β-Blockade and Operative Mortality in Noncardiac Surgery: Harmful or Helpful?

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Original Investigation

β-Blockade and Operative Mortality in Noncardiac Surgery
Harmful or Helpful?

Mark L. Friedell, MD; Charles W. Van Way III, MD; Ron W. Freyberg, MS; Peter L. Almenoff, MD

IMPORTANCE The use of perioperative pharmacologic β-blockade in patients at low risk of myocardial ischemic events undergoing noncardiac surgery (NCS) is controversial because of the risk of stroke and hypotension. Published studies have not found a consistent benefit in this cohort.

OBJECTIVE To determine the effect of perioperative β-blockade on patients undergoing NCS, particularly those with no risk factors.

DESIGN, SETTING, AND PARTICIPANTS This is a retrospective observational analysis of patients undergoing surgery in Veterans Affairs hospitals from October 1, 2008, through September 31, 2013.

METHODS β-Blocker use was determined if a dose was ordered at any time between 8 hours before surgery and 24 hours postoperatively. Data from the Veterans Affairs electronic database included demographics, diagnosis and procedural codes, medications, perioperative laboratory values, and date of death. A 4-point cardiac risk score was calculated by assigning 1 point each for renal failure, coronary artery disease, diabetes mellitus, and surgery in a major body cavity. Previously validated linear regression models for all hospitalized acute care medical or surgical patients were used to calculate predicted mortality and then to calculate odds ratios (ORs).

MAIN OUTCOMES AND MEASURES The end point was 30-day surgical mortality.

RESULTS There were 326 489 patients in this cohort: 314 114 underwent NCS and 12 375 underwent cardiac surgery. β-Blockade lowered the OR for mortality significantly in patients with 3 to 4 cardiac risk factors undergoing NCS (OR, 0.63; 95% CI, 0.43-0.93). It had no effect on patients with 1 to 2 risk factors. However, β-blockade resulted in a significantly higher chance of death in patients (OR, 1.19; 95% CI, 1.06-1.35) with no risk factors undergoing NCS.

CONCLUSIONS AND RELEVANCE In this large series, β-blockade appears to be beneficial perioperatively in patients with high cardiac risk undergoing NCS. However, the use of β-blockers in patients with no cardiac risk factors undergoing NCS increased risk of death in this patient cohort.

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Perioperative β-blockade is widely accepted in patients who undergo cardiac surgery. However, its use in patients undergoing noncardiac surgery (NCS) is controversial. After its initial success in patients with cardiac disease, β-blockade was recommended liberally for patients undergoing NCS.[1-4] Many studies[1,2] used to determine treatment algorithms for β-blockade were randomized clinical trials (RCTs) with relatively small numbers that may not have included the broad spectrum of patients seen in routine clinical practice. These initial studies[1,2] found a net benefit with β-blockade. Subsequently, other studies[5-8] found no advantage. Only 2 large, retrospective, heterogeneous, multicenter studies[9,10] have looked at the use of β-blockade with a risk assessment tool. Both studies[9,10] concurred that β-blockade was beneficial in patients with multiple cardiac risk factors undergoing NCS, and one study[10] found a possible risk of harm from β-blockade in patients without such risk factors. Recently, in a large RCT, some patients experienced hypotension and stroke with β-blockade, which created the current considerable uncertainty about the use of perioperative β-blockade, particularly in patients without risk factors.[11]

This study was undertaken because of this persistent controversy. Our hypothesis was that β-blockade is beneficial in patients at high cardiac risk but may be harmful in those with little or no risk. The investigation used recent data from the Veterans Health Administration (VHA) to assess risk-adjusted outcomes in patients with differing levels of cardiac risk after perioperative β-blockade who were undergoing NCS. Our outcome was 30-day surgical mortality.

Methods

This is a retrospective observational cohort study of patients admitted to 119 VHA hospitals. The study was approved by the institutional review board of the Kansas City Veterans Administration (VA) Medical Center without the need for patient-level informed consent. It used administrative and clinical data collected from the VHA electronic medical record system by the VA Inpatient Evaluation Center, a national VHA program that measures and reports risk-adjusted outcomes and implements evidence-based practices to improve patient safety and quality.[12] It includes demographic information, admission and discharge dates, *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes for diagnostic and surgical procedures, source of admission, and outcome data (survival at 30 days from hospital admission). Clinical data included laboratory values in the 24 hours surrounding the first acute care ward stay during the hospitalization. Pharmacy data were collected from the VHA Inpatient Pharmacy files, which contain information on medication orders. Order start date and VA drug class were used to determine the presence or absence of β-blockers.

