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

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Abstract

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

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

Results—There were 204,981 patients who underwent major abdominal surgery. Beta-blocker exposure was: perioperative initiation within 60 days of surgery for 4,026 (2.0%) patients, chronic beta-blocker therapy for 45,424 (22.2%) patients, and beta blocker naïve for 155,531 (75.9%) patients. The unadjusted frequency of stroke for patients with beta-blocker initiation (0.4%, 17/4,026) and chronic beta-blocker therapy (0.4%, 171/45,424) was greater than beta-blocker naïve patients (0.2%, 235/155,531) (P <0.001). After propensity score weighting, patients initiated

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Competing interest: Dr. Daniel Rubin is the president of DRDR Mobile Health, a company that creates mobile applications for healthcare, 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.

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on a beta-blocker within 60 days of surgery (OR: 0.90, 95% CI: 0.31 – 2.04; P = 0.757) or on chronic beta-blocker therapy (OR: 0.86, 95% CI: 0.65 – 1.15; P = 0.901) demonstrated similar stroke risk compared to beta blocker naïve patients. Patients on chronic beta blocker therapy demonstrated lower adjusted risk of major adverse cardiac events compared to beta blocker naïve patients (OR: 0.81, 95% CI: 0.72 – 0.91; P = 0.007), despite higher unadjusted absolute event rate [2.6%, (1,173/45,424) vs 0.6%, (872/155,531)].

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

Introduction:

Major adverse cardiac events following major non-cardiac 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 10-65%.[1,2] Few preventative measures have proven effective to reduce the risk of these perioperative major adverse cardiac events. Perioperative beta-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.[2,3,4,5] As a result, beta-blockers were incorporated into the American College of Cardiology and American Heart Association practice guidelines and further supported by the Surgical Care Improvement Project (SCIP) CARD-2 measure that encouraged administration of a beta-blocker within a day of surgery if the patient had been on a beta-blocker previously.[6] The Perioperative Ischemic Evaluation Study (POISE) demonstrated that aggressive beta-blocker initiation within 2 to 4 hours of surgery was associated with an 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 beta-blocker initiation hours prior to surgery in beta-blocker naïve patients who were at an increased risk for major adverse cardiac events. Following POISE, there was a significant reduction in new beta-blocker prescriptions within 60 days of major noncardiac surgery.[8,9] Despite this apparent practice change, the effect of beta-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 beta-blocker dispensing (> 60 days before surgery) on perioperative stroke in non-cardiac surgery is unclear in the current literature.[11]

Our study had two main aims. The first aim was to identify whether preoperative beta-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 beta-blocker dispensing (> 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 beta-blocker initiation within 60 days of surgery nor chronic beta-blocker dispensing (> 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 considered this study exempt from review as the MarketScan® databases do not contain patient identifiers. Data used for the analysis were derived from the 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 years respectively. These databases provide unique identifiers that allow enrollees to be followed across institutions, 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 (Figure 1):

The sample size was based on the available data that met our inclusion criteria. Patients who had undergone major abdominal surgery from January 1, 2005 to December 31, 2015 were identified with an International Classification of Disease, Ninth Revision-Clinical Modification (ICD-9-CM) or International Classification of Disease, Tenth Revision-Clinical Modification (ICD-10-CM) 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 for a table of ICD-9 and 10-CM 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 non-cardiac 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 2005-2015 was 449,903 patients. Patients were excluded from the analysis if they did not meet inclusion criteria: 1) under 18 years old (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), 4) the subject was not insured for one year prior to the surgery (n=132,939). Patients were also excluded for missing data: 1) 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) (Figure 1). Missing drug or mortality data was assumed to be at random due to administrative error. The remaining cohort consisted of 204,981 insured individuals.

