55. DOI: 10.1097/ALN.0000000000004404

Perioperative β-blocker therapy initiated within hours before surgery has been shown to reduce the frequency of myocardial infarction and in-hospital mortality in small randomized controlled trials.[2–5] As a result, β-blockers were incorporated into the American College of Cardiology (Washington, D.C.) and American Heart Association (Dallas, Texas) practice guidelines and further supported by the Surgical Care Improvement Project Card-2 measure that encouraged administration of a β-blocker within a day of surgery if the patient had been on a β-blocker previously.[6] The Perioperative Ischemic Evaluation Study (POISE) demonstrated that aggressive β-blocker initiation within 2 to 4 h of surgery was associated with a greater risk of acute stroke and all-cause mortality, despite a reduction in the frequency of myocardial infarction.[7] The POISE trial studied high-dose β-blocker initiation hours before surgery in β-blocker–naïve patients who were at an increased risk for major adverse cardiac events. After POISE, there was a significant reduction in new β-blocker prescriptions within 60 days of major noncardiac surgery.[8,9] Despite this apparent practice change, the effect of β-blocker initiation in the weeks before major noncardiac surgery on the risk of stroke or major adverse cardiac events in routine practice remains unknown.[10] Further, the effects of chronic β-blocker dispensing (more than 60 days before surgery) on perioperative stroke in noncardiac surgery is unclear in the current literature.[11]

Our study had 2 main aims. The first aim was to identify whether preoperative β-blocker initiation within 60 days of elective major abdominal surgery was associated with higher risk of stroke or lower risk of perioperative major adverse cardiac events. The second aim was to determine whether chronic β-blocker dispensing (more than 60 days before surgery) before elective major abdominal surgery was associated with higher risk of stroke or lower risk of perioperative major adverse cardiac events. We hypothesized that neither preoperative β-blocker initiation within 60 days of surgery nor chronic β-blocker dispensing (more than 60 days before surgery) would be associated with a higher risk of stroke or with a lower risk of major adverse cardiac events.

Materials and Methods

Data Source

The University of Chicago Institutional Review Board (Chicago, Illinois) considered this study exempt from review as the MarketScan databases do not contain patient identifiers. Data used for the analysis were derived from the IBM (USA) Truven Health MarketScan 2004 to 2015 Commercial and Medicare Supplemental Databases. These administrative databases represent the health service claims of approximately 250 million employees, dependents, and retirees in the United States. The records are not directly obtained from patients' electronic medical records. The Commercial and Medicare Supplemental Databases are generally representative of the population of the United States in terms of sex (48% male), and the mean ages of the commercial and Medicare supplemental populations were 33 and 74 yr, respectively. These databases provide unique identifiers that allow enrollees to be followed across institutions, across providers, and over time. All enrollment records and inpatient, outpatient, ancillary, and drug claims were collected in accordance with the Health Insurance Portability and Accountability Act, and all patient data were de-identified. Certain populations without employer-sponsored insurance, including uninsured and Medicaid patients, are not represented in these databases.

Cohort Selection

The sample size was based on the available data that met our inclusion criteria (fig. 1). Patients who had undergone major abdominal surgery from January 1, 2005, to December 31, 2015, were identified with an International Classification of Diseases, Ninth Revision–Clinical Modification, or International Classification of Diseases, Tenth Revision–Clinical Modification, principal procedure code for open or laparoscopic small bowel resection, large bowel resection, gastrectomy, total pancreatic resection, cystectomy, and nephrectomy. See Supplemental Digital Content 1 (http://links.lww.com/ALN/C952) for a table of International Classification of Diseases, Ninth Revision–Clinical Modification, and International Classification of Diseases, Tenth Revision–Clinical Modification, codes used to identify patients undergoing major abdominal surgery. Major abdominal procedures were chosen as these are identified by the Revised Cardiac Risk Index as a high-risk major noncardiac surgical procedure.[12] The initial cohort of individuals with inpatient claims for major abdominal surgery from the Truven Health MarketScan Commercial and Medicare Supplemental Databases from 2005 to 2015 was 449,903 patients. Patients were excluded from the analysis if they did not meet inclusion criteria: (1) the patient was younger than 18 yr (n = 7,327); (2) the surgery was an emergency, which was identified by an associated emergency room service claim from the same date as the surgical procedure (n = 83,227); (3) the surgery was not the patient's first procedure of interest during the study period (n = 9,476); and (4) the subject was not insured for 1 yr before the surgery (n = 132,939). Patients were also excluded for missing data: (1) there were no drug benefit data available in the MarketScan database for the patient (n = 85), or (2) there was no discharge status variable, which provides information on inpatient mortality (n = 11,868; fig. 1). Missing drug or mortality data were assumed to be at random due to administrative error. The remaining cohort consisted of 204,981 insured individuals.

β-Blocker use was the exposure variable of interest. It was defined using medication dispensing records from the MarketScan drug benefit database. It was classified into 3 distinct categories: (1) preoperative initiation if a new β-blocker was dispensed within 60 days before the surgical

