Early Resumption of β Blockers Is Associated with Decreased Atrial Fibrillation after Noncardiothoracic and Nonvascular Surgery

A Cohort Analysis

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ABSTRACT

Background: Beta (β) blockers reduce the risk of postoperative atrial fibrillation and should be restarted after surgery, but it remains unclear when best to resume β blockers postoperatively. The authors thus evaluated the relationship between timing of resumption of β blockers and atrial fibrillation in patients recovering from noncardiothoracic and nonvascular surgery.

Methods: The authors evaluated 8,201 adult β-blocker users with no previous history of atrial fibrillation who stayed at least two nights after noncardiothoracic and nonvascular surgery as a retrospective observational cohort. After propensity score matching on baseline and intraoperative variables, 1,924 patients who did resume β blockers by the end of postoperative day 1 were compared with 973 patients who had not resumed by that time on postoperative atrial fibrillation using logistic regression. A secondary matched analysis compared 3,198 patients who resumed β blockers on the day of surgery with 3,198 who resumed thereafter.

Results: Of propensity score–matched patients who resumed β blockers by end of postoperative day 1, 4.9% (94 of 1,924) developed atrial fibrillation, compared with 7.0% (68 of 973) of those who resumed thereafter (adjusted odds ratio, 0.69; 95% CI, 0.50–0.95; $P = 0.026$). Patients who resumed β blockers on day of surgery had an atrial fibrillation incidence of 4.9% *versus* 5.8% for those who started thereafter (odds ratio, 0.84; 95% CI, 0.67–1.04; $P = 0.104$).

Conclusions: Resuming β blockers in chronic users by the end of the first postoperative day may be associated with lower odds of in-hospital atrial fibrillation. However, there seems to be little advantage to restarting on the day of surgery itself.
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THE incidence of atrial fibrillation after noncardiac surgery ranges from 3 to 15%.[1–4] Patients who develop this arrhythmia after noncardiac surgery have longer and more costly hospital stays and greater mortality.[1] Furthermore, new clinically detected atrial fibrillation is an independent predictor of stroke in this population.[5] Modifiable factors that influence postoperative atrial fibrillation are thus of considerable interest.

Many patients having noncardiac surgery take long-term beta (β) blockers. A role for these medications as prophylaxis in the population at high risk for coronary artery disease and vascular disease has long been established.[6,7] Many people also take these drugs routinely for management of hypertension and as prophylaxis against arrhythmias. The Perioperative Ischemic Evaluation study showed that perioperative β blockade caused a reduction in new clinically detected atrial

Editor's Perspective

What We Already Know about This Topic

- Use of beta (β) blockers in the perioperative period is associated with reduced incidence of postoperative atrial fibrillation
- In chronic β-blocker users, optimal timing for β-blocker resumption in the postoperative setting is unclear

What This Article Tells Us That Is New

- Resumption of postoperative β-blocker therapy by the end of postoperative day 1 is associated with reduced incidence of postoperative atrial fibrillation in general surgical patients (noncardiac, nonthoracic, nonvascular surgeries) when compared with patients who resumed β-blocker therapy after postoperative day 1
- There was not a significant difference in incidence of postoperative atrial fibrillation for those patients who postoperatively resumed β-blocker therapy on the day of surgery *versus* anytime thereafter

This article is featured in "This Month in Anesthesiology," page 1A. Part of the work presented in this article has been presented as a best-of-meeting abstract for clinical sciences at the American Society of Anesthesiologists (ASA) meeting in Boston, Massachusetts, October 21–25, 2017.

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fibrillation, myocardial infarctions, and referrals for cardiology care, but there was an increase in bradycardia, hypotension, strokes, and all-cause mortality.[5] The American Heart Association, in its revised guidelines for perioperative β blockade, recommends that β blockers should be continued after noncardiac surgery in patients who take the drugs chronically.[8]

Beta-blocker therapy initiated in the perioperative period reduces the risk of supraventricular arrhythmias in noncardiac surgery patients.[9] However, the benefit of this risk reduction is offset by potential intraoperative hypotension and a consequent increase in cerebrovascular events, acute kidney injury, myocardial injury, and mortality.[5,10] Restarting chronically used β blockers before discharge from the postanesthesia care unit increases cerebrovascular events.[2] In contrast, restart during the first two postoperative days reduces cerebrovascular and cardiovascular events and 30-day mortality.[2] Re-initiating β blockers after surgery may be delayed by potential drug interactions, *nil per os* status, an unstable hemodynamic profile, recent vasopressor use, or inadequate review of patients' home medication profiles. It thus remains unclear when it is best to restart β blockers to maximize benefit and minimize potential risks.

Little is known about the relationship between postoperative atrial fibrillation and when home β blockers should be restarted in patients recovering from noncardiac surgery. We therefore assessed whether resuming β blockers by the end of postoperative day 1 is associated with reduced odds of new-onset and paroxysmal atrial fibrillation in patients recovering from noncardiothoracic and nonvascular surgery. Secondarily, we assessed whether resuming β blockers on the day of surgery is associated with reduced odds of new-onset and paroxysmal atrial fibrillation.