Beta-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 three

distinct categories: 1) Preoperative initiation if a new beta-blocker was dispensed within 60 days prior to the surgical procedure and no other beta-blocker dispensing was identified within the year before their surgery. 2) Chronic if a patient had beta-blockers dispensed prior to 60 days before surgery, or 3) Naïve if no beta-blockers were dispensed within 365 days prior to surgery. All cardiac beta-blocker dispensing was identified using the MarketScan® drug benefit database.[13] Dispensing of non-cardiac related beta-blockers is coded under a different variable and was not included as an exposure variable in this study. See Supplemental Digital Content 2 for a table of the MarketScan® therapeutic class codes used to identify beta-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 ICD-9-CM and ICD-10-CM codes and Current Procedural Terminology (CPT) codes. See Supplemental Digital Content 3 for a table of ICD-9/10-CM code and CPT 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, 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 ICD-9-CM or ICD-10-CM codes were present in at least one inpatient or outpatient claim within a year prior to 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 prior to surgery.

We included preoperative cardiovascular testing and medications as covariables because they may impact the initiation of a preoperative beta-blocker dispensing and are associated with the primary outcome.[16] Subjects who underwent cardiac testing before surgery, including exercise or pharmacological stress tests, myocardial nuclear imaging, stress magnetic resonance imaging, electrocardiogram, heart catheterization, percutaneous coronary intervention (PCI), and echocardiogram were identified using CPT codes for these

tests. See Supplemental Digital Content 4 for a table of CPT codes used to identify cardiac testing. Testing was categorized as within 60 days of surgery or within the year before surgery due to a prior 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, anti-arrhythmic, anti-lipemic/statin, insulin, oral hypoglycemics, anti-coagulant, anti-platelet, 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 they are 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 beta-blocker was dispensed. See Supplemental Digital Content 2 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 prior to 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 was 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 prior to analysis. The primary analysis focused on the average treatment effect on the treated of preoperative beta-blocker initiation within 60 days of surgery on the frequency of stroke and major adverse cardiac events as compared to beta-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.[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 prior*i analysis can be seen in the Supplemental Digital Content 7-12.[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 beta-blocker initiation, chronic beta-blocker, or beta-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 beta-blocker

preoperative dispensing rate by metropolitan statistical area, presurgical cardiac testing and presurgical medications excluding beta-blocker therapy. The absolute standardized difference of the covariates in the weighted sample were less than 10%, except for (preoperative beta-blocker compared to beta blocker naïve) metropolitan statistical area of beta 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 beta-blocker to beta blocker naïve. See Tables 1 and 2 for a table of 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 beta-blocker within 60 days of surgery as compared to beta blocker naïve patients and chronic beta blocker patients as compared to beta 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 beta-blocker initiation within 60 days of surgery to beta-blocker naïve patients, the analysis was repeated with two different inclusion criteria for a preoperative beta-blocker: beta-blocker initiation within 90 days of surgery and beta-blocker initiation within 180 days of surgery.

In order to analyze the trend of preoperative beta-blocker use prior to surgery, a logistic regression model was used to determine the change in preoperative beta-blocker dispensing from 2005 to 2015. The regression model was adjusted for all demographic information, medication therapies, and cardiac testing as described above. The regression estimated the odds of preoperative beta-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 (SAS Institute Inc, Cary, NC) 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 240,981 patients who underwent major abdominal surgery. In the cohort, 155,531 patients (75.9%) were beta-blocker naïve, 4,026 patients (2.0%) initiated a preoperative beta-blocker within 60 days of surgery, and 45,424 patients (22.2%) were on a chronic (> 60 days) beta-blocker before surgery. Patients who were beta-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 beta-blocker. Patients on a chronic beta-blocker were older, had a greater Revised Cardiac Risk Index, and were on more medications than patients who were initiated on a preoperative beta-blocker (Table 1 and Table 2).

The overall frequency of stroke was 0.2% (423/204,981) in the cohort (Table 3). Patients on a chronic beta-blocker had the highest rate of perioperative strokes (0.4%, 171/45,424),

followed by patients with preoperative beta-blocker initiation within 60 days of surgery (0.4%, 17/4,026) and then beta-blocker naïve patients (0.2%, 235/155,531).