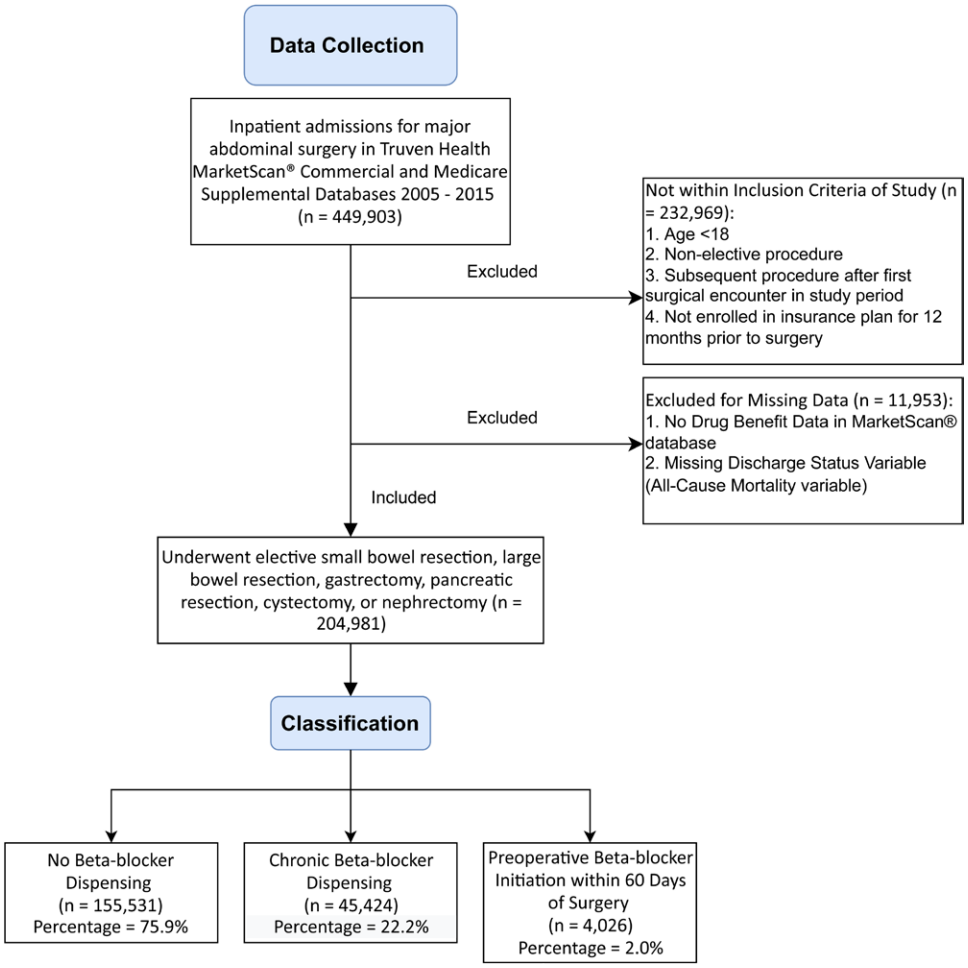

Fig. 1. Flow chart of the cohort selection of patients who underwent an elective major abdominal surgery from the MarketScan Inpatient Database (IBM, USA) from 2005 to 2015. There were 449,903 individuals with major abdominal surgery inpatient claims from the Truven Health MarketScan Commercial and Medicare Supplemental Databases from 2005 to 2015. Patients were excluded if they already had a surgical encounter within the year (n = 9,476), were under the age of 18 yr (n = 7,327), were uninsured within the year of surgery (n = 132,939), underwent a nonelective procedure (n = 83,227), did not have MarketScan drug benefit data were excluded (n = 85), or were missing the discharge status variable that encodes in-hospital mortality (n = 11,868).

procedure and no other β-blocker dispensing was identified within the year before their surgery, (2) chronic if a patient had β-blockers dispensed before 60 days before surgery, or (3) naïve if no β-blockers were dispensed within 365 days before surgery. All cardiac β-blocker dispensing was identified using the MarketScan drug benefit database.[13] Dispensing of noncardiac-related β-blockers is coded under a different variable and was not included as an exposure variable in this study. See Supplemental Digital Content 2 (http://links.lww.com/ALN/C952) for a table of the MarketScan therapeutic class codes used to identify β-blocker use.

Outcome

The primary outcome was stroke after major abdominal surgery. Stroke included a new diagnosis of a stroke at any point during the inpatient admission. The secondary outcomes were the composite of major adverse cardiac events and the frequency of each component. Major adverse cardiac events included (1) all-cause mortality, (2) myocardial infarction, (3) cardiac arrest, and (4) revascularization, defined by percutaneous coronary artery stenting or coronary artery bypass grafting at any point during the inpatient admission for the surgery.

Stroke, myocardial infarction, cardiac arrest, and revascularization were identified using the appropriate International Classification of Diseases, Ninth Revision–Clinical Modification, and International Classification of Diseases, Tenth Revision–Clinical Modification, codes and Current Procedural Terminology codes. See Supplemental Digital Content 3 (http://links.lww.com/ALN/C952) for a table of International Classification of Diseases,

Ninth Revision–Clinical Modification/International Classification of Diseases, Tenth Revision–Clinical Modification, code and Current Procedural Terminology codes used to identify patients with a stroke, myocardial infarction, cardiac arrest, or revascularization. All-cause mortality was identified with the discharge status variable in the Truven Health MarketScan Commercial and Medicare Inpatient Admission Database.

Patient Characteristics and Covariates

Patient characteristics analyzed were age, sex, procedure type, geographical region, insulin-dependent diabetes mellitus, history of cerebrovascular accident, chronic kidney disease, coronary artery disease, valvular pathology, and heart failure. The database did not contain sufficient laboratory data in our cohort to rely on obtaining an estimated glomerular filtration rate of 45 ml/min per 1.73 m^2; thus, we used the diagnosis of chronic kidney disease stage III or higher as indicative of an estimated glomerular filtration rate of 45 ml/min per 1.73 m^2.[14]

The Elixhauser comorbidity score was included as a covariable used to account for overall comorbidity burden.[15] Comorbidity diagnoses for cohort subjects were included if the International Classification of Diseases, Ninth Revision–Clinical Modification, or International Classification of Diseases, Tenth Revision–Clinical Modification, codes were present in at least one inpatient or outpatient claim within a year before the admission for the surgical procedure. Patients were considered to have insulin-dependent diabetes mellitus if insulin was dispensed to them one or more times within the year before surgery.

We included preoperative cardiovascular testing and medications as covariables because they may impact the initiation of a preoperative β-blocker dispensing and are associated with the primary outcome.[16] Subjects who underwent cardiac testing before surgery, including exercise or pharmacologic stress tests, myocardial nuclear imaging, stress magnetic resonance imaging, electrocardiogram, heart catheterization, percutaneous coronary intervention, and echocardiogram, were identified using Current Procedural Terminology codes for these tests. See Supplemental Digital Content 4 (http://links.lww.com/ALN/C952) for a table of Current Procedural Terminology codes used to identify cardiac testing. Testing was categorized as within 60 days of surgery or within the year before surgery due to a previous test potentially preventing the use of a repeated preoperative cardiac test. Subjects with diuretic, angiotensin-converting enzyme inhibitors, cardiac glycosides, cardiac drugs, calcium entry blocker, antiarrhythmic, antilipemic/statin, insulin, oral hypoglycemics, anticoagulant, antiplatelet, hypotensive, thrombolytic, vasodilator, or bronchodilator dispensing were identified using the MarketScan drug benefit database and the MarketScan therapeutic drug classifications. Angiotensin II receptor blocker dispensing was not specifically accounted for because it is not identified in the MarketScan database. Drug variables provided by MarketScan therapeutic class codes are not specific in their classifications but are exhaustive and allowed us to control for their impact on whether or not a β-blocker was dispensed. See Supplemental Digital Content 2 (http://links.lww.com/ALN/C952) for a table of MarketScan therapeutic class codes used to identify dispensing of these drugs. We did not have access to any individual medication records beyond the individual claims of the study cohort. Medications were categorized as within 60 days of surgery or within the year before surgery.

Our cohort of 204,981 patients was restricted to individuals with insurance in the year before surgery with available MarketScan drug benefit data and discharge status. For this cohort, data were complete besides the region of service variable (missing data, n = 1,576) as represented by the Metropolitan Statistical Area. Records with a missing Metropolitan Statistical Area variable were classified as unknown as these records represent rural areas and were important to include in the analysis. There were no missing data otherwise. No variables were analyzed as effect measure modifiers.