Materials and Methods

With institutional review board approval and waiver of informed consent, data were obtained from the Cleveland Clinic Perioperative Health Documentation System for 8,201 adult β-blocker users who had noncardiac surgery, excluding thoracic and vascular surgery, from June 1, 2008 through January 31, 2016 and stayed at least two postoperative nights at the Cleveland Clinic's Main Campus (Cleveland, Ohio). Patients who had atrial fibrillation at admission or a history of atrial fibrillation were excluded. We further excluded patients in whom key data were missing. When patients had multiple surgeries meeting our inclusion and exclusion criteria, only the first surgery was included in our analysis. New-onset atrial fibrillation was diagnosed when patients were in sinus rhythm preoperatively (as determined by the most recent clinic visit or the day of surgery documentation of vital signs), and subsequently developed atrial fibrillation during their hospitalization. The onset of atrial fibrillation was determined *via* a manual chart review of available documentation of vital signs and physician notes.

Discontinuation of β blockers was defined as the complete cessation of β blockers during the perioperative period (before and day of surgery); *early resumption* was defined as restarting β blockers before the end of the first postoperative day, whereas *late resumption* was defined as restarting β blockers after the end of the first postoperative day including a complete failure to restart β blockers during hospitalization.

Patients categorized by β-blocker resumption day (postoperative day 0, postoperative day 1, postoperative day 2+) were compared on demographic, baseline, and intraoperative variables using Pearson chi-square analysis for categorical variables, one-way ANOVA for normally distributed continuous variables, and Kruskal–Wallis test for ordinal or nonnormal continuous variables.

Primary Analysis

We compared patients who did and did not restart β blockers by the end of the first postoperative day on the incidence of postoperative atrial fibrillation. We excluded 112 patients who experienced new-onset atrial fibrillation before the end of the first postoperative day to avoid immortal time bias; thus, only patients who were still at risk of developing postoperative atrial fibrillation at the end of postoperative day 1 were included.

To control for observed potential confounding variables, we matched each patient who restarted β blockers after the end of postoperative day 1 (late resumption) to a maximum of two patients who restarted by the end of postoperative day 1 (early resumption) using exact and propensity score matching.[11] Specifically, we first estimated the probability of restarting β blockers late (*i.e.*, propensity score) for each patient using logistic regression with late restart (*vs.* early restart) as the outcome and prespecified potential confounding variables listed in the table 1 as independent variables.

Our prespecified list of potential confounding variables includes age, sex, race, body mass index, congestive heart failure, valvular heart disease, hypertension, thyroid disease, coronary artery disease, diabetes, year and duration of surgery, percent of surgery time with mean arterial blood pressure less than 70 mmHg, estimated blood loss, amount of colloids, amount of crystalloids, erythrocyte transfusion, fresh frozen plasma transfusion, platelets transfusion, cryoprecipitate transfusion, and postoperative vasopressor use. Matching was then implemented through a greedy algorithm (SAS macro: gmatch), restricting successful matches to those with the same type of surgery (*i.e.*, first exact matching on type of surgery because it is so related to both exposure and outcome and thus such an important confounder) and those whose estimated propensity score logits (*i.e.*, estimated propensity score) were within 0.2 propensity score logit standard deviations of each other.[12–14] Surgery type was characterized into one of the 244 mutually exclusive clinically appropriate categories using the Agency for Healthcare Research and Quality's single-level Clinical Classifications Software

Table 1. Demographics Baseline and Intraoperative Characteristics (N = 8,201)

Variable	β-Blocker Resumption after Surgery			
	Postoperative Day 0 (N = 4,265)	Postoperative Day 1 (N = 2,932)	Postoperative Day 2+ (N = 1,004)	*P* Value†
Age, yr	65 ± 14	65 ± 13	64 ± 13	0.019‡
Gender (male)	55%	53%	42%	<0.001
Race				
Caucasian	80%	87%	86%	<0.001
African American	18%	12%	13%	
Others	2%	1%	2%	
Body mass index, kg/m^2	29 [25, 34]	30 [26, 35]	29 [25, 34]	<0.001‡
Congestive heart failure	18%	13%	13%	<0.001
Valvular heart disease	11%	10%	10%	0.413
Hypertension	66%	72%	69%	<0.001
Hypertension with complications	23%	17%	18%	<0.001
Thyroid disease	16%	17%	18%	0.077
Coronary artery disease	41%	35%	33%	<0.001
Diabetes type				
No diabetes	66%	71%	74%	<0.001
Type I diabetes	3%	2%	2%	
Type II diabetes	31%	28%	25%	
Type of surgery*				<0.001
Laminectomy	5%	7%	4%	
Arthroplasty knee	4%	7%	6%	
Hip replacement	4%	7%	6%	
Nephrectomy	4%	6%	5%	
Colorectal resection	4%	5%	7%	
Year of surgery				
2008	11%	15%	12%	<0.001
2009	13%	18%	19%	
2010	12%	14%	14%	
2011	15%	11%	11%	
2012	16%	11%	12%	
2013	12%	10%	9%	
2014	10%	10%	11%	
2015	11%	11%	11%	
2016	1%	1%	<1%	
Duration of surgery, hours	3.7 [2.6, 5.3]	4.1 [3.0, 5.8]	4.5 [3.2, 6.4]	<0.001§
% of surgery with mean arterial pressure <70 mmHg	9 [2, 21]	9 [2, 21]	12 [4, 25]	<0.001§
Estimated blood loss, cc	100 [50, 300]	200 [50, 400]	200 [71, 500]	<0.001§
Amount of colloids, cc	0 [0, 500]	500 [0, 500]	500 [0, 1000]	<0.001§
Amount of crystalloids, L	2.2 [1.3, 3.2]	2.6 [1.8, 3.6]	2.9 [2.0, 4.0]	<0.001§
Erythrocyte transfusion	16%	17%	24%	< 0.001
Fresh frozen plasma transfusion	3%	3%	8%	< 0.001
Platelets transfusion	3%	2%	6%	< 0.001
Cryoprecipitate transfusion	0%	0%	2%	< 0.001
Usage of vasopressor	65%	67%	73%	<0.001

Summary statistics are presented as % of patients, mean ± SD, or median [Q1, Q3], respectively.