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

The average effect of the treatment on the treated did not demonstrate a lesser odds of stroke for patients initiated on a preoperative beta-blocker within 60 days of surgery as compared to beta-blocker naïve patients (OR: 0.90, 95% CI: 0.31 – 2.04; P = 0.757) (Table 4). Further, there was no difference in the odds of major adverse cardiac events between preoperative beta-blocker therapy initiation within 60 days of surgery and beta blocker naïve patients (OR = 1.11; 95% 0.80 – 1.53; P = 0.203). Additionally, there was no association between preoperative beta-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 beta-blocker as compared to beta-blocker naïve patients demonstrated a reduction in the odds of major adverse cardiac events (OR = 0.81, 95% CI: 0.72 – 0.91, P = 0.007) but not stroke (OR = 0.85; 95% CI 0.65 – 1.15; P = .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 (OR = 0.81; 95% CI 0.69 – 0.95; P = 0.002) and myocardial infarction (OR = 0.78; 95% CI 0.65 – 0.93; P = 0.001) (Table 4).

Dispensing of preoperative beta-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) (Figure 2).

Sensitivity Analysis:

We performed additional analyses to explore different time cut points for the initiation of a preoperative beta-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 above to determine the average treatment effect on the treated between patients initiated on a preoperative beta blocker and beta blocker naïve patients. For both cut points there was no change in the odds of stroke or the composite of major 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).

Discussion:

Our retrospective cohort study did not identify a risk adjusted association between preoperative beta-blocker initiation within 60 days of surgery or chronic beta-blocker dispensing and perioperative stroke after elective major abdominal surgery. These results suggest that beta-blocker initiation before the day of surgery is unlikely to impact

perioperative stroke risk after major abdominal surgery. While the patients initiated on preoperative beta-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 prior to major non-cardiac surgery and suggest alternative therapies are needed to reduce the frequency of perioperative major adverse cardiac events in high-risk patients.

Beta-blocker therapy initiated prior to major non-cardiac surgery remains controversial. Multiple small trials of perioperative beta-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 beta-blocker naive patients within two to four hours of surgery. Beta-blocker administration in POISE was associated with clinically significant post-operative hypotension, likely from blunting sympathetic activity and heart rate which resulted in the inability to augment cardiac output and subsequent cerebral hypoperfusion. Thus, following the POISE trial, preoperative initiation of beta-blockers has been discouraged. Our study is consistent with other studies that identified a reduction in the frequency of new beta blocker prescriptions in the years that followed the POISE trial.[8,9] However, it remained unclear if beta-blocker initiation in the outpatient setting in the weeks before surgery increased the risk of stroke for patients undergoing noncardiac surgery. Beta-blocker therapy prior to 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 beta-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 beta blocker therapy. We did not identify a reduction in the odds of perioperative major adverse cardiac events in patients initiated on a beta blocker within 60 days prior to major abdominal surgery. Prior analyses have demonstrated mixed results on the impact of preoperative initiation of beta blocker therapy prior to the day of surgery on perioperative major adverse cardiac events. In a retrospective propensity matched cohort of Taiwanese diabetic patients, Chen et al. demonstrated no association between beta blocker therapy initiated less than 30 days before major non-cardiac 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 beta blockade therapy more than 1 week prior to surgery.[22] Additionally, in a retrospective propensity matched cohort of patients in the Veterans Health Administration, London et al demonstrated a reduction of 30-day mortality and cardiac morbidity in patients that initiated a beta blocker therapy within 30 days prior to surgery.[16] Further complicating the analysis is 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 beta-blocker therapy trials have been constrained by enrollment, making the path to determining the optimal perioperative beta-blocker strategy more challenging.[23] Taken together, our study suggests that the initiation of beta blocker therapy prior to the day of surgery is not associated with an higher risk of stroke but is also not associated with a lower risk of major adverse cardiac events.

Our findings on chronic beta-blocker therapy are also important as prior studies have suggested an increased risk of perioperative stroke in patients on chronic beta-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 was the result of an increase in chronic beta-blocker dispensing from 2004 to 2013 given their relationship in prior studies.[11] Our study suggests that chronic beta-blocker dispensing is not associated with a higher risk of perioperative strokes. Further, our findings support current guidelines that recommend the continued use of beta-blocker therapy leading up to non-cardiac 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 data bases.[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 health care 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 which is 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 beta-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 beta-blocker or the dose dispensed, and we are not able to make any inferences with regards to the type of beta-blocker used or dosage (e.g.: metoprolol vs. atenolol). This is important as some beta-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 beta-blocker dispensing from the data. Additionally, we cannot be sure patients were taking their dispensed beta-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 thus 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 beta-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 beta-blocker initiation within 60 days of surgery or chronic beta-blocker dispensing and higher risk of perioperative stroke. Additionally, we did not identify an association with perioperative initiation of beta-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 beta blocker prior to major non-cardiac surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary Statement:

The initiation of a beta-blocker outside of a clinical trial within 2 months prior to major abdominal surgery is not associated with higher risk of stroke.

