ORIGINAL ARTICLE

Perioperative Beta-Blocker Therapy and Mortality after Major Noncardiac Surgery

Peter K. Lindenauer, M.D., Penelope Pekow, Ph.D., Kaijun Wang, M.S., Dheeresh K. Mamidi, M.B., B.S., M.P.H., Benjamin Gutierrez, Ph.D., and Evan M. Benjamin, M.D.

ABSTRACT

BACKGROUND

Despite limited evidence from randomized trials, perioperative treatment with beta-blockers is now widely advocated. We assessed the use of perioperative beta-blockers and their association with in-hospital mortality in routine clinical practice.

METHODS

We conducted a retrospective cohort study of patients 18 years of age or older who underwent major noncardiac surgery in 2000 and 2001 at 329 hospitals throughout the United States. We used propensity-score matching to adjust for differences between patients who received perioperative beta-blockers and those who did not receive such therapy and compared in-hospital mortality using multivariable logistic modeling.

RESULTS

Of 782,969 patients, 663,635 (85 percent) had no recorded contraindications to beta-blockers, 122,338 of whom (18 percent) received such treatment during the first two hospital days, including 14 percent of patients with a Revised Cardiac Risk Index (RCRI) score of 0 and 44 percent with a score of 4 or higher. The relationship between perioperative beta-blocker treatment and the risk of death varied directly with cardiac risk; among the 580,665 patients with an RCRI score of 0 or 1, treatment was associated with no benefit and possible harm, whereas among the patients with an RCRI score of 2, 3, or 4 or more, the adjusted odds ratios for death in the hospital were 0.88 (95 percent confidence interval, 0.80 to 0.98), 0.71 (95 percent confidence interval, 0.63 to 0.80), and 0.58 (95 percent confidence interval, 0.50 to 0.67), respectively.

CONCLUSIONS

Perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk, patients undergoing major noncardiac surgery. Patient safety may be enhanced by increasing the use of beta-blockers in high-risk patients.

From the Division of Healthcare Quality, Baystate Medical Center, Springfield, Mass. (P.K.L., P.P., E.M.B.); the Department of Medicine, Tufts University School of Medicine, Boston (P.K.L., E.M.B.); the School of Public Health and Health Sciences, University of Massachusetts at Amherst, Amherst (P.P., K.W., D.K.M.); and Premier Healthcare Informatics, Premier Inc., Charlotte, N.C. (B.G.) Address reprint requests to Dr. Lindenauer at the Division of Healthcare Quality, Baystate Medical Center, 759 Chestnut St. P-5928, Springfield, MA 01199, or at Peter.Lindenauer@bhs.org.

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More than 20 million operations are performed annually at hospitals throughout the United States,[1] and although advances in operative and anesthetic techniques have reduced the risks associated with many procedures, some 1 in 10 patients can be expected to have a complication within 30 days after undergoing major surgery.[2] Although they occur infrequently, postoperative cardiovascular complications are associated with a substantial risk of other complications and death,[3,4] and preventing such complications is often the rationale for preoperative medical consultation.

Although the problem of postoperative myocardial infarction has been recognized for over 50 years,[5] few prevention measures have proven effective. Conventional strategies have relied on prediction instruments to identify patients at heightened cardiac risk,[6-9] noninvasive testing, cardiac catheterization followed by revascularization in selected patients, and careful perioperative monitoring. In the past decade, two influential randomized trials found that treatment with beta-blockers can decrease the incidence of myocardial infarction and death after noncardiac surgery.[10,11] Because they appear efficacious, are inexpensive, and have few risks, beta-blockers are now widely advocated.[12-16] In *Making Health Care Safer*, the Agency for Healthcare Research and Quality identified the perioperative use of beta-blockers among intermediate- and high-risk patients as one of the nation's "clear opportunities for safety improvement."[17] The National Quality Forum subsequently placed the use of beta-blockers among high-risk surgical patients on its list of 30 *Safe Practices for Better Healthcare*.[18] Yet, two recent randomized trials[19-21] reported no benefit from perioperative beta-blocker therapy and raised questions about the generalizability of earlier studies. While awaiting the results of large randomized trials,[22] we evaluated the use and effectiveness of perioperative beta-blocker therapy in routine clinical practice.