Statistical Analysis

The primary analysis, sensitivity analysis, and primary outcomes were determined *a priori*. No minimal clinically meaningful odds ratio was determined before analysis. The primary analysis focused on the average treatment effect on the treated of preoperative β-blocker initiation within 60 days of surgery on the frequency of stroke and major adverse cardiac events as compared to β-blocker–naïve patients. To reduce bias, we applied propensity score weighting to balance the three groups using the Toolkit for Weighting and Analysis of Nonequivalent Groups Macro package for SAS v3.1.2 (SAS Institute Inc., USA).[17] This approach was in response to peer review as our initial approach used the CAUSALTRT procedure to create two independent sets of propensity score weights, whereas here we implemented multinomial propensity scores generated with a generalized boosted model to create weighted propensity scores for each of the three treatment categories. The original *a priori* analysis can be seen in the Supplemental Digital Content 7 through 12 (http://links.lww.com/ALN/C952).[18,19]

For our analysis that used the Toolkit for Weighting and Analysis of Nonequivalent Groups, we generated propensity scores to estimate the probability that a patient was exposed to treatment (preoperative β-blocker initiation, chronic β-blocker, or β-blocker–naïve patients [control]) to calculate weights and generalized boosted regression.[17,20] Patient characteristics included in the weighting algorithm were age group, year, sex, procedure type, geographical region, comorbidities, Elixhauser score, quintile of the β-blocker preoperative dispensing rate by metropolitan statistical area, presurgical cardiac testing, and presurgical

medications excluding β-blocker therapy. The absolute standardized difference of the covariates in the weighted sample when comparing preoperative β-blocker to β-blocker–naïve were less than 10%, except for metropolitan statistical area of β-blocker dispensing (13%), calcium channel inhibitor (12%), and ECG (10%). There were no absolute standardized differences greater than 10% when comparing the propensity weights for chronic β-blocker to β-blocker–naïve. See tables 1 and 2 for the absolute standardized difference of all covariates before and after propensity score weighting. To estimate the treatment effects, we applied the PROC SURVEYLOGISTIC procedure in SAS. We estimated the average treatment effect on the treated for patients initiated on a preoperative β-blocker within 60 days of surgery as compared to β-blocker–naïve patients and chronic β-blocker patients as compared to β-blocker–naïve patients for stroke, major adverse cardiac events, and each component outcome of major adverse cardiac events.

To test the sensitivity of the results comparing patients on preoperative β-blocker initiation within 60 days of surgery to β-blocker–naïve patients, the analysis was repeated with two different inclusion criteria for a preoperative β-blocker: β-blocker initiation within 90 days of surgery and β-blocker initiation within 180 days of surgery.

In order to analyze the trend of preoperative β-blocker use before surgery, a logistic regression model was used to determine the change in preoperative β-blocker dispensing from 2005 to 2015. The regression model was adjusted for all demographic information, medication therapies, and cardiac testing as described earlier in this section. The regression estimated the odds of preoperative β-blocker dispensing (within 60 days of surgery) in a given year. The reference year was the first year of collected data (2005).

The statistical analyses were completed using SAS software, Version 9.4, and R statistical software environment version 3.6.1. All tests were two-sided, and statistical significance was considered with a P value less than 0.05.

Results

The study cohort consisted of 204,981 patients who underwent major abdominal surgery. In the cohort, 155,531 patients (75.9%) were β-blocker–naïve, 4,026 patients (2.0%) initiated a preoperative β-blocker within 60 days of surgery, and 45,424 patients (22.2%) were on a chronic (more than 60 days) β-blocker before surgery. Patients who were β-blocker–naïve were younger, had a lower Revised Cardiac Risk Index, were on fewer medications, and underwent less cardiac testing than patients who were on a chronic or preoperative β-blocker. Patients on a chronic β-blocker were older, had a greater Revised Cardiac Risk Index, and were on more medications than patients who were initiated on a preoperative β-blocker (tables 1 and 2).

The overall frequency of stroke was 0.2% (423 of 204,981) in the cohort (table 3). Patients on a chronic β-blocker had the highest rate of perioperative strokes (0.4%; 171 of 45,424), followed by patients with preoperative β-blocker initiation within 60 days of surgery (0.4%; 17 of 4,026) and then β-blocker–naïve patients (0.2%; 235 of 155,531).

The overall frequency of major adverse cardiac events was 1.3% (2,663 of 204,981) in the cohort (table 3). Patients on a chronic β-blocker had the highest rate of perioperative major adverse cardiac events (2.6%; 1,173 of 45,424), followed by patients initiated on a preoperative β-blocker within 60 days of surgery (2.2%; 89 of 4,026) and β-blocker–naïve patients (0.9%; 1,401 of 155.531).

The average effect of the treatment on the treated did not demonstrate a lower odds of stroke for patients initiated on a preoperative β-blocker within 60 days of surgery as compared to β-blocker–naïve patients (odds ratio, 0.90; 95% CI, 0.31 to 2.04; $P = 0.757$; table 4). Further, there was no difference in the odds of major adverse cardiac events between preoperative β-blocker therapy initiation within 60 days of surgery and β-blocker–naïve patients (odds ratio, 1.11; 95% CI, 0.80 to 1.53; $P = 0.203$). Additionally, there was no association between preoperative β-blocker initiation within 60 days of surgery and any of the individual major adverse cardiac events (table 4).

The average treatment effect on the treated for patients on a chronic β-blocker as compared to β-blocker–naïve patients demonstrated a reduction in the odds of major adverse cardiac events (odds ratio, 0.81; 95% CI, 0.72 to 0.91; $P = 0.007$) but not stroke (odds ratio, 0.85; 95% CI, 0.65 to 1.15; $P = 0.901$; table 4). Of the components of major adverse cardiac events ,the average treatment effect on the treated demonstrated a reduction in the odds of all-cause mortality (odds ratio, 0.81; 95% CI, 0.69 to 0.95; $P = 0.002$) and myocardial infarction (odds ratio, 0.78; 95% CI, 0.65 to 0.93; $P = 0.001$; table 4).

Dispensing of preoperative β-blockers increased from 2.6% (n = 14,513) in 2005 to 3.0% (n = 12,476) in 2007 ($P = 0.021$) and then decreased throughout the rest of the study period to 1.2% (n = 17,189) in 2015 ($P < 0.001$; table 5; fig. 2).

Sensitivity Analysis

We performed additional analyses to explore different time cut points for the initiation of a preoperative β-blocker as therapy initiated within 90 days of surgery and within 180 days of surgery. We generated new multinomial propensity scores for these cut points using the same methods as described in the first two paragraphs of Statistical Analysis to determine the average treatment effect on the treated between patients initiated on a preoperative β-blocker and β-blocker naïve patients. For both cut points, there was no change in the odds of stroke or the composite of major

Table 1. Patient and Clinical Characteristics for Patients with No β-Blocker Therapy and Preoperative β-Blocker Therapy Initiated within 60 Days of Surgery

Study Patients, (%)