All 343 645 patients undergoing NCS within 24 hours of admission at 119 VA medical centers from October 1, 2008, through July 31, 2013, were included in the analysis. Subsequently, all percutaneous arterial and venous procedures (except endovascular abdominal aortic aneurysm repair), endoscopic procedures, and pacemaker insertions were removed from the cohort, leaving 326 489 patients. The use of β-blockers was determined using the start date of the order for the β-blockade. If the start date was between 8 hours before admission to the acute care ward and 24 hours after admission, use was indicated.

The end point for the analysis was death within 30 days of hospital admission. Patients undergoing more than one operation within the observation period were allowed to reenter the registry as long as the subsequent operation was more than 30 days after the preceding one. The outcome (dead or alive) was assigned to the first hospitalization within a 30-day index period. Each index period could only have one outcome—alive or dead.

A simple cardiac risk score, fashioned after the Revised Cardiac Risk Index (RCRI),[13] was determined for each patient by assigning 1 point for the presence of each of the following 4 conditions: renal failure (serum creatinine level >2.0 mg/dL [to convert to micromoles per liter, multiply by 88.4]), *ICD-9-CM* codes for coronary artery disease, *ICD-9-CM* codes for diabetes, and surgery in a major body cavity (abdomen or thorax). The diagnostic performance (C statistic = 0.81) and validation of the RCRI are detailed in the original study[13] and subsequently.[14] The Elixhauser algorithm[15] was also used for comorbid diagnoses of the first 3 conditions. These scores were then grouped into 3 categories: no risk factors, 1 to 2 risk factors, or 3 to 4 risk factors.

Statistical Analysis

A logistic regression model that predicts death at hospital discharge was used to account for variation in patient characteristics and control for severity of illness. This risk adjustment model was previously validated[16,17] and has been used in studies to investigate incidence and outcomes associated with other diagnoses and health conditions.[18,19] The model uses age, laboratory data from the acute care ward stay (sodium, blood urea nitrogen, creatinine, glucose, bilirubin, and albumin levels, hematocrit, white blood cell count, partial pressure of oxygen, and a combined variable of partial pressure of carbon dioxide and pH), source of admission, diagnosis, and comorbid disease burden as predictors. For each laboratory variable, the value deviating most from the reference range in the 24 hours surrounding the acute care ward admission is selected.[20,21] Patients are each assigned to 1 of 8 mutually exclusive groups defining the patient's location before acute care ward admission (emergency department, outpatient clinic, operating room, nursing home, other hospital, psychiatric ward, or rehabilitation ward) and 1 of 72 mutually exclusive admission diagnoses based on *ICD-9-CM* coding from the index hospitalization.[22] Comorbid disease burden is determined using the index hospitalization *ICD-9-CM* codes grouped into 31 comorbid diseases, including diabetes, applying a validated method[16,22] modified from Elixhauser et al.[15] The logistic regression model uses binary variables to represent diagnostic groups, comorbid conditions, and source of admission and uses restricted cubic splines for continuous variables, such as laboratory values and age.

We used a 2-level logistic regression model to determine the independent contribution of β-blockers and cardiac risk

Table 1. Demographic Data of the Study Patients

Variable	Study Patients, %		
	All (N = 326 489)	Cardiac Surgery (n = 12 375)	Noncardiac Surgery (n = 314 114)
Sex			
Male	93.1	98.6	92.9
Female	6.9	1.4	7.1
Age group, y			
<40	4.4	0.6	4.5
40-59	29.7	20.1	30.1
60-79	58.7	73.7	58.1
≥80	7.2	5.6	7.3
β-Blocker therapy			
Yes	43.2	69.3	42.2
No	56.8	30.7	57.8
Cardiac risk factors			
0	48.9	3.1	50.7
1-2	49.0	65.6	48.3
3-4	2.2	31.3	1.0
0 Cardiac risk factors			
β-Blocker therapy	33.5	54.7	33.4
No β-blocker therapy	66.5	45.3	66.4
1-2 Cardiac risk factors			
β-Blocker therapy	51.8	68.5	50.9
No β-blocker therapy	48.2	31.5	49.1
3-4 Cardiac risk factors			
β-Blocker therapy	70.8	72.4	68.8
No β-blocker therapy	29.2	27.6	31.2

to mortality. The first level calculated the predicted hospital mortality for each patient, using the independent variables described previously. The second-level regression model used the predicted mortality risk for each patient from the first regression analysis together with the cardiac risk index and the presence or absence of β-blockers. Odds ratios (ORs) and 95% CIs were calculated to compare those with the presence of β-blockers and those without, stratified by cardiac risk score, for all surgical patients: those undergoing cardiac surgery and those undergoing noncardiac surgery. Risk-adjusted predicted mortality was classified into 3 groups: less than 10% predicted mortality, 10% to 50% predicted mortality, and 50% or greater predicted mortality. Analyses were conducted with SAS statistical software, version 9.3 (SAS Institute Inc).