*Only most frequent five categories are reported because of limited space.

†Pearson's chi-square test, unless specified.

‡one-way ANOVA.

§Kruskal–Wallis one-way ANOVA by ranks.

for International Classification of Diseases, 9th Revision, Clinical Modification procedure codes. We chose this fairly granular method of adjusting for type of surgery because surgical procedure has been shown to be a strong confounding variable in observational studies in perioperative medicine.[12]

Assessment of balance on the covariables used for the propensity score matching was performed using absolute standardized differences (*i.e.*, the absolute difference in means or proportions divided by the pooled SD). Imbalance was defined as a standardized difference greater than 0.10 in

absolute value; any such covariables were included in the models comparing early and late β-blocker patients on outcomes to reduce potential confounding.[13,14]

The matched groups were compared on postoperative atrial fibrillation using a multivariable logistic regression, adjusting for covariables that were still imbalanced after the matching.

In a sensitivity analysis, instead of using the propensity-matched groups, we included all available patients and used a multivariable model to adjust for confounding. We compared late (restart β blockers after the end of the first postoperative day) and early (restart β blockers by the end of the first postoperative day) restart times using all patients, and included potential confounding variables in the model *via* backward selection, with a significance criterion to leave the model of $P > 0.05$.

Secondary Analysis

In this analysis we changed the early restart period to before end of the day of surgery (instead of end of postoperative day 1 as in primary analysis). We thus compared postoperative atrial fibrillation between patients who did and did not restart β blockers on the day of surgery. In this analysis, 39 patients who experienced postoperative atrial fibrillation right after surgery on the same day were excluded because we wanted to include only the patients who were still at risk of developing postoperative atrial fibrillation at the end of the day of surgery. We one-to-one matched patients who did and did not restart β blockade on the same day of surgery using the same approach as the primary analysis. The matched groups were compared on postoperative atrial fibrillation using a multivariable logistic regression, adjusting for covariables that were still imbalanced after the matching.

We conducted additional sensitivity analyses further varying both the early and late restart periods and comparing groups on atrial fibrillation occurring after the early restart exposure period. For example, when comparing restart by end of postoperative day 0 with restart by end of postoperative day 2, the "outcome period" for both groups would start on postoperative day 1, just after the end of the early restart period. Groups were compared using multivariable logistic regression adjusting for all baseline confounding variables significant at the 0.30 level (0.30 to enter, 0.40 to stay) using stepwise selection. We varied the early restart period from by the end of postoperative day 0 to postoperative day 1, and the late restart period from on or after postoperative day 1 to postoperative day 4.

Sample size for the study was based on the algorithm in figure 1, using all patients during the given time frame of June 1, 2008, to January 31, 2016, who met all predetermined inclusion and exclusion criteria from the protocol. The beginning date for the study was chosen as the earliest data for which the exposure and outcome variables were reliably collected. With the attained data, we were able to estimate CIs for the associations of interest with acceptable precision.

All tests were two-sided, and statistical significance when assessing the associations of interest was claimed when $P < 0.05$. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., USA).

Results

From June 1, 2008 to January 1, 2016, a total of 8,201 adult β-blocker users who had noncardiothoracic and nonvascular surgery and stayed at least two nights after surgery at Cleveland Clinic main campus were included in our analysis (fig. 1 and table 1). Our patients were a mean of 65 (SD = 13) years old. The median duration of surgery was 4.0 (Q1, Q3: 2.8, 5.6) hours and median length of hospital stay after surgery was 6 (4, 8) days. Among these patients, 4,265 (52%) restarted β blockers on the day of surgery, 2,932 (36%) on postoperative day 1, 612 (7%) on postoperative day 2, 174 (2%) on postoperative day 3, 92 (1%) on postoperative day 4, and 126 (2%) after postoperative day 4, respectively. Four hundred eighty-four (484) patients experienced postoperative atrial fibrillation (5.9% of 8,201), where 39 (8% of 484) patients had postoperative atrial fibrillation on the same day of surgery, 73 (15%), 105 (22%), 83 (17%), 60 (12%), and 124 (26%) on postoperative day 1 to 4 and after postoperative day 4, respectively.

Among 8,089 patients who were still at risk of developing postoperative atrial fibrillation at the end of postoperative day 1, 7,095 had already restarted β blockers (early group) and 994 patients had not (late group). The incidence of postoperative atrial fibrillation was 4.2% for the early group and 7.1% for the late group. We successfully matched 973 patients (98% of 994) in the late group with 1,924 patients in the early group. Because of the results of matching the two groups were much better balanced on all the prespecified potential confounding variables, only percentage of surgery time with map < 70 mmHg was imbalanced after the matching (table 2, left panel and fig. 2). Within the subset of matched patients, 4.9% (94 of 1,924) retaking β blockers by the end of postoperative day 1 experienced postoperative atrial fibrillation, which was significantly lower than 7.0% (68 of 973) in those retaking after postoperative day 1, giving an odds ratio (early *vs.* Late) of 0.69 (95% CI, 0.50–0.95; $P = 0.026$). Sensitivity analyses provided consistent results (table 3, fig. 3).