Variable	No β-Blocker Dispensing (n = 155,531)	Preoperative β-Blocker Initiation within 60 Days of Surgery (n = 4,026)	Unweighted Standardized Mean Difference	Standardized Mean Difference after Weighting
Sex				
Male	69,165 (44.5%)	2,248 (55.8%)	0.23	0.00
Female	86,366 (55.5%)	1,778 (44.2%)	0.23	0.00
Mean age, yr	55.1 (95% CI, 55.0–55.2)	62.5 (95% CI, 62.1–62.9)	—	—
Age group				
18–49 yr	51,092 (32.9%)	583 (14.5%)	0.39	0.08
50–64 yr	70,152 (45.1%)	1,888 (46.9%)	0.04	0.00
65–74 yr	18,552 (11.9%)	759 (18.9%)	0.21	0.06
≥75 yr	15,735 (10.1%)	796 (19.8%)	0.32	0.07
Procedure type				
Small bowel resection	8,840 (5.7%)	166 (4.1%)	0.07	0.04
Large bowel resection	80,626 (51.8%)	1,949 (48.4%)	0.07	0.02
Pancreatic resection	3,616 (2.32%)	144 (3.58%)	0.08	0.02
Gastrectomy	34,813 (22.4%)	547 (13.6%)	0.21	0.00
Cystectomy	4,186 (2.7%)	231 (5.7%)	0.19	0.02
Nephrectomy	23,450 (15.1%)	929 (24.57%)	0.27	0.04
Region				
North central	41,988 (27.0%)	1,344 (33.4%)	0.14	0.01
Northeast	22,895 (14.7%)	671 (16.7%)	0.06	0.00
South	62,309 (40.1%)	1,337 (33.2%)	0.14	0.02
West	27,154 (17.5%)	657 (16.3%)	0.03	0.01
Unknown/missing	1,185 (0.8%)	17 (0.4%)	0.04	0.02
Metropolitan Statistical Area quintile of β-blocker dispensing				
First quintile	4,396 (2.8%)	9 (0.2%)	0.16	0.13
Second quintile	19,738 (12.7%)	274 (6.8%)	0.18	0.04
Third quintile	74,026 (47.6%)	1,696 (42.1%)	0.11	0.01
Fourth quintile	40,303 (25.9%)	1,215 (30.2%)	0.10	0.04
Fifth quintile	17,068 (11.0%)	832 (20.7%)	0.31	0.07
Comorbidities				
Insulin-dependent diabetes mellitus	5,163 (3.3%)	275 (6.8%)	–0.16	–0.06
Cerebrovascular accident	4,122 (2.7%)	274 (6.8%)	–0.26	–0.03
Chronic kidney disease	2,897 (1.9%)	199 (4.9%)	–0.23	–0.02
Coronary artery disease	8,518 (5.5%)	805 (20.0%)	–0.64	–0.01
Heart failure	2,915 (1.9%)	298 (7.4%)	–0.41	–0.02
Valve pathology	8,316 (5.4%)	538 (13.4%)	–0.36	–0.04
Revised Cardiac Risk Index Score of 2 or greater	3,315 (2.1%)	365 (9.6%)	–0.16	–0.06
Perioperative medications (within 60 days)				
Diuretic	12,736 (8.2%)	699 (17.4%)	–0.34	–0.06
Angiotensin-converting enzyme inhibitor	16,780 (10.8%)	860 (21.4%)	–0.34	–0.05
Cardiac glycoside	659 (0.4%)	91 (2.3%)	–0.28	–0.03
Calcium channel inhibitor	13,020 (8.4%)	689 (17.1%)	–0.32	–0.08
Anticoagulant	5,056 (3.3%)	223 (5.8%)	–0.14	–0.02
Antiplatelet	1,541 (1.0%)	289 (4.7%)	–0.37	–0.01
Antiarrhythmic	532 (0.3%)	79 (2.0%)	–0.28	–0.03
Antilipidemic/statin	26,641 (17.1%)	1,330 (33.0%)	–0.42	–0.06
Insulin	3,281 (2.1%)	223 (5.54%)	–0.24	–0.02
Antidiabetic	12,496 (8.0%)	575 (14.3%)	–0.35	–0.05
Bronchodilator	225 (0.1%)	5 (0.1%)	–0.01	–0.01
Thrombolytic	3 (0.0%)	0 (0.0%)	Not included in analysis	Not included in analysis
Cardiac drugs	12,119 (7.79%)	527 (13.1%)	–0.24	–0.04
Hypotensive medication	2,401 (1.5%)	207 (5.15)	–0.22	–0.04
Vasodilator	759 (0.5%)	178 (4.4%)	–0.56	–0.01
Existing medications (within 365 days)				
Diuretic	21,712 (14.0%)	798 (19.8%)	–0.17	–0.09

(*Continued*)

Table 1. (Continued)

Study Patients, (%)

Variable	No β-Blocker Dispensing (n = 155,531)	Preoperative β-Blocker Initiation within 60 Days of Surgery (n = 4,026)	Unweighted Standardized Mean Difference	Standardized Mean Difference after Weighting
Angiotensin-converting enzyme inhibitor	25,311 (16.3%)	1,013 (25.2%)	–0.24	–0.09
Cardiac glycoside	944 (0.6%)	80 (2.0%)	–0.18	–0.04
Calcium channel inhibitor	18,333 (11.8%)	779 (19.4%)	–0.24	–0.12
Anticoagulant	5,189 (3.3%)	201 (5.0%)	–0.09	0.00
Antiplatelet	2,806 (1.8%)	202 (5.0%)	–0.24	–0.05
Antiarrhythmic	847 (0.5%)	53 (1.3%)	–0.11	–0.02
Antilipidemic/statin	41,708 (26.8%)	1,552 (38.6%)	–0.27	–0.08
Insulin	4,767 (3.1%)	219 (5.4%)	–0.14	0.00
Antidiabetic	18,369 (11.8%)	728 (18.1%)	–0.19	–0.06
Bronchodilator	404 (0.3%)	8 (0.2%)	0.01	0.00
Thrombolytic	2 (0.0%)	0 (0.0%)	Not included in analysis	Not included in analysis
Cardiac drugs	17,565 (11.3%)	654 (16.2%)	–0.16	–0.08
Hypotensive medication	3,885 (2.5%)	226 (5.6%)	–0.20	–0.05
Vasodilator	1,722 (1.1%)	129 (3.2%)	–0.20	–0.02
Cardiac testing (within 60 days)				
Stress echocardiography	2,248 (1.5%)	179 (4.5%)	–0.25	–0.04
Other echocardiography	8,916 (5.7%)	935 (23.2%)	–0.75	–0.05
Electrocardiography	77,371 (49.8%)	2,706 (67.2%)	0.35	–0.10
Exercise treadmill or pharmacologic stress test	8,949 (5.8%)	974 (24.2%)	–0.79	–0.06
Myocardial nuclear imaging	6,303 (4.1%)	791 (19.7%)	–0.79	–0.03
Stress magnetic resonance imaging	7 (0.0%)	0 (0.0%)	Not included in analysis	Not included in analysis
PCI	8 (0.0%)	5 (0.1%)	Not included in analysis	Not included in analysis
Heart catheterization	277 (0.2%)	104 (2.6%)	–0.57	–0.01
Cardiac testing (within 365 days)				
Stress echocardiography	2,391 (1.5%)	56 (1.4%)	–0.01	0.00
Other echocardiography	12,118 (7.8%)	437 (10.9%)	–0.11	–0.02
Electrocardiography	48,233 (31.0%)	1,431 (35.5%)	–0.10	–0.03
Exercise treadmill or pharmacologic stress test	9,397 (6.0%)	348 (8.6%)	–0.11	–0.03
Myocardial nuclear imaging	6.621 (4.3%)	307 (7.6%)	–0.17	–0.03
Stress magnetic resonance imaging	6 (0.0%)	1 (0.0%)	Not included in analysis	Not included in analysis
PCI	15 (0.0%)	1 (0.0%)	Not included in analysis	Not included in analysis
Heart catheterization	456 (0.3%)	25 (0.6%)	–0.06	–0.05

Frequencies and percentages are reported for categorical variables, and 95% CIs are reported for continuous variables. Propensity score weighting was used to determine the standardized difference between the no β-blocker group and the two other groups.