Results

Of the 326 489 patients included in the analysis, 12 375 (3.8%) underwent cardiac surgery and 314 114 (96.2%) underwent NCS. Noncardiac surgery included vascular, orthopedic, abdominal, thoracic, otolaryngologic, gynecologic, urologic, ophthalmologic, plastic, oromaxillofacial, and neurosurgical operations. Overall, 141 185 patients (43.2%) received a β-blocker. Of the patients undergoing cardiac surgery, 8571 (69.3%) received a β-blocker, whereas only 132 614 (42.2%) of the patients undergoing NCS received one. **Table 1** presents the demographic data for all surgical patients. **Table 2** presents unadjusted mortality and risk-adjusted outcomes for all surgical patients and those who underwent cardiac and noncardiac surgery. The unadjusted 30-day mortality rates in patients undergoing NCS for those not receiving β-blockers with no cardiac risk factors, 1 to 2 cardiac risk factors, and 3 to 4 cardiac risk factors were 0.5%, 1.4%, and 6.7%, respectively. For those patients undergoing NCS who did receive β-blockers, the unadjusted 30-day mortality rates for those with no cardiac risk factors, 1 to 2 risk factors, and 3 to 4 risk factors were 1.0%, 1.7%, and 3.5%, respectively.

Table 2. 30-Day Unadjusted and Risk-Adjusted Mortality

Variable	Study Patients, %		
	All (N = 326 489)	Cardiac Surgery (n = 12 375)	Noncardiac Surgery (n = 314 114)
Unadjusted mortality	1.2	1.9	1.2
No β-blocker therapy			
0 Cardiac risk factors	0.6	4.1	0.5
1-2 Cardiac risk factors	1.5	2.6	1.4
3-4 Cardiac risk factors	4.5	2.5	6.7
β-Blocker therapy			
0 Cardiac risk factors	1.0	1.9	1.0
1-2 Cardiac risk factors	1.7	1.6	1.7
3-4 Cardiac risk factors	2.3	1.4	3.5
Predicted mortality			
<10%	98.3	97.9	98.3
10%-50%	1.6	2.0	1.6
≥50%	0.1	0.1	0.1

The second-level logistic regression analysis of the noncardiac surgery group revealed a significant interaction term between the number of cardiac risk factors and the use of β-blockers (P = .004) (**Table 3**). This finding indicates that the effect of β-blocker use on mortality varies significantly with the number of cardiac risk factors. **Figure 1** illustrates how the use of β-blockers on patients having NCS significantly decreases mortality as the number of cardiac risk factors increases. Among patients with no cardiac risk factors undergoing noncardiac surgery, those receiving β-blockers were 1.2 times more likely to die than those not receiving β-blockers (OR, 1.19; 95% CI, 1.06-1.35). Although the mortality risk decreased for those with 1 to 2 risk factors, the reduction was not significant (OR, 0.95; 95% CI, 0.87-1.03). However, for patients having noncardiac surgery with 3 to 4 cardiac risk factors, those receiving β-blockers were significantly less likely to die than those not receiving β-blockers (OR, 0.63; 95% CI, 0.43-0.93).

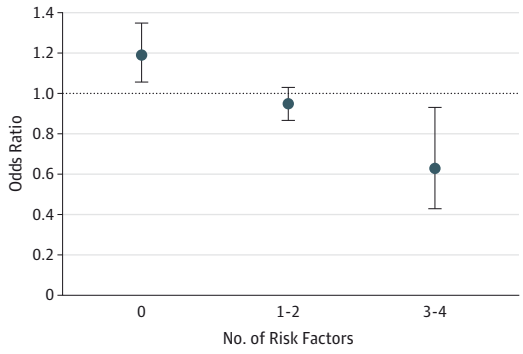
We did not see similar results in patients who underwent cardiac surgery. None of the terms in the second-level logistic regression analysis of the cardiac surgery group were significant (Table 3). In addition, the ORs revealed no consistent pattern of effect of β-blocker use on mortality with the number of cardiac risk factors (**Figure 2**).