Second, we successfully matched 3,198 patients who restarted β blockers on the day of surgery with 3,198 patients who restarted after the day of surgery (table 2, right panel). The incidence of postoperative atrial fibrillation was 4.9% for patients who restarted on the day of surgery and 5.8% for patients who did not, giving a nonsignificant odds ratio of 0.84 (95% CI, 0.67–1.04; $P = 0.107$; table 3, fig. 3).

Finally, when we varied the early and late restart periods in sensitivity analyses using multivariable regression to adjust for confounding (table 4, fig. 4), we found that early restart by the end of postoperative day 0 was not associated with atrial fibrillation, independent of whether the late period was

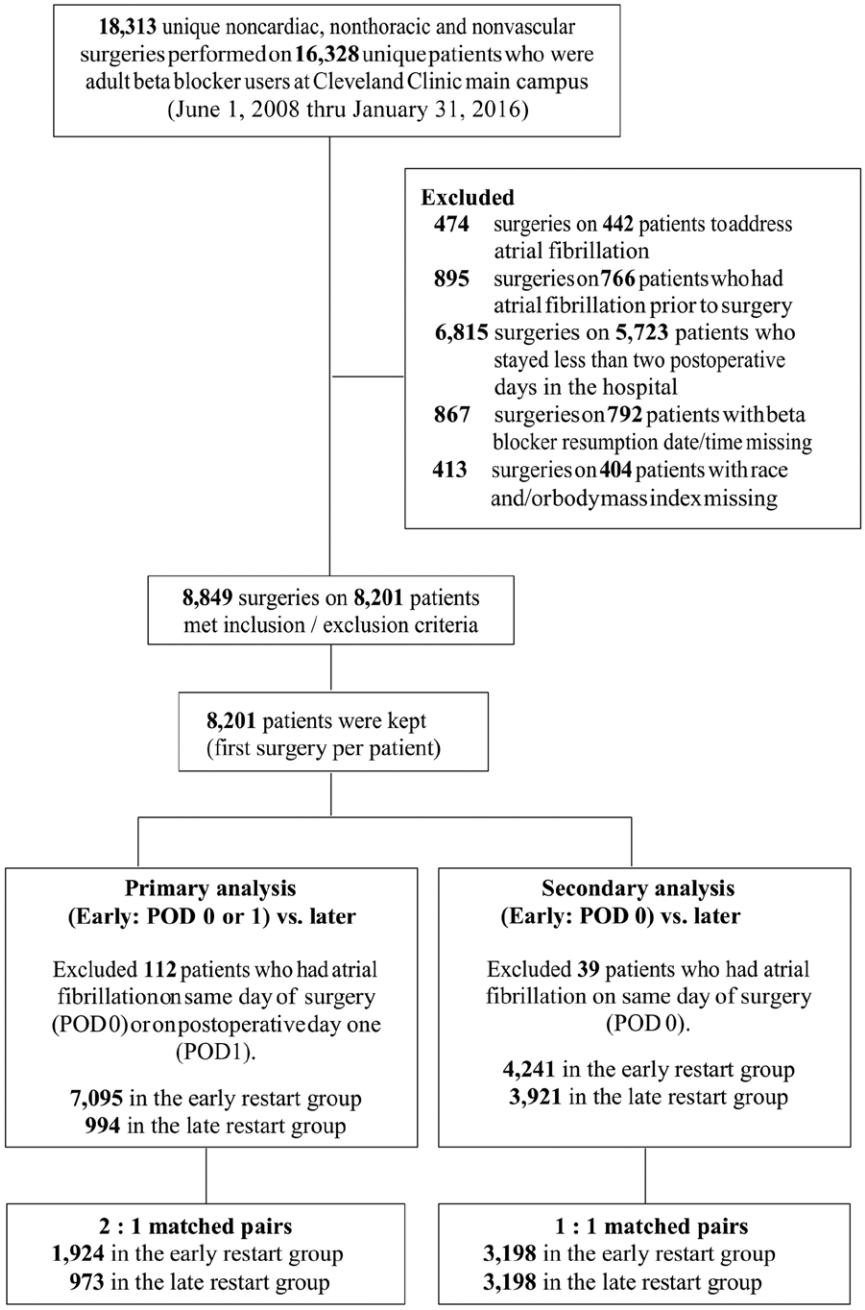

Fig. 1. Study flow chart. POD, postoperative day.

defined as those restarting on or after postoperative day 1 (P = 0.793), postoperative day 2 (P = 0.060), postoperative day 3 (P = 0.074), or postoperative day 4 (P = 0.452). However, early restart by the end of postoperative day 1 was associated with lower odds of atrial fibrillation compared with late restart defined as on or after postoperative day 2 (odds ratio [95% CI] of 0.66 [0.49–0.87], P = 0.004) and postoperative day 3 (0.65 [0.43–0.98], P = 0.039), but not postoperative day 4 (P = 0.436). We note, though, that sample size was smaller at later restart times, which reduced power for detecting associations.