METHODS

SETTING AND SUBJECTS

We conducted a retrospective cohort study using data from 329 hospitals that participate in Premier's Perspective, a database developed for measuring quality and use of health care. Participating hospitals represent all regions of the United States, are predominantly small-to-mid-size nonteaching facilities, and serve a largely urban patient population. In addition to the information available in the standard hospital-discharge file, the Perspective database contains a date-stamped log of all billed items, including medications and laboratory, diagnostic, and therapeutic services, for each patient.

Patients were included in our database if they were 18 years of age or older and had undergone major noncardiac surgery between January 1, 2000, and December 31, 2001. Surgical procedures were categorized with the use of APR-DRG software (version 15.0, 3M) and, on the basis of prior studies, were considered major if the median length of stay for patients in a given diagnosis-related group exceeded two days.[9] Patients undergoing obstetrical procedures were excluded. Permission to conduct the study was granted by the institutional review board at Baystate Medical Center, where the study was conducted, and the need for written informed consent was waived.

DATA ELEMENTS

For each patient, we noted the type of surgery, whether the admission was elective or emergency, and the hospital at which the operation took place. In addition to age, sex, and race or ethnic group, we recorded the presence or absence of known ischemic heart disease, congestive heart failure, cerebrovascular disease, hypertension, renal insufficiency, diabetes, and hyperlipidemia. The presence or absence of coexisting conditions was assessed with the use of the secondary diagnoses of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). Furthermore, we considered a patient to have diabetes if there was a secondary diagnosis of diabetes mellitus or if the patient received treatment with an oral hypoglycemic agent during the hospitalization. In a secondary analysis, we expanded our definition of diabetes to include patients who were treated with insulin whether or not they received oral hypoglycemic agents or had a documented diagnosis of diabetes.

Perioperative administration of angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, antiplatelet agents, lipid-lowering medications, loop diuretics, thiazide diuretics, antiarrhythmic agents, and dopamine or dobutamine was assessed with the use of pharmacy records. Information on prophylactic antibiotic administration and the use of pharmacologic and mechanical measures for the prevention of venous thromboembolism was gathered simi-

Table 1. Characteristics of Patients Undergoing Major Noncardiac Surgery without Known Contraindications to Beta-Blockers, According to Whether They Received Beta-Blockers Perioperatively.*

Characteristic	All Patients (N=663,635)	Patients Given Beta-Blockers (N=122,338)	Patients Not Given Beta-Blockers (N=541,297)†	Rate of Use of Beta-Blockers	Odds Ratio for Perioperative Treatment (95% CI)
				%	
Age					
Median — yr	62	68	60		
Interquartile range	47–74	56–76	46–73		
<65 yr — no. (%)‡	359,282 (54)	50,507 (41)	308,775 (57)	14.1	1.00
≥65 yr — no. (%)	304,353 (46)	71,831 (59)	232,522 (43)	23.6	1.89 (1.87–1.91)
Sex — no. (%)§					
Male‡	304,795 (46)	57,381 (47)	247,414 (46)	18.8	1.00
Female	358,824 (54)	64,954 (53)	293,870 (54)	18.1	0.95 (0.94–0.97)
Race or ethnic group — no. (%)¶					
White‡	449,765 (68)	85,153 (70)	364,612 (67)	18.9	1.00
Black	71,587 (11)	13,490 (11)	58,097 (11)	18.8	0.99 (0.97–1.01)
Hispanic	26,203 (4)	4,122 (3)	22,081 (4)	15.7	0.80 (0.77–0.83)
Asian	9,696 (1)	1,528 (1)	8,168 (2)	15.8	0.80 (0.76–0.85)
Other or American Indian	106,384 (16)	18,045 (15)	88,339 (16)	17.0	0.87 (0.86–0.89)
Medical history — no. (%)					
Hypertension	255,498 (38)	77,366 (63)	178,132 (33)	30.3	3.51 (3.46–3.55)
Diabetes‖	113,425 (17)	30,323 (25)	83,102 (15)	26.7	1.82 (1.79–1.84)
Diabetes (expanded definition)**	137,919 (21)	35,307 (29)	102,612 (19)	25.6	1.73 (1.71–1.76)
Ischemic heart disease	86,171 (13)	35,352 (29)	50,819 (9)	41.0	3.92 (3.86–3.98)
Renal insufficiency	26,377 (4)	8,224 (7)	18,153 (3)	31.2	2.08 (2.02–2.13)
Hyperlipidemia	31,535 (5)	9,726 (8)	21,809 (4)	30.8	2.06 (2.01–2.11)
Cerebrovascular disease	8,947 (1)	3,089 (3)	5,858 (1)	34.5	2.37 (2.27–2.47)
Type of procedure — no. (%)					
Vascular‡	51,095 (8)	15,793 (13)	35,302 (7)	30.9	1.00
Orthopedic	245,571 (37)	47,035 (38)	198,536 (37)	19.2	0.53 (0.52–0.54)
Abdominal	222,268 (33)	33,700 (28)	188,568 (35)	15.2	0.40 (0.39–0.41)
Thoracic	47,730 (7)	10,317 (8)	37,413 (7)	21.6	0.62 (0.60–0.63)
Other	96,971 (15)	15,493 (13)	81,478 (15)	16.0	0.43 (0.41–0.44)
Type of admission — no. (%)					
Elective‡	343,718 (52)	66,159 (54)	277,559 (51)	19.2	1.00
Urgent	115,871 (17)	21,380 (17)	94,491 (17)	18.5	0.95 (0.93–0.97)
Emergency	204,046 (31)	34,799 (28)	169,247 (31)	17.1	0.86 (0.85–0.88)
RCRI score — no. (%)††					
0‡	329,171 (50)	47,261 (39)	281,910 (52)	14.4	1.00
1	251,494 (38)	47,116 (39)	204,378 (38)	18.7	1.38 (1.36–1.39)
2	67,955 (10)	21,972 (18)	45,983 (8)	32.3	2.85 (2.80–2.90)
3	13,744 (2)	5,433 (4)	8,311 (2)	39.5	3.90 (3.76–4.04)
≥4	1,271 (<1)	556 (<1)	715 (<1)	43.7	4.64 (4.15–5.18)