Table 3. Second-Level Logistic Regression Analysis Results

Variable	All (N = 326 489)	Cardiac Surgery (n = 12 375)	Noncardiac Surgery (n = 314 114)
C statistic	0.87	0.72	0.87
HLGOF test (*P* value)	14.7 (.06)	5.5 (.70)	17.9 (.02)
Type 3 effects *P* value			
Risk-adjusted mortality	<.001	<.001	<.001
β-Blocker therapy	.005	.58	.005
Cardiac risk factors	.053	.69	.03
Cardiac risk factors × β-blocker	.004	.59	<.001
Odds ratio (95% CI) for β-blocker therapy vs no β-blocker therapy			
0 Cardiac risk factors	1.19 (1.05-1.35)	0.70 (0.20-2.49)	1.19 (1.0-1.35)
1-2 Cardiac risk factors	0.97 (0.89-1.05)	1.25 (0.90-1.73)	0.95 (0.87-1.03)
3-4 Cardiac risk factors	0.76 (0.56-1.03)	1.02 (0.62-1.68)	0.63 (0.43-0.93)

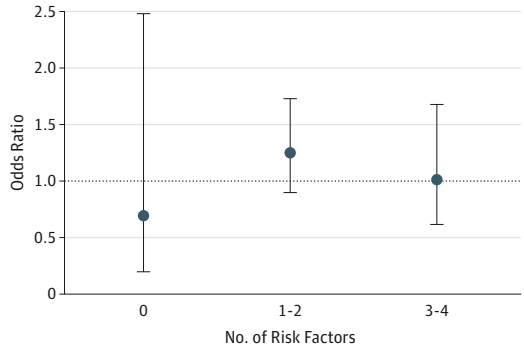
Abbreviation: HLGOF, Hosmer-Lemeshow goodness of fit.

Figure 1. Odds Ratios for Mortality Associated With the Use of β-Blockers in Noncardiac Surgery Stratified by Number of Cardiac Risk Factors



Error bars indicate 95% CIs.

Figure 2. Odds Ratios for Mortality Associated With the Use of β-Blockers in Cardiac Surgery Stratified by Number of Cardiac Risk Factors



Error bars indicate 95% CIs.

Discussion

After years of research, the use of perioperative β-blockade in NCS still remains uncertain for low-risk patients. As Eldrup-Jorgensen commented, "The irony of the beta blocker story is that there have been hundreds of studies, over nine randomized clinical trials, seven meta-analyses, and many editorial opinions and recommendations, yet we still lack clarity."[23(p 853)] Clinical investigations have swung from positive to negative, contradict one another, and have in some cases even been labeled as deceitful.

In the first RCT in 1996, Mangano et al[1] found a significant improvement in cardiac outcome with β-blockade 6 months and 2 years after NCS. The trial was criticized because of the exclusion of deaths in the immediate postoperative period, which, if included, would have negated the significance of the study. However, the American College of Medicine used the data to propose that β-blockers should be used perioperatively in all patients with possible coronary artery disease.[3] In 1999, Poldermans et al[2] reported on the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) trial, which consisted of 112 patients with clinical risk factors and a positive result on dobutamine echocardiogram who were randomized to β-blockade or placebo. The patients who received bisoprolol had such significant reductions in perioperative cardiac death and nonfatal myocardial infarction that the study was stopped prematurely. The data seemed so compelling that the vascular surgery community recommended perioperative β-blockers in all cases.[4] The Vascular Study Group of New England began an initiative promoting β-blockers in 2003.[23] However, despite the significantly increased use of β-blockers, there was no discernible effect on postoperative myocardial infarction rates or postoperative mortality.

In the mid-2000s, the results of several more RCTs were published that failed to confirm the positive results found by the DECREASE trial.[5-8] None of these studies found any improvement in survival or cardiac morbidity.

A 2005 retrospective multicenter analysis[9] of 782 969 patients who underwent NCS in 329 hospitals was the first study to look at β-blockade with a risk assessment tool, in this case, a variation of the RCRI, with 5 rather than 6 variables. Only in-hospital mortality was examined. The results indicated that in moderate- to high-risk patients (RCRI score >2) β-blocker therapy were clearly beneficial, but more importantly, in low-risk patients (RCRI scores of 0 or 1), there was no benefit and possible harm.