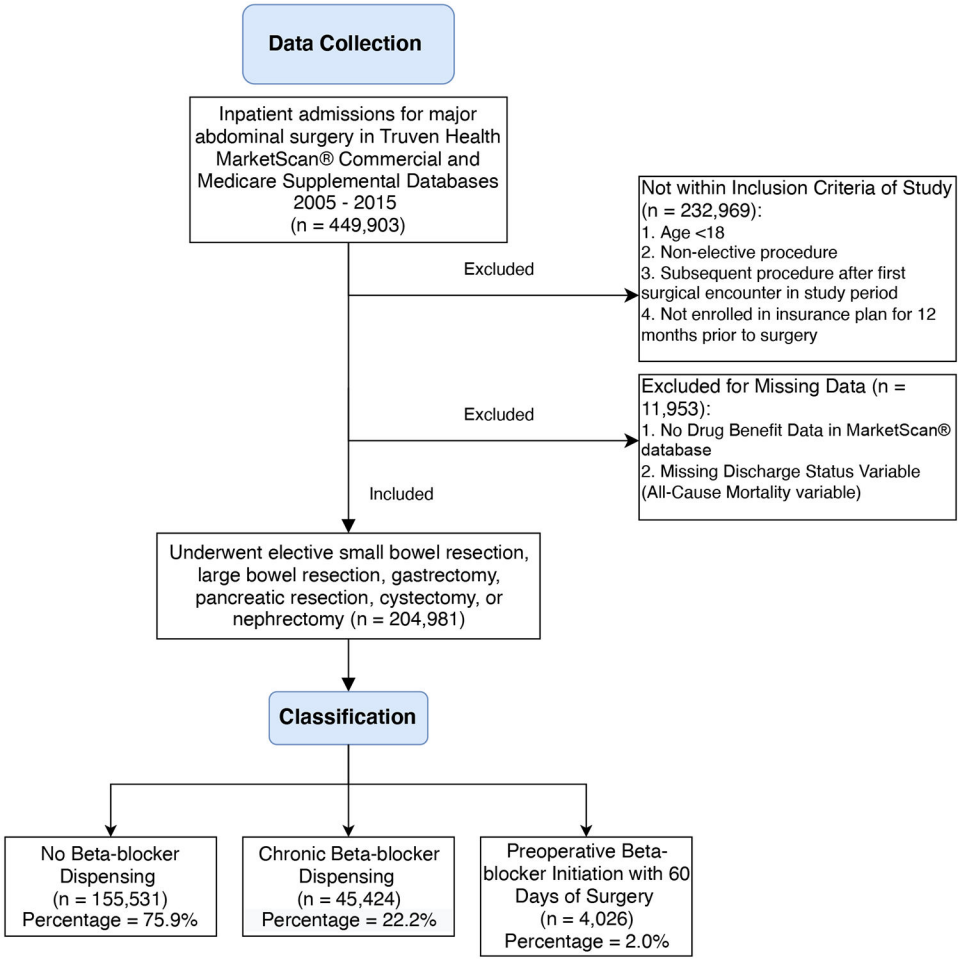

Figure 1:

Flow Chart of the Cohort Selection of Patients who underwent an Elective Major Abdominal Surgery from the MarketScan® Inpatient 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 2005-2015. Patients who had already had a surgical encounter within the year (n = 9,476), were under the age of 18 (n = 7,327), were uninsured within the year of surgery (n = 132,939), underwent a non-elective procedure (n = 83,227), did not have MarketScan® drug benefit data were excluded (n = 85) or the discharge status variable that encodes in-hospital mortality was missing (n=11,868).