Discussion

The period immediately after surgery is a high-risk period for new-onset or recurrent atrial fibrillation. β blockers are widely used in patients at risk for perioperative myocardial events. They provide heart rate control and reduce sympathetic drive, thus improving myocardial oxygen supply–demand balance. A Cochrane analysis that included nearly 20,000 patients concluded that β blockers prevent supraventricular rhythms after cardiac surgery. However, their role in noncardiac surgery remains unclear because supraventricular arrhythmias are much less common and

Table 2. Demographics Baseline and Intraoperative Characteristics after Propensity Score Matching

Variable	Primary Analysis: Comparing Patients Who Retook β Blockers by the End of Postoperative Day 1 *Versus* After			Secondary Analysis: Comparing Patients Who Retook β Blockers on Day of Surgery *Versus* After		
	Postoperative Day 0, 1 (N = 1,924)	Postoperative Day 2+ (N = 973)	Absolute Standardized Difference†	Postoperative Day 0 (N = 3,198)	Postoperative Day 1+ (N = 3,198)	Absolute Standardized Difference†
Age	64 ± 14	64 ± 13	0.037	65 ± 13	65 ± 13	<0.01
Gender (male)	42%	42%	0.005	52%	52%	< 0.01
Race			0.010			0.030
Caucasian	86%	86%		84%	85%	
African American	12%	12%		15%	14%	
Others	1%	1%		1%	1%	
Body mass index, kg/m^2	29 [25, 35]	29 [25, 35]	0.008	29 [25, 35]	29 [25, 35]	0.012
Congestive heart failure	12%	13%	0.026	15%	14%	0.005
Valvular heart disease	9%	10%	0.056	10%	11%	0.023
Hypertension	68%	69%	0.031	70%	69%	0.006
Hypertension with complications	20%	18%	0.046	19%	19%	0.009
Thyroid disease	18%	18%	0.006	17%	17%	0.010
Coronary artery disease	32%	33%	0.020	37%	37%	0.006
Diabetes type			0.055			0.005
No diabetes	74%	73%		70%	70%	
Type I diabetes	3%	2%		2%	2%	
Type II diabetes	24%	25%		28%	28%	
Type of surgery*			0.000			0.000
Laminectomy	5%	5%		7%	7%	
Arthroplasty knee	6%	6%		6%	6%	
Hip replacement	6%	6%		6%	6%	
Nephrectomy	6%	6%		6%	6%	
Colorectal resection	8%	8%		5%	5%	
Year of surgery			0.043			0.053
2008	11%	12%		12%	13%	
2009	17%	19%		14%	18%	
2010	13%	14%		12%	13%	
2011	13%	10%		14%	11%	
2012	14%	12%		15%	11%	
2013	10%	9%		12%	10%	
2014	10%	12%		10%	11%	
2015	11%	11%		10%	12%	
2016	1%	< 1%		1%	1%	
Duration of surgery, hours	4.3 [3.1, 6.1]	4.5 [3.2, 6.2]	0.071	4.0 [2.9, 5.5]	4.1 [3.0, 5.7]	0.063
% of surgery with mean arterial pressure <70 mmHg	9.7 [3.0, 23.4]	11.6 [4.2, 24.5]	0.109	8.1 [2.1, 20.3]	9.4 [2.7, 21.7]	0.076
Estimated blood loss, cc	200 [50, 450]	200 [50, 500]	0.038	150 [50, 350]	150 [50, 400]	0.041
Amount of colloids, mL	500 [0, 1000]	500 [0, 1000]	0.014	0 [0, 500]	0 [0, 500]	0.019
Amount of crystalloids, L	2.8 [1.8, 4.0]	2.85 [1.9, 4.0]	0.036	2.45 [1.6, 3.5]	2.5 [1.7, 3.5]	0.065
Erythrocyte transfusion	22%	22%	0.008	16%	18%	0.053
Fresh frozen plasma transfusion	4%	6%	0.081	3%	4%	0.030
Platelets transfusion	4%	5%	0.068	3%	3%	0.028
Cryoprecipitate transfusion	1%	1%	0.026	0%	< 1%	0.024
Usage of vasopressor	31%	28%	0.059	33%	32%	0.013

Summary statistics are presented as % of patients, mean ± SD, or median [Q1, Q3], respectively.

*Only most frequent five categories are reported because of limited space.

†Absolute standardized difference refers to the absolute difference in means or proportions divided by the pooled SD; any covariables with absolute standard difference ≥0.10 after the propensity score matching would be adjusted for in the analyses.

the presumed benefit is offset by potential hypotension and consequent risk of mortality and strokes.[1,9] Therefore, patients previously on home β blockers are often not restarted on this medication in a timely fashion, presumably because the balance between these competing interests remains unclear. Our results show that resuming chronically used β blockers before the end of postoperative day 1 significantly decreases the odds of postoperative