PCI, percutaneous coronary intervention.

adverse cardiac events (see Supplemental Digital Content 5 and Supplemental Digital Content 6 for tables of the odds ratio estimates of the average effect of treatment on the treated http://links.lww.com/ALN/C952).

Discussion

Our retrospective cohort study did not identify a risk-adjusted association between preoperative β-blocker initiation within 60 days of surgery or chronic β-blocker dispensing and perioperative stroke after elective major abdominal surgery. These results suggest that β-blocker initiation before the day of surgery is unlikely to impact perioperative stroke risk after major abdominal surgery. While the patients initiated on preoperative β-blocker therapy demonstrated a high risk of major adverse cardiac events, our analysis demonstrated that preoperative initiation within 60 days of surgery is also not associated with a lower risk of perioperative major adverse cardiac events. These results highlight the continued challenge clinicians face to identify interventions to reduce cardiovascular risk before major noncardiac surgery and suggest alternative therapies are needed to reduce

Table 2. Patient and Clinical Characteristics for Patients with No β-Blocker Therapy and Chronic β-Blocker Therapy

Study Patients, (%)				
Variable	**No β-Blocker Dispensing (n = 155,531)**	**Chronic β-Blocker Dispensing (n = 45,424)**	**Unweighted Standardized Mean Difference**	**Standardized Mean Difference after Weighting**
Sex				
Male	69,165 (44.5%)	23,060 (50.8%)	0.13	0.06
Female	86,366 (55.5%)	22,364 (49.2%)	0.13	0.06
Mean age, yr	55.1 (95% CI, 55.0–55.2)	63.8 (95% CI, 63.7–63.9)	—	—
Age group				
18–49 yr	51,092 (32.9%)	5,852 (12.9%)	0.43	0.05
50–64 yr	70,152 (45.1%)	19,233 (42.3%)	0.06	0.01
65–74 yr	18,552 (11.9%)	9,704 (21.4%)	0.29	0.02
≥75 yr	15,735 (10.1%)	10,605 (23.4%)	0.44	0.04
Procedure type				
Small bowel resection	8,840 (5.7%)	2,701 (6.0%)	0.01	0.01
Large bowel resection	80,626 (51.8%)	22,543 (49.6%)	0.04	0.03
Pancreatic resection	3,616 (2.32%)	1,100 (2.42%)	0.00	0.01
Gastrectomy	34,813 (22.4%)	8,043 (17.7%)	0.11	0.04
Cystectomy	4,186 (2.7%)	1,781 (3.9%)	0.08	0.01
Nephrectomy	23,450 (15.1%)	9,256 (20.4%)	0.14	0.01
Region				
North central	41,988 (27.0%)	14,808 (32.6%)	0.13	0.01
Northeast	22,895 (14.7%)	6,634 (14.6%)	0.00	0.01
South	62,309 (40.1%)	16,306 (35.9%)	0.09	0.00
West	27,154 (17.5%)	7,412 (16.3%)	0.03	0.00
Unknown/missing	1,185 (0.8%)	264 (0.6%)	0.02	0.01
Metropolitan Statistical Area quintile of β-blocker dispensing				
First quintile	4,396 (2.8%)	1,172 (2.6%)	0.02	0.01
Second quintile	19,738 (12.7%)	5,182 (11.4%)	0.04	0.02
Third quintile	74,026 (47.6%)	21,082 (46.4%)	0.02	0.01
Fourth quintile	40,303 (25.9%)	12.298 (27.1%)	0.03	0.00
Fifth quintile	17,068 (11.0%)	5.690 (22.6%)	0.05	0.00
Comorbidities				
Insulin-dependent diabetes mellitus	5,163 (3.3%)	4,049 (8.9%)	0.24	0.01
Cerebrovascular accident	4,122 (2.7%)	3,562 (7.8%)	0.32	0.03
Chronic kidney disease	2,897 (1.9%)	3,430 (7.6%)	0.42	0.02
Coronary artery disease	8,518 (5.5%)	12,467 (27.5%)	0.97	0.01
Heart failure	2,915 (1.9%)	5,043 (11.1%)	0.68	0.01
Valve pathology	8,316 (5.4%)	6,298 (13.9%)	0.38	0.04
Revised Cardiac Risk Index Score of 2 or greater	3,315 (2.1%)	6,698 (14.7%)	0.24	0.01
Perioperative medications (within 60 days before)				
Diuretic	12,736 (8.2%)	10,059 (22.1%)	0.51	0.04
Angiotensin-converting enzyme inhibitor	16,780 (10.8%)	9,454 (20.8%)	0.32	0.04
Cardiac glycoside	659 (0.4%)	1,255 (2.8%)	–0.36	–0.02
Calcium channel inhibitor	13,020 (8.4%)	8,642 (19.0%)	–0.39	–0.05
Anticoagulant	5,056 (3.3%)	3,841 (8.5%)	–0.29	–0.02
Antiplatelet	1,541 (1.0%)	3,432 (7.6%)	–0.66	–0.01
Antiarrhythmic	532 (0.3%)	967 (2.1%)	–0.31	–0.02
Antilipidemic/statin	26,641 (17.1%)	17,780 (39.1%)	–0.58	–0.04
Insulin	3,281 (2.1%)	2,633 (5.8%)	–0.26	–0.01
Antidiabetic	12,496 (8.0%)	7,281 (16.0%)	–0.29	–0.03
Bronchodilator	225 (0.1%)	74 (0.2%)	–0.01	0.00
Thrombolytic	3 (0.0%)	0 (0.0%)	Not included in analysis	Not included in analysis
Cardiac drugs	12,119 (7.79%)	7,180 (15.8%)	–0.30	–0.04
Hypotensive medication	2,401 (1.5%)	2,820 (6.2%)	–0.38	–0.02
Vasodilator	759 (0.5%)	2,060 (4.5%)	–0.58	–0.02
Existing medications (within 365 days before)				
Diuretic	21,712 (14.0%)	17,053 (37.5%)	–0.68	–0.05
Angiotensin-converting enzyme inhibitor	25,311 (16.3%)	15,447 (34.0%)	–0.48	–0.05
Cardiac glycoside	944 (0.6%)	2,046 (4.5%)	–0.50	–0.02
Calcium channel inhibitor	18,333 (11.8%)	13,406 (29.5%)	–0.55	–0.06
Anticoagulant	5,189 (3.3%)	5,568 (12.3%)	–0.50	–0.01
Antiplatelet	2,806 (1.8%)	6,079 (13.4%)	–0.87	–0.01

(*Continued*)

Table 2. (Continued)

Study Patients, (%)