Table 1. (Continued.)

Characteristic	All Patients (N=663,635)	Patients Given Beta-Blockers (N=122,338)	Patients Not Given Beta-Blockers (N=541,297)†	Rate of Use of Beta-Blockers	Odds Ratio for Perioperative Treatment (95% CI)
				%	
Expanded RCRI score — no. (%)‡‡					
0‡	317,969 (48)	45,239 (37)	272,730 (50)	14.2	1.00
1	251,612 (38)	46,932 (38)	204,680 (38)	18.7	1.38 (1.36–1.40)
2	76,983 (12)	23,488 (19)	53,495 (10)	30.5	2.65 (2.60–2.70)
3	15,655 (2)	6,060 (5)	9,595 (2)	38.7	3.81 (3.68–3.93)
≥4	1,416 (<1)	619 (<1)	797 (<1)	43.7	4.68 (4.21–5.20)
High-risk surgery — no. (%)	198,826 (30)	32,603 (27)	166,223 (31)	16.4	0.82 (0.81–0.83)
Type of insurance — no. (%)					
Medicare‡	300,135 (45)	69,949 (57)	230,186 (43)	23.3	1.00
Private	267,131 (40)	40,848 (33)	226,283 (42)	15.3	0.59 (0.58–0.60)
Medicaid	35,175 (5)	4,705 (4)	30,470 (6)	13.4	0.51 (0.49–0.52)
Uninsured	24,467 (4)	2,100 (2)	22,367 (4)	8.6	0.31 (0.30–0.32)
Other	36,727 (6)	4,736 (4)	31,991 (6)	12.9	0.49 (0.47–0.50)
Medications — no. (%)					
Antibiotics	405,622 (61)	77,737 (64)	327,885 (61)	19.2	1.13 (1.12–1.15)
DVT prophylaxis					
Pharmacologic	227,364 (34)	53,670 (44)	173,694 (32)	23.6	1.65 (1.63–1.68)
Mechanical	240,160 (36)	46,270 (38)	193,890 (36)	19.3	1.09 (1.08–1.10)
Lipid-lowering agents	62,221 (9)	25,170 (21)	37,051 (7)	40.4	3.53 (3.46–3.59)
Calcium-channel blockers	89,476 (13)	27,923 (23)	61,553 (11)	31.2	2.31 (2.27–2.34)
ACE inhibitor	76,382 (12)	25,522 (21)	50,860 (9)	33.4	2.54 (2.50–2.58)
Antiplatelet agents	65,923 (10)	23,574 (19)	42,349 (8)	35.8	2.81 (2.76–2.86)
Loop diuretics	76,084 (11)	23,896 (20)	52,188 (10)	31.4	2.28 (2.24–2.31)
Angiotensin-receptor blockers	18,613 (3)	6,365 (5)	12,248 (2)	34.2	2.37 (2.30–2.45)
Thiazide	21,625 (3)	7,304 (6)	14,321 (3)	33.8	2.34 (2.27–2.40)
Antiarrhythmic	6,650 (1)	2,169 (2)	4,481 (1)	32.6	2.16 (2.05–2.28)
Dopamine or dobutamine	14,815 (2)	4,101 (3)	10,714 (2)	27.7	1.72 (1.66–1.78)
Type of hospital — no. (%)					
Nonteaching‡	521,470 (79)	93,142 (76)	428,328 (79)	17.9	1.00
Teaching	142,165 (21)	29,196 (24)	112,969 (21)	20.5	1.19 (1.17–1.21)
No. of beds in hospital — no. (%)					
1–200‡	87,640 (13)	13,089 (11)	74,551 (14)	14.9	1.00
201–400	225,809 (34)	41,050 (34)	184,759 (34)	18.2	1.27 (1.24–1.29)
401–600	180,622 (27)	33,653 (28)	146,969 (27)	18.6	1.30 (1.28–1.33)
601–800	119,065 (18)	22,323 (18)	96,742 (18)	18.8	1.31 (1.28–1.35)
801–1000	50,499 (8)	12,223 (10)	38,276 (7)	24.2	1.82 (1.77–1.87)