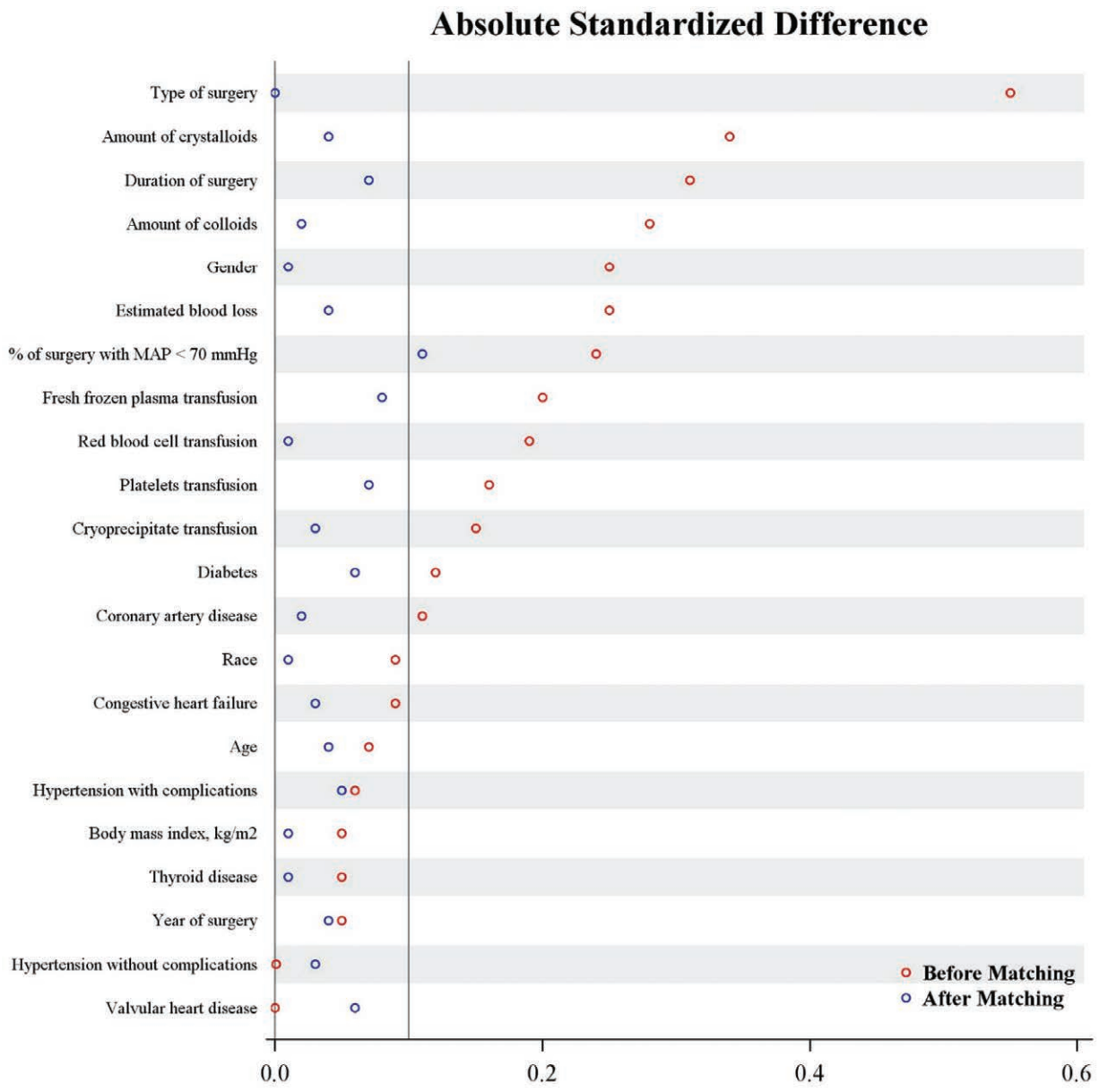

Fig. 2. Plot of absolute standardized difference of covariables used to estimate the propensity score before and after the propensity score matching. MAP, mean arterial pressure.

new-onset and paroxysmal atrial fibrillation after noncardiothoracic and nonvascular surgery.

Bhave *et al.*[1] reported an incidence of postoperative atrial fibrillation of 3% in a large cohort of patients after noncardiac surgery. In the final adjusted analysis, perioperative administration of statins, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors were associated with a lower risk, whereas β blockers appeared to not make a difference. Their results thus differed from ours, possibly because we clearly separated exposure (timing of β-blocker restart) and outcome (timing of postoperative atrial fibrillation). In contrast, some of the patients Bhave *et al.*[1] considered may have already developed atrial fibrillation before β blockers were restarted. Furthermore, Bhave *et al.*'s analysis did not differentiate between β blockers that were newly started in the postoperative period or restarted after previous chronic use. Alonso-Coello *et al.*[15] did not find a significant association of metoprolol use in a model to predict atrial fibrillation after noncardiac surgery based on data from the Perioperative Ischemic Evaluation study.[15] However, whereas patients of the Perioperative Ischemic Evaluation study were randomized to receive extended-release metoprolol succinate or placebo starting 2 to 4 h before surgery, our analysis specifically aimed to see the association of postoperative initiation of β blockers and we did not include only a singular class of β blockers (*e.g.*, extended release metoprolol).