Variable	No β-Blocker Dispensing (n = 155,531)	Chronic β-Blocker Dispensing (n = 45,424)	Unweighted Standardized Mean Difference	Standardized Mean Difference after Weighting
Antiarrhythmic	847 (0.5%)	1,686 (3.7%)	–0.43	–0.03
Antilipidemic/statin	41,708 (26.8%)	27,142 (59.8%)	–0.74	–0.05
Insulin	4,767 (3.1%)	3,851 (8.5%)	–0.31	–0.02
Antidiabetic	18,369 (11.8%)	10,642 (23.4%)	–0.36	–0.05
Bronchodilator	404 (0.3%)	139 (0.3%)	–0.01	–0.01
Thrombolytic	2 (0.0%)	1 (0.0%)	Not included in analysis	Not included in analysis
Cardiac drugs	17,565 (11.3%)	11,128 (24.5%)	–0.42	–0.05
Hypotensive medication	3,885 (2.5%)	4,523 (10.0%)	–0.48	–0.03
Vasodilator	1,722 (1.1%)	4,696 (10.3%)	–0.88	–0.02
Cardiac testing (within 60 days before)				
Stress echocardiography	2,248 (1.5%)	923 (2.0%)	–0.05	–0.02
Other echocardiography	8,916 (5.7%)	4,751 (10.5%)	–0.20	–0.03
Electrocardiography	77,371 (49.8%)	26,046 (57.3%)	–0.15	–0.02
Exercise treadmill or pharmacologic stress test	8,949 (5.8%)	5,367 (11.8%)	–0.26	–0.02
Myocardial nuclear imaging	6,303 (4.1%)	4,627 (10.25)	–0.31	–0.02
Stress magnetic resonance imaging	7 (0.0%)	4 (0.0%)	Not included in analysis	Not included in analysis
PCI	8 (0.0%)	21 (0.15)	Not included in analysis	Not included in analysis
Heart catheterization	277 (0.2%)	336 (0.7%)	–0.13	–0.01
Cardiac testing (within 365 days before)				
Stress echocardiography	2,391 (1.5%)	1,215 (2.7%)	–0.09	–0.02
Other echocardiography	12,118 (7.8%)	9,479 (20.9%)	–0.48	–0.03
Electrocardiography	48,233 (31.0%)	23,099 (50.9%)	–0.43	–0.06
Exercise treadmill or pharmacologic stress test	9,397 (6.0%)	7,309 (16.1%)	–0.42	–0.04
Myocardial nuclear imaging	6,621 (4.3%)	6,342 (14.0%)	–0.48	–0.04
Stress magnetic resonance imaging	6 (0.0%)	10 (0.0%)	Not included in analysis	Not included in analysis
PCI	15 (0.0%)	70 (0.2%)	Not included in analysis	Not included in analysis
Heart catheterization	456 (0.3%)	901 (2.05)	–0.31	–0.01

Frequencies and percentages are reported for categorical variables, and 95% CIs are reported for continuous variables. Propensity score weighting was used to determine the standardized difference between the no β-blocker group and the two other groups.

PCI, percutaneous coronary intervention.

the frequency of perioperative major adverse cardiac events in high-risk patients.

β-blocker therapy initiated before major noncardiac surgery remains controversial. Multiple small trials of perioperative β-blockers in patients with established coronary artery disease or increased cardiovascular risk demonstrated a reduction of perioperative myocardial infarctions, especially among patients with a Revised Cardiac Risk Index of 0 or 1.[3,5] Subsequently, the POISE trial confirmed a large reduction in perioperative myocardial infarctions, but found that this came at the cost of increased risk of stroke and all-cause mortality.[7] This finding was likely due to the large dose of metoprolol given to β-blocker–naïve patients within 2 to 4 h of surgery. β-blocker administration in POISE was associated with clinically significant postoperative hypotension, likely from blunting sympathetic activity and heart rate, which resulted in the inability to augment cardiac output and subsequent cerebral hypoperfusion. Thus, after the POISE trial, preoperative initiation of β-blockers has been discouraged. Our study is consistent with other studies that identified a reduction in the frequency of new β-blocker prescriptions in the years that followed the POISE trial.[8,9] However, it remained unclear if β-blocker initiation in the outpatient setting in the weeks before surgery increased the risk of stroke for patients undergoing noncardiac surgery. β-Blocker therapy before the day of surgery allows time to assess clinical tolerability, including resting heart rate, blood pressure, and symptoms. Our study supports the hypothesis that preoperative β-blocker therapy initiated within 60 days before major abdominal surgery in patients with cardiac risk factors is not associated with higher risk of perioperative stroke.

Nonetheless, our study also adds to the controversy regarding the theoretical benefit of preoperative initiation of β-blocker therapy. We did not identify a reduction in the odds of perioperative major adverse cardiac events in patients initiated on a β-blocker within 60 days before major abdominal surgery. Previous analyses have demonstrated mixed results on the impact of preoperative initiation of β-blocker therapy before the day of surgery on perioperative major adverse cardiac events. In a retrospective propensity-matched cohort of Taiwanese diabetic patients,

Table 3. Unadjusted Frequency of Stroke and Major Adverse Cardiac Events for Patients Undergoing Elective Major Abdominal Surgery Stratified by β-Blocker Therapy

Primary Outcomes	Entire Cohort (n = 204,981)	No β-Blocker Dispensing (n = 155,531)	Chronic β-Blocker Dispensing (n = 45,424)	Preoperative β-Blocker Initiation within 60 Days of Surgery (n = 4,026)	*P* Value
Stroke	423 (0.2%)	235 (0.2%)	171 (0.4%)	17 (0.4%)	< 0.001
Major adverse cardiac event	2,663 (1.3%)	1,401 (0.9%)	1,173 (2.6%)	89 (2.2%)	< 0.001
All-cause mortality	1,535 (0.8%)	872 (0.6%)	626 (1.4%)	37 (0.9%)	< 0.001
Myocardial infarction	1,111 (0.5%)	504 (0.3%)	555 (1.2%)	52 (1.3%)	< 0.001
Cardiac arrest	313 (0.2%)	175 (0.1%)	129 (0.3%)	9 (0.2%)	< 0.001
Revascularization	12 (0.0%)	4 (0.0%)	8 (0.0%)	0 (0.0%)	< 0.001

Frequencies and percentages are reported for categorical variables. Chi-square analysis was used to determine significant differences among the groups.

Table 4. Average Treatment Effect on the Treated of Preoperative β-Blocker Therapy Initiation within 60 Days of Surgery and Chronic β-Blocker Therapy Compared to β-Blocker–naïve Patients

Primary Outcomes	Preoperative β-Blocker Initiation within 60 Days of Surgery, Odds Ratio (95% CI)	*P* Value	Chronic β-Blocker Dispensing, Odds Ratio (95% CI)	*P* Value
Stroke	0.90 (0.31–2.04)	0.757	0.86 (0.65–1.15)	0.901
Major adverse cardiac events	1.11 (0.80–1.53)	0.203	0.81 (0.72–0.91)	0.007
All-cause mortality	1.65 (0.99–2.72)	0.062	0.81 (0.69–0.95)	0.002
Myocardial infarction	0.70 (0.45–1.06)	0.272	0.78 (0.65–0.93)	0.001
Cardiac arrest	1.54 (0.56–4.20)	0.299	0.81 (0.56–1.16)	0.166
Revascularization	Cannot be computed		1.04 (0.24–4.61)	0.802

Odds ratios, 95% CI, and *P* values are reported for each propensity weight analysis of the average treatment effect on the treated. A *P* value less than 0.05 was considered significant. Revascularization could not be computed due to insufficient events.