Table 1. (Continued.)

Characteristic	All Patients (N=663,635)	Patients Given Beta-Blockers (N=122,338)	Patients Not Given Beta-Blockers (N=541,297)†	Rate of Use of Beta-Blockers	Odds Ratio for Perioperative Treatment (95% CI)
				%	
Region — no. (%)					
South‡	373,033 (56)	69,563 (57)	303,470 (56)	18.7	1.00
Northeast	45,065 (7)	9,806 (8)	35,259 (7)	21.8	1.21 (1.18–1.24)
Midwest	160,397 (24)	30,577 (25)	129,820 (24)	19.1	1.03 (1.01–1.04)
West	85,140 (13)	12,392 (10)	72,748 (13)	14.6	0.74 (0.73–0.76)
Population served by hospital — no. (%)					
Rural‡	111,078 (17)	18,917 (15)	92,161 (17)	17.0	1.00
Urban	552,557 (83)	103,421 (85)	449,136 (83)	18.7	1.12 (1.10–1.14)
In-hospital mortality — no. (%)	13,454 (2)	2,839 (2)	10,615 (2)	21.1	
Length of stay — days					
Median	5	5	5		
Interquartile range	3–8	3–8	3–8		
Cost — $					
Median	8,537	9,419	8,333		
Interquartile range	5,472–13,236	6,182–14,411	5,332–12,956		

* CI denotes confidence interval, RCRI Revised Cardiac Risk Index, DVT deep venous thrombosis, and ACE angiotensin-converting enzyme.
† Patients who received beta-blockers after the second hospital day were included in the group that did not receive beta-blockers.
‡ This group served as the reference group.
§ Information about sex was missing for 16 patients.
¶ Race or ethnic group was self-assigned.
‖ Diabetes was defined on the basis of the secondary diagnoses of the ICD-9-CM code or the in-hospital use of an oral hypoglycemic agent.
** The expanded definition of diabetes was based on the secondary diagnoses of the ICD-9-CM code or the in-hospital use of an oral hypoglycemic agent or insulin.
†† The primary definition of diabetes was used.
‡‡ The expanded definition of diabetes was used.

larly. Data on in-hospital mortality, length of stay, and costs were obtained from the Perspective discharge file. In addition to information related to the admission, we noted each hospital's size, teaching status, and geographic location and whether it was urban or rural.

Adapting a classification scheme developed by Lee and colleagues, we calculated a Revised Cardiac Risk Index (RCRI) score for each patient, assigning one point for each of the following risk factors: high-risk surgery, ischemic heart disease, cerebrovascular disease, renal insufficiency, and diabetes mellitus.[9] The category of high-risk surgery included all intrathoracic, intraperitoneal, and suprainguinal vascular procedures. Patients were excluded if they had received a secondary diagnosis that could be considered a contraindication to beta-blocker therapy; these included bradycardia, heart block, heart failure, hypotension, chronic obstructive pulmonary disease, and asthma.