Administration of β blockers may reduce long-term mortality in noncardiac patients at a high risk for cardiac events,[16–18]

Table 3. Associations between Timing of β-Blocker Resumption and Postoperative Atrial Fibrillation

Compare Propensity Score–Matched Patients* (Number of Matched: Early *vs.* Late)	Incidence of POAF, Postoperative Atrial Fibrillation (Early *vs.* Late)	Odds Ratio (95% CI) (Early *vs.* Late)	*P* Value
Primary analysis: comparing patients who did and did not restart β blockers by end of POD1			
1-to-2 matching† (N = 1,924 *vs.* N = 973)	94 (4.9%) *vs.* 68 (7.0%)	0.69 (0.50, 0.95)	0.026
Sensitivity analysis			
All patients‡ (N = 7,095 *vs.* N = 994)	301 (4.2%) *vs.* 71 (7.1%)	0.66 (0.50, 0.88)	0.004
Secondary analysis: comparing patients who did and did not restart β blockers by end of POD0			
1-to-1 matching (N = 3,198 *vs.* N = 3,198)	156 (4.9%) *vs.* 185 (5.8%)	0.84 (0.67, 1.04)	0.107

Early indicates restarted β blockers by end of POD1 (primary analysis) or POD0 (secondary analysis). *Late* indicates did not restart β blockers by end of POD1 (primary analysis) or POD0 (secondary analysis).

*Exactly matched on type of surgery and propensity score–matched on all the other potential confounding variables listed in table 1. The matched subsets were compared on postoperative atrial fibrillation using multivariable logistic regression model.

†Adjusted for percent of surgery time with mean arterial pressure < 70 mmHg, which was imbalanced (*i.e.*, absolute standardized difference > 0.10) after the matching.

‡Adjusted for age, congestive heart failure, valvular heart disease, diabetes, coronary artery disease, fresh frozen plasma transfusion, amount of crystalloids, percent of surgery time with mean arterial pressure < 70 mmHg, and year and duration of surgery, which were retained in the multivariable logistic regression model *via* the backward model selection. One hundred twelve patients who had postoperative atrial fibrillation on day of surgery and postoperative day 1 were excluded from this analysis.

POAF, postoperative atrial fibrillation; POD, postoperative day.

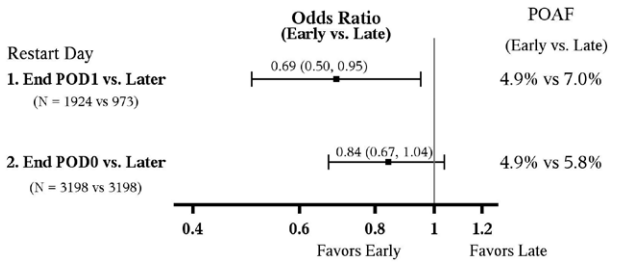

Fig. 3. Forest plot depicting the primary and secondary analysis using propensity score matching to compare the two different early restart groups with postoperative atrial fibrillation (POAF). POD, postoperative day.

and withdrawal of β-blocker therapy perioperatively may increase mortality for noncardiac surgery patients at all levels of cardiac risk.[17–19] In addition, noncardiac surgical patients on a chronic β-blocker regimen may be at lower risk for major postoperative cardiac events compared with patients who start taking β blockers within a few days of surgery.[20] Existing evidence thus suggests that although *initiating* perioperative β-blocker therapy harms noncardiac surgical patients, continuing or rapidly resuming β-blocker therapy after surgery is cardioprotective. Our results extend previous understanding by suggesting that resuming β blockers before the end of the first postoperative day is preferable to resuming later.

The Surgical Care Improvement Project originally defined continuation of therapy as extending from 24 h before incision to discharge from the postanesthesia care unit.[21] The 2012 revision extended continuation to include the first two postoperative days.[21] Continuation of β blockers before discharge from the postanesthesia care unit or on the day of surgery was associated with increased cerebrovascular events but not improved cardiovascular event outcomes. However, β-blocker resumption within two postoperative days was associated with reduced cerebrovascular and cardiovascular events, and also 30-day mortality.[2] Our findings are consistent with the reduction of cardiovascular events, however we did not report cerebrovascular events or mortality in our cohort.

In our secondary analysis, we compared patients who restarted β blockers before the end of the day of surgery (about half the patients) with those who started thereafter. It is important to note that the comparison group for this comparison (resumption after the day of surgery) differs from our primary analysis in which the comparison was with patients who restarted β blockers on the second postoperative day or thereafter. We did not find a significant difference in the incidence of postoperative new onset and paroxysmal atrial fibrillation at this comparison time point.

Several factors may explain the apparent lack of benefit from restarting β blockers on postoperative day 0. First, the outcome of interest (atrial fibrillation) is more common on postoperative days 1 and 2 (37% of our patients) *versus* on postoperative day 0 (just 8% of our patients). Second, some patients may have discontinued their β blockers on the day of surgery; it is likely that many used long-acting or sustained-release preparations, which would have provided continued protected on the day of surgery. These findings were further confirmed in our sensitivity analysis, where we varied the early and late restart periods using multivariable regression to adjust for confounding. Our interpretation is that restarting chronically used home β blockers by the end of the first postoperative day is protective compared with restarting thereafter. However, restarting these agents earlier (by the end of the day of surgery) does not seem to provide the same benefit.