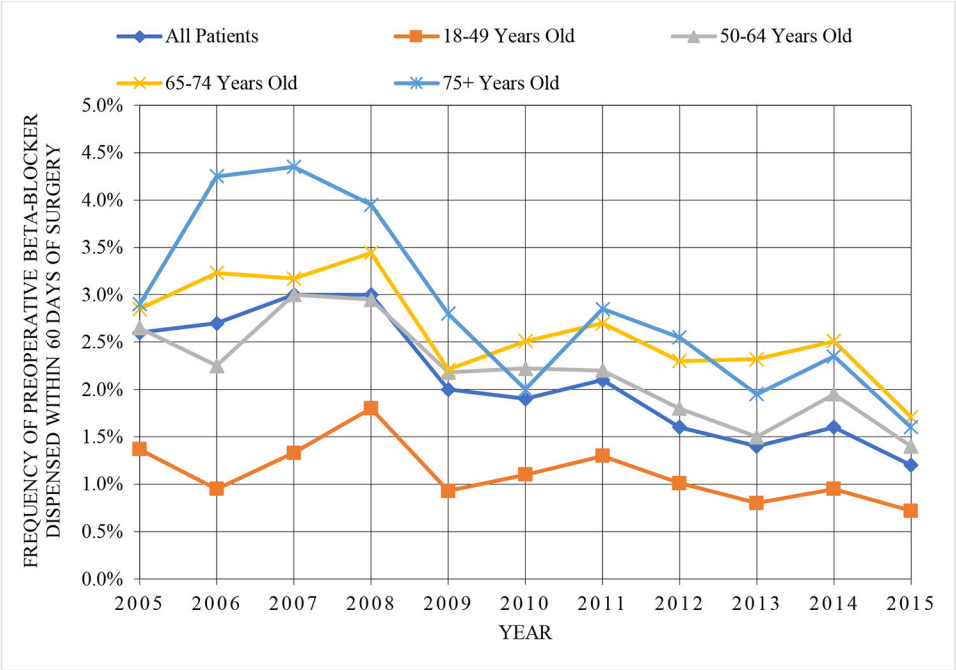

Figure 2.

Frequency of Preoperative Beta-Blocker Dispensed Within 60 Days of Surgery in Patients Undergoing Elective Major Abdominal Surgery Stratified by Age. Perioperative Beta-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).

Table 1.

Patient and clinical characteristics for patients with no beta blocker therapy and preoperative beta blocker therapy initiated within 60 days of surgery.

Study Patients, (% percentage)				
Variable	**No Beta Blocker Dispensing (n = 155,531)**	**Preoperative Beta 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, (years)	55.1 (55.0-55.2, 95% CI)	62.5 (62.1-62.9 95% CI)	-	-
Age Group				
18-49 years	51,092 (32.9%)	583 (14.5%)	0.39	0.08
50-64 years	70,152 (45.1%)	1,888 (46.9%)	0.04	0.00
65-74 years	18,552 (11.9%)	759 (18.9%)	0.21	0.06
≥ 75 years	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 Beta-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

Study Patients, (% percentage)				
Variable	**No Beta Blocker Dispensing (n = 155,531)**	**Preoperative Beta Blocker Initiation within 60 Days of Surgery (n = 4,026)**	**Unweighted Standardized Mean Difference**	**Standardized Mean Difference After Weighting**
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
Anti-platelet	1,541 (1.0%)	289 (4.7%)	−0.37	−0.01
Anti-arrhythmic	532 (0.3%)	79 (2.0%)	−0.28	−0.03
Anti-lipidemic/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
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
Anti-Platelet	2,806 (1.8%)	202 (5.0%)	−0.24	−0.05
Anti-arrhythmic	847 (0.5%)	53 (1.3%)	−0.11	−0.02
Anti-Lipidemic/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
Anti-diabetic	18,369 (11.8%)	728 (18.1%)	−0.19	−0.06
Bronchodilator	404 (0.3%)	8 (0.2%)	0.01	0.00

Study Patients, (% percentage)				
Variable	**No Beta Blocker Dispensing (n = 155,531)**	**Preoperative Beta Blocker Initiation within 60 Days of Surgery (n = 4,026)**	**Unweighted Standardized Mean Difference**	**Standardized Mean Difference After Weighting**
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
ECG	77,371 (49.8%)	2,706 (67.2%)	0.35	−0.10
Exercise Treadmill or Pharmacological 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
Percutaneous Coronary Intervention (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
ECG	48,233 (31.0%)	1,431 (35.5%)	−0.10	−0.03
Exercise Treadmill or Pharmacological 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
Percutaneous Coronary Intervention (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 precents are reported for categorical variables, and 95% confidence intervals are reported for continuous variables. Propensity score weighting was used to determine the standardized difference between the no beta blocker group and the two other groups.