USE OF BETA-BLOCKERS

We identified whether a beta-blocker had been administered either orally or intravenously at any time during the hospitalization, and if so, the date the medication was first administered. Because we lacked information about the date of the principal procedure as well as the goals of the ordering physicians, we considered a patient to have received beta-blocker therapy for prophylaxis, whether intentionally or not, if the first record of treatment occurred on the first or second hospital day. Patients who had treatment initiated on the third hospital day or later were grouped with those who did not receive a beta-blocker during the hospitalization, since this former group may have had therapy pre-

Table 2. Characteristics of the 329 Hospitals.*

Characteristic	Hospitals (N=329)	Patients (N=663,635)	Mortality Rate	Rate of Use of Beta-Blockers
	number (percent)		*percent*	
Type of hospital				
Nonteaching	296 (90)	521,470 (79)	1.7±1.0	16.0±7.0
Teaching	33 (10)	142,165 (21)	4.1±10.5	18.4±8.0
No. of beds in hospital				
1–200	134 (41)	87,640 (13)	1.5±1.2	13.9±7.7
201–400	112 (34)	225,809 (34)	1.9±0.8	17.6±5.7
401–600	54 (16)	180,622 (27)	2.3±0.7	17.7±6.9
601–800	23 (7)	119,065 (18)	4.9±12.5	18.3±5.6
801–100	6 (2)	50,499 (8)	2.1±0.5	23.9±7.6
Region				
South	176 (53)	373,033 (56)	2.2±4.6	16.5±6.2
Midwest	76 (23)	160,397 (24)	1.6±0.9	17.5±8.3
West	56 (17)	85,140 (13)	1.7±1.1	12.8±6.4
Northeast	21 (6)	45,065 (7)	2.0±1.3	19.4±8.2
Population served				
Urban	224 (68)	552,557 (83)	2.2±4.2	17.0±7.0
Rural	105 (32)	111,078 (17)	1.6±0.9	14.7±7.1

* Plus–minus values are means ±SD.

scribed for the treatment of complications rather than for their prevention.

STATISTICAL ANALYSIS

Summary statistics were constructed with the use of frequencies and proportions for categorical data and means, medians, and interquartile ranges for continuous variables. We compared the characteristics of patients who received perioperative beta-blocker therapy during the first two hospital days with those who did not receive beta-blockers during the first two days. Chi-square and z tests were used to assess the relationship between treatment with beta-blockers and the risk of death in the hospital and any potential confounders.

We created a nonparsimonious logistic-regression model to derive a propensity score for early treatment with beta-blockers that included all patient and hospital characteristics as well as selected interaction terms. Each patient was assigned a propensity score that reflected the probability that they would receive early treatment. Using a Greedy 5-to-1 digit-matching algorithm,[23] we matched each patient who received perioperative beta-blocker therapy with up to two patients who did not receive this therapy, starting with all five-digit propensity-score matches before moving to those with four or fewer matches, in an iterative process. These matching techniques were used to reduce bias introduced by incomplete or inexact matching.

The matched cohort was evaluated for differences between treatment groups in each of the potential confounding factors, and conditional logistic regression was used to assess the effect of beta-blockers on the risk of death in the hospital, after adjustment for any residual differences (given a P value of less than 0.01). Using both the matched and entire study cohorts, we examined the association between beta-blocker therapy and the risk of death in the hospital among patients on the basis of the RCRI score. In addition, in the entire study cohort we evaluated models for selected subpopulations, including patients with hypertension and an RCRI score of 0 and patients with an RCRI score of 1 and each of the individual RCRI factors. Interactions between beta-blocker treatment and unbal-

anced covariates were also evaluated for each model and retained if the resulting P value was less than 0.05. The Hosmer–Lemeshow goodness-of-fit test and the area under the curve were used to assess the fit of the model. All analyses were carried out with the use of SAS software (version 9.1).