Table 5. Multivariable Logistic Regression Analysis of Dispensing Rates of Preoperative β-Blocker Initiation within 60 Days of Surgery

Year (Reference = 2005)	Preoperative β-Blocker Initiation with 60 Days of Surgery, Frequency (%)	Adjusted Odds Ratio	95% Wald Confidence Limits
2005	376 (2.6%)	—	—
2006	331 (2.7%)	1.01	(0.87–1.18)
2007	376 (3.0%)	1.20	(1.03–1.29)
2008	371 (3.0%)	1.25	(1.07–1.45)
2009	321 (2.0%)	0.83	(0.71–0.97)
2010	337 (1.9%)	0.78	(0.67–0.91)
2011	500 (2.1%)	0.81	(0.71–0.94)
2012	441 (1.6%)	0.68	(0.59–0.79)
2013	335 (1.4%)	0.57	(0.49–0.67)
2014	440 (1.6%)	0.74	(0.63–0.86)
2015	198 (1.2%)	0.52	(0.44–0.63)

Adjusted odds ratio and 95% CI of the likelihood of different prescription rates between year 2005 and the selected year are reported. A *P* value less than 0.05 was considered significant.

Chen *et al*. demonstrated no association between β-blocker therapy initiated less than 30 days before major noncardiac surgery and 30-day mortality after surgery.[21] Conversely, in a retrospective observation cohort of vascular surgery patients, Flu *et al*. demonstrated improved mortality and fewer cardiac events for patients who initiated β blockade therapy more than 1 week before surgery.[22] Additionally, in a retrospective propensity-matched cohort of patients in the Veterans Health Administration (Washington, D.C.), London *et al*. demonstrated a reduction of 30-day mortality and cardiac morbidity in patients who initiated a β-blocker therapy within 30 days before surgery.[16] Further complicating the analysis are the different time periods of what constitutes preoperative initiation, different patient cohorts, and whether titration and other steps were taken to adjust the dose and assess for clinical tolerability by the patient. Our analysis is important as perioperative β-blocker therapy trials have been constrained by enrollment, making the path to determining the optimal perioperative β-blocker strategy more challenging.[23] Taken together, our study suggests that the initiation of β-blocker therapy before the day of surgery is not associated with a higher risk of stroke but is also not associated with a lower risk of major adverse cardiac events.

Our findings on chronic β-blocker therapy are also important as previous studies have suggested an increased

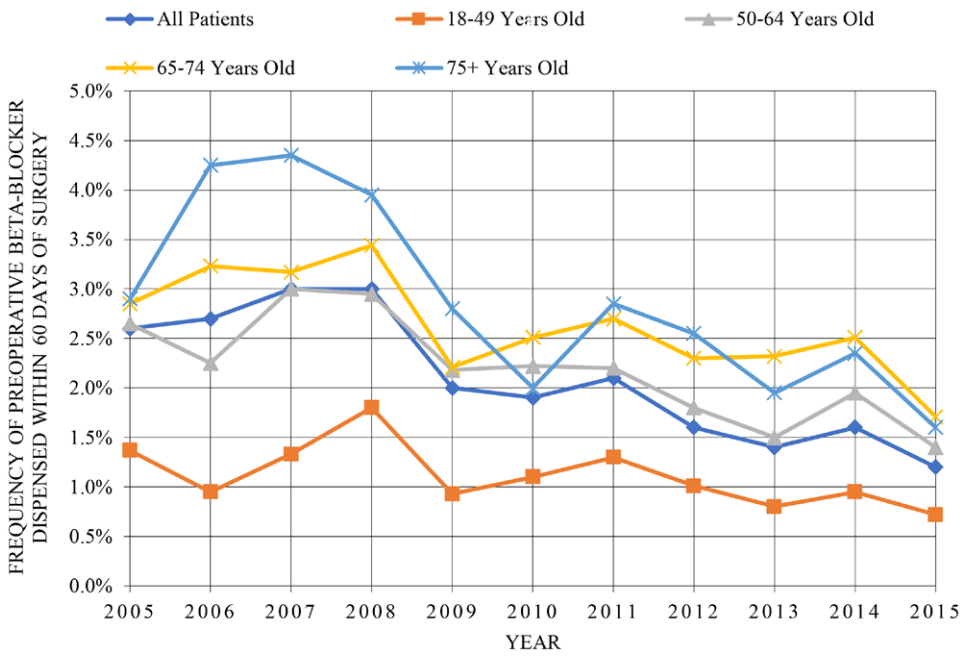

Fig. 2. Frequency of preoperative β-blocker dispensed within 60 days of surgery in patients undergoing elective major abdominal surgery stratified by age. Perioperative β-blocker dispensing increased from 2.6% in 2005 to 3.0% in 2007 ($P = 0.018$) and decreased throughout the rest of the study period to 1.2% in 2015 ($P < 0.001$). The reference year was the first year of collected data (2005).

risk of perioperative stroke in patients on chronic β-blocker medications.[24] Further, a recent analysis of perioperative major adverse cardiac events and stroke in noncardiac surgeries by Smilowitz *et al.* identified an increased frequency of perioperative stroke with a decreased frequency of perioperative myocardial infarction from 2004 to 2013.[11] The authors suggested that the increased frequency of strokes and decreased frequency of major adverse cardiac events were the result of an increase in chronic β-blocker dispensing from 2004 to 2013 given their relationship in previous studies.[11] Our study suggests that chronic β-blocker dispensing is not associated with a higher risk of perioperative strokes. Further, our findings support current guidelines that recommend the continued use of β-blocker therapy leading up to noncardiac surgery and that continued use should not impact perioperative risk of stroke and may be associated with lower risk of perioperative major adverse cardiac events.[2]

Our study has limitations similar to other retrospective studies using administrative databases.[25] Our study design did not account for laboratory results, such has hemoglobin, or vital signs that may impact clinical decision-making during the patient's admission. Similarly, there is variability in coding of primary diagnosis among healthcare providers. We have combatted this limitation by assessing all coded diagnoses for our outcome variables. There also may have been errors in coding of the various variables in our study, a form of information bias. The MarketScan Commercial and Supplemental Medicare Databases are not nationally representative databases and only include patients with private health insurance or supplemental Medicare insurance. Therefore, our study does not reflect the health of the Medicare population, traditionally at higher risk of perioperative stroke and major adverse cardiac events, which explains why our overall frequency of these outcomes is lower when compared to other studies.[7] Further, there were only 17 strokes in the perioperative β-blocker initiation cohort (0.4%), which was the highest frequency of the three cohorts in our study; thus, the low frequency of stroke in our study limits the accuracy of our estimates. The database does not contain data about the type of β-blocker or the dose dispensed, and we are not able to make any inferences with regards to the type of β-blocker used or dosage (*e.g.*, metoprolol *vs.* atenolol). This is important as some β-blockers, such as metoprolol, have had stronger associations with perioperative stroke than others.[7,24] Further, we are unable to determine the primary reason for the β-blocker dispensing from the data. Additionally, we cannot be sure patients were taking their dispensed β-blocker therapy as prescribed throughout the preoperative period. Our analysis of outcomes is limited to those that happened in-hospital with patients undergoing major abdominal surgeries and cannot be extrapolated to other noncardiac surgeries. We cannot infer long-term mortality, as it is possible the patient changed insurance, and therefore we can no longer follow

them. MarketScan Database accuracy relies on continuous enrollment with an insurer, which is why patients without insurance in the year leading up to surgery were excluded. Finally, we cannot evaluate if there is a causal relationship between β-blockers and stroke or major adverse cardiac events from our observational analysis due to unmeasured confounding variables or exposures.