The distinction between restarting on the day of surgery *versus* the first postoperative day is important. The immediate postoperative period is often associated with hypotension and bradycardia consequent to insufficient vascular volume, unrecognized bleeding, vasoplegia, residual

Table 4. Sensitivity Analyses Using Multivariable Models for Association between Early or Late Restart and Postoperative Atrial Fibrillation

Model	Early Period Restart	Late Period Restart	Early Restart % (no. events/total)	Late Restart % (no. events/total)	Odds Ratio (CI)	*P* Value
1	POD0	≥POD1	5.3% (226/4241)	5.6% (219/3921)	1.03 (0.84, 1.3)	0.793
2	POD0	≥POD2	5.3% (226/4241)	7.7% (77/1000)	0.76 (0.57, 1.01)	0.060
3	POD0	≥POD3	5.3% (226/4241)	9.0% (35/390)	0.69 (0.46, 1.04)	0.074
4	POD0	≥POD4	5.3% (226/4241)	7.8% (17/217)	0.81 (0.47, 1.4)	0.452
5*	POD0/1	≥POD2	4.2% (301/7095)	7.1% (71/994)	0.66 (0.49, 0.87)	0.004
6	POD0/1	≥POD3	4.2% (301/7095)	8.0% (31/386)	0.65 (0.43, 0.98)	0.039
7	POD0/1	≥POD4	4.2% (301/7095)	6.5% (14/214)	0.79 (0.44, 1.4)	0.436

Early Period Restart indicates patients restarted β blockers by end of given day (e.g., POD0/1: before end of POD1). *Late Period Restart* indicates patients restarted β blockers on or after the given day.

No. events/total in the Early Restart % and Late Restart % columns indicate the number of patients who developed atrial fibrillation after the restart period divided by number of patients who restarted beta-blockers during the given time period. The given percent is this ratio times 100.

*Model 5 is primary analysis definition of groups; here using multivariable model, not propensity score matching. Multivariable models adjusted for all baseline variables significant at $P < 0.30$ in stepwise regression.

POD, postoperative day.

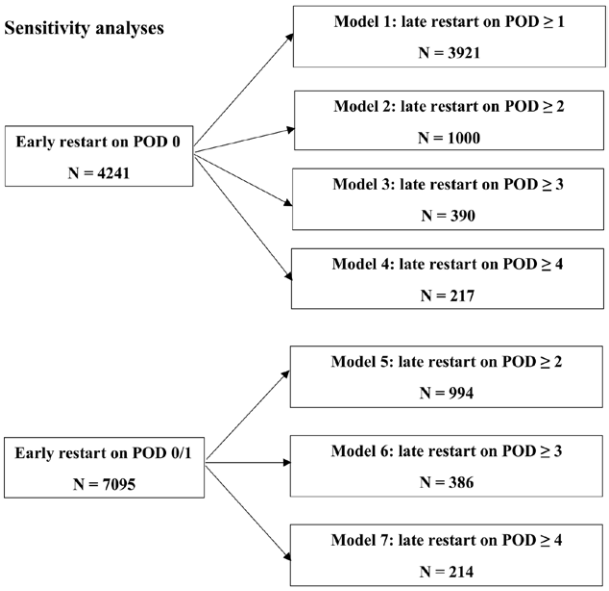

Fig. 4. Detailed flowchart on sample sizes for sensitivity analyses (corresponding to table 4). POD, postoperative day.

neuraxial anesthesia, and anesthetic-induced cardiac depression. Restarting β blockers on the day of surgery is thus more likely to potentially provoke hypotension and bradycardia than starting later. Our results suggest that restarting β blockers by the end of the first postoperative day prevents atrial fibrillation—and may potentially be safer compared with a restart by the end of postoperative day zero, especially in a population with preexisting hypotension and bradycardia.

Despite carefully matching for known potential confounding variables, there is an inherent risk of bias from unknown confounders. For example, it remains likely that patients who were sicker (for example, septic or hemodynamically unstable) were both more likely to develop atrial fibrillation and less likely to be given β blockers because of their unstable condition. Because we selected for patients who stayed at least two nights in the hospital, it could well be that patients in this study were likely sicker and undergoing larger procedures than the overall surgical population in our cohort. An important trade-off for early β-blocker initiation may be increased cerebrovascular events and mortality with the probable benefit of an improvement in cardiovascular events. Our cohort did not include data for mortality, myocardial injury, or cerebrovascular events and was not powered for these rare outcomes. In addition, we did not see a benefit when β blockers were started before the end of postoperative day zero, and our interpretation of the potential for hypotension or bradycardia remains speculative in the absence of data in this dataset. Furthermore, our results have limits on generalizability because we excluded both thoracic and vascular surgery, two of the highest-risk populations, even though the practice at our institution is to re-initiate β blockers at the earliest in these patients. An additional limitation is that we did not distinguish among types of β blockers used, nor do we know exactly when β blockers were stopped preoperatively. To the extent that patients took extended-release or long-acting preparations and stopped the morning of surgery, they would continue to be β blocked for a day or so. However, knowing that generic metoprolol is the most common β blocker used in our hospital, our results were reliable for this common β blocker. We also could not account for some other drugs (amiodarone, calcium channel blockers, statins, angiotensin-converting enzyme inhibitors) that have been shown to be protective against perioperative atrial fibrillation. Finally, we could not evaluate the duration of chronic β-blocker use, which is of interest in terms of upregulation of β receptors.

In conclusion, resuming administration of chronically used β blockers before the end of postoperative day 1 significantly decreased the odds of postoperative atrial fibrillation in patients recovering from noncardiothoracic and nonvascular surgery. Restarting on the day of surgery appears to offer little advantage and may increase the risk of hypotension and bradycardia, especially in a high-risk population.

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Competing Interests

The authors declare no competing interests.

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