RESULTS

A total of 782,969 patients 18 years of age or older underwent major noncardiac surgery during the study period. Among this group, 119,334 (15 percent) had one or more documented potential contraindications to beta-blockade. Thus, 663,635 patients appeared to be eligible for perioperative treatment with beta-blockers. The median age was 62 years; slightly more than half were women, and two thirds were white (Table 1). Hypertension, diabetes, and ischemic heart disease were the most common coexisting conditions. Fifty percent had an RCRI score of 0, and 38 percent had an RCRI score of 1.

In the secondary analysis, using the expanded definition of diabetes, we identified an additional 4 percent of the population as having this diagnosis; the additional patients classified as having diabetes shifted RCRI scores upward slightly. Orthopedic and abdominal operations accounted for 70 percent of procedures, 30 percent of the procedures were categorized as high risk, and just over half the admissions were elective. The median length of stay was five days. Overall, 13,454 eligible patients (2.0 percent) died during the hospitalization: 2839 of the 122,338 patients who received early treatment with beta-blockers (2.3 percent) and 10,615 of the 541,297 patients who did not receive beta-blockers or received them after the second hospital day (2.0 percent, P<0.001).

The majority of participating hospitals were in the South. Seventy-five percent had a capacity of 400 beds or less, 90 percent were nonteaching facilities, and 68 percent were in urban areas (Table 2).

USE OF BETA-BLOCKERS AMONG PATIENTS UNDERGOING MAJOR NONCARDIAC SURGERY

Of the 663,635 eligible patients, 122,338 (18 percent) received a beta-blocker on the first or second day of the hospitalization. Women were less likely than men to receive beta-blockers, and Hispanics, Asians, and other racial or ethnic groups were treated less frequently than whites and blacks (Table 1). A history of ischemic heart disease, a higher RCRI score, and hypertension were the characteristics most strongly associated with beta-blocker treatment. Treatment rates ranged from 14 percent among patients with an RCRI score of 0 to 44 percent among those with a score of 4 or higher. Patients whose operations were scheduled electively had higher rates of beta-blocker use than those whose procedures were classified as urgent or emergency, and patients who underwent vascular surgery were more likely to receive beta-blockers than were those undergoing other types of procedures. Hospitals located in the Northeast that served urban populations, had a bed capacity of at least 200, and were designated teaching hospitals were more likely to deliver beta-blocker therapy than were other types of hospitals.

BETA-BLOCKER THERAPY AND IN-HOSPITAL MORTALITY

Sixteen patients were excluded from multivariable modeling owing to missing data. We successfully matched 119,632 patients (98 percent) who received a beta-blocker in the early perioperative period with at least 1 patient who did not receive a beta-blocker or received it after the second hospital day (79 percent with two matches and 19 percent with one match) on the basis of the propensity score. In this propensity-matched cohort (Table 3), 2790 of 119,632 patients treated with beta-blockers died, as compared with 5123 of 216,290 patients who did not receive such therapy or who received it after the second hospital day (2.3 percent vs. 2.4 percent; match-adjusted odds ratio, 0.99; 95 percent confidence interval, 0.95 to 1.04; P=0.68).

The preoperative RCRI score significantly modified the association between beta-blocker treatment and the risk of death in the hospital. Among the subgroup of patients included in the propensity analysis, early beta-blocker treatment was associated with a reduced risk of death among patients with scores of 3 or higher (Fig. 1), with odds ratios ranging from 1.43 (95 percent confidence interval, 1.29 to 1.58) among patients in the lowest RCRI category to 0.57 (95 percent confidence interval, 0.42 to 0.76) among those with an RCRI score of 4 or higher.

Similar results were observed in the entire study cohort, except that a significant benefit of treatment was also observed among patients with an RCRI score of 2 (Fig. 1). In a subgroup analysis of patients who had an RCRI score of 0 and hypertension, the odds ratio of death in the hospital was

Table 3. Characteristics of the Patients Who Received Beta-Blockers Perioperatively and Those Who Did Not Receive Such Therapy in the Propensity-Matched Cohort.*