Most recently, a large RCT—the Perioperative Ischemia Study Evaluation (POISE) trial—negatively affected the use of perioperative β-blockade.[11] It enrolled 8351 patients from 190 hospitals in 23 countries during a 5-year period and was published in 2008. Patients were randomized to extended-release metoprolol or placebo 2 to 4 hours before surgery. Although fewer patients in the metoprolol group had a myocardial infarction than in the placebo group, there were significantly more strokes and deaths in the metoprolol group.

Of interest, significantly more patients undergoing β-blockade died of sepsis or infection. The investigators hypothesized that the hypotension from β-blockers could have predisposed patients to nosocomial infection and delayed the recognition of sepsis by preventing tachycardia. In the analysis of the POISE data, many critics believed that the dose of extended-release metoprolol used was higher than customary, which could explain the intraoperative bradycardia and hypotension seen in this study compared with previous RCTs. Of note, the trial excluded any patient who was taking a β-blocker preoperatively as a home medication.

In 2011, the argument for perioperative use of β-blockers was further questioned by the discovery that the data from the DECREASE family of trials—the original bedrock of evidence for the use of perioperative β-blockade—were no longer secure.[24,25] This led Bouri et al[25] to perform a meta-analysis of "secure" RCTs in 2013. Nine trials totaling 10 529 patients met their criteria. Initiation of a course of β-blockade before surgery caused a 27% risk increase in 30-day all-cause mortality (P = .04). In the "secure" trials, β-blockers reduced nonfatal myocardial infarction but increased stroke and hypotension, largely because this study was dominated by the POISE data. One of the conclusions of the paper was that the European Society of Cardiology should retract its perioperative β-blocker recommendations. Their most recent guidelines (2009) included the following Class I recommendations for β-blockers: (1) continuation in patients previously treated with them, (2) use in patients with known coronary artery disease or ischemia on preoperative testing, and (3) use in high-risk surgery.[26] These recommendations could be interpreted by many as a need to use β-blockade in many patients undergoing NCS, particularly those undergoing vascular surgery.

Cardiology guidelines for β-blockers in the United States have been modified significantly in the past decade. Most recently, the 2009 Class I guidelines recommended that therapy with β-blockers should be continued only in patients who already take them and included the statement, "In light of the POISE results, routine administration of perioperative beta blockade, particularly in higher fixed-dose regimens begun on the day of surgery, cannot be advocated."[27(p e68)]

Apart from the study by Lindenauer et al,[9] the only other multicenter analysis of the risk of perioperative β-blockade use in NCS is a recent VHA study of 136 745 patients, 55 138 (40.3%) of whom were exposed to therapy with β-blockers.[10] The study used VA Surgical Quality Improvement Program data and 6 cardiac risk factors. Similar to our study, patients underwent many different types of NCS. Also, as in our study, there was no distinguishing between acute or home use of the β-blocker or a dosage analysis. Perioperative β-blockade use was associated with lower rates of 30-day all-cause mortality in patients with 2 or more risk factors. The use of β-blockers in patients with no or one risk factor was not associated with mortality. By contrast, our analysis of a much larger number of patients revealed a significant risk from β-blockade in patients with no cardiac risk factors undergoing NCS.

We acknowledge several limitations to our study. First, being a VA population of patients, our patients were predominantly men. Second, the specific β-blocker administered to the patients was identified only by drug class rather than specific drug. Third, it is unclear whether the patient was first given the β-blocker in the hospital or if it was a home medication. Fourth, if the patient was first given a β-blocker in the hospital, it is unknown if it was given preoperatively or postoperatively. In addition, if given postoperatively, was it for treatment of a complication? Fifth, the causes of death and the number of strokes are unknown.

Conclusions

We believe that our hypothesis has been confirmed by this large generalizable, retrospective cohort study. β-Blockade is beneficial perioperatively for patients with 3 to 4 cardiac risk factors undergoing NCS but not in patients with 1 to 2 cardiac risk factors. Most important, the use of β-blockers in patients with no cardiac risk factors appears to be associated with a higher risk of death, which has, to our knowledge, not been previously reported.

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Study concept and design: Friedell, Van Way, Almenoff.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Friedell, Van Way, Freyberg, Almenoff.
Critical revision of the manuscript for important intellectual content: Friedell, Van Way, Almenoff.
Statistical analysis: Freyberg.
Administrative, technical, or material support: Van Way.
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