Table 2.

Patient and clinical characteristics for patients with no beta blocker therapy and chronic beta blocker therapy.

Study Patients, (% percentage)				
Variable	**No Beta Blocker Dispensing (n = 155,531)**	**Chronic Beta 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, (years)	55.1 (55.0-55.2, 95% CI)	63.8 (63.7-63.9 95% CI)	-	-
Age Group				
18-49 years	51,092 (32.9%)	5,852 (12.9%)	0.43	0.05
50-64 years	70,152 (45.1%)	19,233 (42.3%)	0.06	0.01
65-74 years	18,552 (11.9%)	9,704 (21.4%)	0.29	0.02
≥ 75 years	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 Beta-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

Study Patients, (% percentage)				
Variable	**No Beta Blocker Dispensing (n = 155,531)**	**Chronic Beta Blocker Dispensing (n = 45,424)**	**Unweighted Standardized Mean Difference**	**Standardized Mean Difference After Weighting**
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 prior)				
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
Anti-platelet	1,541 (1.0%)	3,432 (7.6%)	−0.66	−0.01
Anti-arrhythmic	532 (0.3%)	967 (2.1%)	−0.31	−0.02
Anti-lipidemic/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 prior)				
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
Anti-Platelet	2,806 (1.8%)	6,079 (13.4%)	−0.87	−0.01
Anti-arrhythmic	847 (0.5%)	1,686 (3.7%)	−0.43	−0.03
Anti-Lipidemic/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
Anti-diabetic	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

Study Patients, (% percentage)				
Variable	**No Beta Blocker Dispensing (n = 155,531)**	**Chronic Beta Blocker Dispensing (n = 45,424)**	**Unweighted Standardized Mean Difference**	**Standardized Mean Difference After Weighting**
Vasodilator	1,722 (1.1%)	4,696 (10.3%)	−0.88	−0.02
Cardiac Testing (within 60 days prior)				
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
ECG	77,371 (49.8%)	26,046 (57.3%)	−0.15	−0.02
Exercise Treadmill or Pharmacological 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
Percutaneous Coronary Intervention (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 prior)				
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
ECG	48,233 (31.0%)	23,099 (50.9%)	−0.43	−0.06
Exercise Treadmill or Pharmacological 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
Percutaneous Coronary Intervention (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 precents are reported for categorical variables, and 95% confidence intervals are reported for continuous variables. Propensity score weighting was used to determine the standardized difference between the no beta blocker group and the two other groups.

Table 3.

Unadjusted frequency of Stroke and Major Adverse Cardiac Events for Patients undergoing elective major abdominal surgery stratified by beta blocker therapy.

Primary outcomes	Entire Cohort (n = 204,981)	No Beta Blocker Dispensing (n = 155,531)	Chronic Beta Blocker Dispensing (n = 45,424)	Preoperative Beta 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 precents 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 beta-blocker therapy initiation within 60 days of surgery and chronic beta-blocker therapy compared to beta-blocker naïve patients.

Primary outcomes	Preoperative Beta-Blocker Initiation within 60 Days of Surgery Odds Ratio (95% CI)	*P* value	Chronic Beta-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% Confidence intervals, and P-values are reported for each propensity weight analysis of the average treatment effect on the treated. A *P* value < 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 Beta-Blocker Initiation within 60 Days of Surgery.

Year (Reference = 2005)	Preoperative Beta-Blocker Initiation with 60 Days of Surgery, Frequency (Percentage %)	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% confidence intervals of the likelihood of different prescription rates between year 2005 and the selected year are reported. A P value < 0.05 was considered significant.