Characteristic	Beta-Blockers (N=119,632)	No Beta-Blockers (N=216,290)	P Value
Age — yr			<0.001
Median	68	68	
Interquartile range	56–76	57–77	
Female sex — no. (%)	63,866 (53)	118,034 (55)	<0.001
Race or ethnic group — no. (%)			0.003
White	83,130 (69)	148,946 (69)	
Black	13,234 (11)	24,583 (11)	
Hispanic	4,038 (3)	7,338 (3)	
Asian	1,503 (1)	2,692 (1)	
Other or American Indian	17,727 (15)	32,731 (15)	
Medical history — no. (%)			
Hypertension	74,743 (62)	132,691 (61)	<0.001
Diabetes	29,128 (24)	50,303 (23)	<0.001
Ischemic heart disease	32,793 (27)	44,600 (21)	<0.001
Renal insufficiency	7,861 (7)	13,291 (6)	<0.001
Hyperlipidemia	9,198 (8)	14,439 (7)	<0.001
Cerebrovascular disease	2,846 (2)	4,329 (2)	<0.001
Type of procedure — no. (%)			<0.001
Orthopedic	46,253 (39)	85,657 (40)	
Abdominal	33,297 (28)	62,388 (29)	
Thoracic	10,004 (8)	17,630 (8)	
Vascular	14,913 (12)	23,629 (11)	
Other	15,165 (13)	26,986 (12)	
Type of admission — no. (%)			0.888
Elective	64,610 (54)	116,996 (54)	
Urgent	20,885 (17)	37,719 (17)	
Emergency	34,137 (29)	61,575 (28)	
RCRI score — no. (%)			<0.001
0	47,216 (39)	94,700 (44)	
1	46,121 (39)	81,231 (38)	
2	20,825 (17)	32,413 (15)	
3	4,996 (4)	7,264 (3)	
≥4	474 (0.4)	682 (<1)	
High-risk surgery — no. (%)	32,035 (27)	58,067 (27)	0.666
Type of insurance — no. (%)			0.001
Medicare	68,295 (57)	124,351 (57)	
Private	39,958 (33)	71,928 (33)	
Medicaid	4,610 (4)	8,215 (4)	
Uninsured	2,086 (2)	3,392 (2)	
Other	4,683 (4)	8,404 (4)	

Table 3. (Continued.)

Characteristic	Beta-Blockers (N=119,632)	No Beta-Blockers (N=216,290)	P Value
Medications — no. (%)†			
Antibiotics	76,026 (64)	137,844 (64)	<0.001
VTE prophylaxis			
Pharmacologic	51,978 (43)	91,444 (42)	<0.001
Mechanical	45,433 (38)	84,459 (39)	<0.001
Lipid-lowering agents	22,989 (19)	31,350 (14)	<0.001
Calcium-channel blockers	26,767 (22)	45,330 (21)	<0.001
ACE inhibitor	24,202 (20)	39,565 (18)	<0.001
Antiplatelet agents	21,794 (18)	31,508 (15)	<0.001
Loop diuretics	22,632 (19)	36,220 (17)	<0.001
Angiotensin-receptor blockers	6,027 (5)	9,712 (4)	<0.001
Thiazide diuretics	6,988 (6)	11,705 (5)	<0.001
Antiarrhythmic agents	2,061 (2)	3,244 (1)	<0.001
Dopamine or dobutamine	3,923 (3)	6,555 (3)	<0.001
Type of hospital — no. (%)			0.002
Nonteaching	91,323 (76)	166,140 (77)	
Teaching	28,309 (24)	50,150 (23)	
No. of beds in hospital — no. (%)			<0.001
1–200	12,975 (11)	24,549 (11)	
201–400	40,219 (34)	72,698 (34)	
401–600	32,903 (28)	59,367 (27)	
601–800	21,873 (18)	39,988 (18)	
801–1000	11,662 (10)	19,688 (9)	
Region — no. (%)			<0.001
South	67,921 (57)	122,722 (57)	
Midwest	29,947 (25)	53,876 (25)	
West	12,287 (10)	23,087 (11)	
Northeast	9,477 (8)	16,605 (8)	
Population served — no. (%)			0.018
Urban	101,035 (84)	181,994 (84)	
Rural	18,597 (16)	34,296 (16)	
In-hospital mortality — no. (%)	2,790 (2)	5,123 (2)	0.505
Length of stay — days			0.004
Median	5	5	
Interquartile range	3–8	3–8	
Cost — $			<0.001
Median	9,404	9,082	
Interquartile range	6,769–14,389	6,019–13,703	

* The propensity-matched cohort consisted of 119,632 patients who had received a beta-blocker perioperatively, each of whom was matched with either 1 or 2 patients who had not received such therapy. Analyses used the primary definition of diabetes mellitus. Patients who received beta-blockers after the second hospital day were included in the group that did not receive beta-blockers.