In conclusion, our study did not demonstrate a risk-adjusted association between preoperative β-blocker initiation within 60 days of surgery or chronic β-blocker dispensing and higher risk of perioperative stroke. Additionally, we did not identify an association with perioperative initiation of β-blocker therapy and a lower risk of perioperative myocardial infarction, all-cause mortality, or cardiac arrest, which suggests a lack of any short-term benefit to start a β-blocker before major noncardiac surgery.

Research Support

Support was provided solely from institutional and/or departmental sources. N. L. McKenzie received support for his work from the Summer Research Project from the Pritzker School of Medicine (Chicago, Illinois).

Competing Interests

Dr. Rubin is the president of DRDR Mobile Health (Chicago, Illinois), a company that creates mobile applications for health care, including functional capacity assessment applications. He has engaged in consulting for mobile applications as well. He has not taken any salary or money from the company. He has also served as an expert witness for the United States Department of Justice (Washington, D.C.). Dr. Nagele has received research funding from Abbott (Chicago, Illinois) and Roche (Indianapolis, Indiana) and speaker's bureau/honoraria from Becton Dickinson (Franklin Lakes, New Jersey), and is the founder of NitroBiomedical LLC (St. Louis, Missouri). The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Digital Content: http://links.lww.com/ALN/C952
Supplemental Digital Content 1: ICD codes for abdominal surgery
Supplemental Digital Content 2: MarketScan® codes to identify medications
Supplemental Digital Content 3: ICD and CPT codes to identify adverse events
Supplemental Digital Content 4: CPT codes to identify cardiac testing
Supplemental Digital Content 5: Average treatment effect of 90-day β-blocker
Supplemental Digital Content 6: Average treatment effect of 180-day β-blocker
Supplemental Digital Content 7: A Priori Model Effect of 60-Day β-blocker
Supplemental Digital Content 8: A Priori Model Effect of Chronic β-blocker
Supplemental Digital Content 9: Standardized Differences of 60-Day β-blocker Covariates
Supplemental Digital Content 10: Standardized Differences of Chronic β-blocker Covariates
Supplemental Digital Content 11: A Priori Model Effect of 90-Day β-blocker
Supplemental Digital Content 12: A Priori Model Effect of 180-Day β-blocker

References

1. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH: Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005; 173:627–34
2. Patel AY, Eagle KA, Vaishnava P: Cardiac risk of noncardiac surgery. J Am Coll Cardiol 2015; 66:2140–8
3. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, Miller D, Mangano DT: Prophylactic atenolol reduces postoperative myocardial ischemia. Anesthesiology 1998; 88:7–17
4. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996; 335:1713–20
5. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM: Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 2005; 353:349–61
6. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130:2215–45

7. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P; POISE Study Group: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371:1839–47
8. Wijeysundera D, Mamdani M, Laupacis A, Fleisher L, Beattie W, Johnson S, Kolstad J, Neuman M: Clinical evidence, practice guidelines, and β-blocker utilization before major noncardiac surgery. Circ Cardiovasc Qual Outcomes 2012; 5:558–65
9. Patorno E, Wang SV, Schneeweiss S, Liu J, Bateman BT: Patterns of β-blocker initiation in patients undergoing intermediate to high-risk noncardiac surgery. Am Heart J 2015; 170:812–820.e6
10. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani S, Washam J, Fleischmann K, Fleisher L: Perioperative beta blockade in noncardiac surgery: A systematic review for the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 64:2406–25
11. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S: Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. JAMA Cardiol 2017; 2:181–7
12. Lee TH, Marcantonio ER, Mangione CM, Thomas E, Polanczyk C, Cook E, Sugarbaker D, Donaldson M, Poss R, Ho K, Ludwig L, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9
13. Kulaylat AS, Schaefer EW, Messaris E, Hollenbeak CS: Truven Health Analytics MarketScan Databases for clinical research in colon and rectal surgery. Clin Colon Rectal Surg 2019; 32:54–60
14. Levey AS, de Jong PE, Coresh J, Nahas M, Astor B, Matsushita K, Gansevoort R, Kasiske B, Eckardt K: The definition, classification, and prognosis of chronic kidney disease: A KDIGO Controversies Conference report. Kidney Int 2011; 80:17–28
15. Austin SR, Wong Y-N, Uzzo RG, Beck JR, Egleston BL: Why summary comorbidity measures such as the Charlson Comorbidity Index and Elixhauser score work. Med Care 2015; 53:e65–72
16. London MJ, Hur K, Schwartz GG, Henderson WG: Association of perioperative β-blockade with mortality and cardiovascular morbidity following major noncardiac Surgery. JAMA 2013; 309:1704–13
17. Griffin B, Ridgeway G, Morral A, Burgette L, Martin C, Almirall D, Ramchand R, Jaycox L, McCaffrey D. Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) Website. Santa Monica, California, RAND Corporation, 2014. Available at: http://www.rand.org/statistics/twang. Accessed August 1, 2022.
18. Schulte PJ, Mascha EJ: Propensity score methods: Theory and practice for anesthesia research. Anesth Analg 2018; 127:1074–84
19. Lamm M: Estimating causal effects from observational data with the CAUSALTRT procedure. SAS Institute Inc. Published online 2017:18. Accessed August 1, 2022
20. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF: A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med 2013; 32:3388–414
21. Chen RJ, Chu H, Tsai LW: Impact of beta-blocker initiation timing on mortality risk in patients with diabetes mellitus undergoing noncardiac surgery: A nationwide population-based cohort study. J Am Heart Assoc 2017; 6:e004392
22. Flu WJ, van Kuijk JP, Chonchol M, Winkel T, Verhagen H, Bax J, Poldermans D: Timing of pre-operative beta-blocker treatment in vascular surgery patients: Influence on post-operative outcome. J Am Coll Cardiol 2010; 56:1922–9
23. Titz M, Schwameis M, Kienbacher C, Buchtele N, Roth D, Duma A, Nagele P, Schörgenhofer C, Herkner H: Generalizability of randomized trials evaluating perioperative β-blocker therapy in noncardiac surgery. Br J Anaesth 2020; 125:926–34
24. Mashour GA, Shanks AM, Kheterpal S: Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. Anesthesiology 2011; 114:1289–96
25. Khera R, Krumholz HM: With great power comes great responsibility: "Big data" research from the National Inpatient Sample. Circ Cardiovasc Qual Outcomes 2017; 10:e003846