† VTE denotes venous thromboembolism, RCRI Revised Cardiac Risk Index, and ACE angiotensin-converting enzyme.

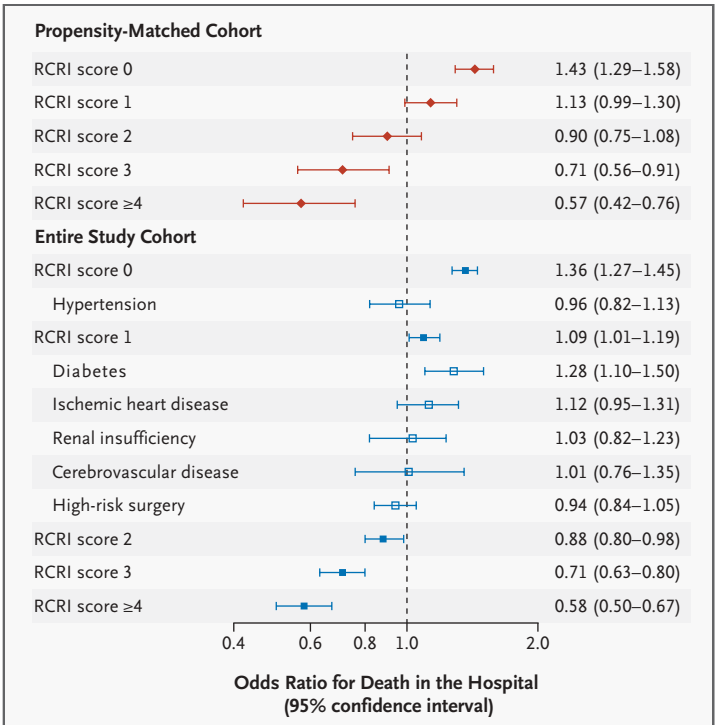

Figure 1. Adjusted Odds Ratio for In-Hospital Death Associated with Perioperative Beta-Blocker Therapy among Patients Undergoing Major Noncardiac Surgery, According to the RCRI Score and the Presence of Other Risk Factors in the Propensity-Matched Cohort and the Entire Study Cohort.

Open boxes represent patient subgroups within the listed RCRI category.

0.96 (95 percent confidence interval, 0.82 to 1.13) among those who received beta-blockers early, as compared with those who did not receive them. Furthermore, among patients with an RCRI score of 1, we found no reduction in the risk of death in the hospital related to beta-blocker use in any subpopulation. On the basis of these results, the number needed to treat to prevent a single death in the hospital was 33 among those at highest risk, whereas, in instances in which the risk was increased with beta-blocker use, the number needed to harm (i.e., the number of patients who would need to be treated for a single death in the hospital to occur) was 208 among the lowest-risk patients, who were least likely to receive treatment with beta-blockers (Table 4).

In a secondary analysis, using the expanded definition of diabetes, we observed generally similar results; however, the benefits of beta-blocker therapy were attenuated and were no longer significant for patients with an RCRI score of 2 (results are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

DISCUSSION

Although evidence from randomized trials remains limited, the treatment of surgical patients with beta-blockers has been championed by clinicians and policymakers for its potential to enhance patient safety. In this large observational study, the perioperative administration of beta-blockers was associated with clear and clinically significant reductions in mortality among the 2 percent of surgical patients at highest risk (those with an RCRI score of 3 or greater) and appeared to be beneficial in the 10 percent of patients with an RCRI score of 2, but was of no benefit — and was possibly harmful — among patients in the lowest risk categories (those with an RCRI score of 0 or 1). Our observation that only a minority of patients at highest risk received beta-blockers underscores the Agency for Healthcare Research and Quality's statement that perioperative use of beta-blockade represents a clear opportunity for safety improvement.[17]

Two randomized trials have shown that the use of beta-blockers decreases the risk of death among surgical patients. The Multicenter Study of Perioperative Ischemia Research Group[10] randomly assigned 200 male veterans with known coronary artery disease or two or more coronary risk factors to receive atenolol or placebo before undergoing major noncardiac surgery and reported that within several months after discharge, treated patients had a significant survival advantage. Poldermans et al.[11] randomly assigned 112 patients with abnormal stress echocardiograms to receive bisoprolol or placebo before and after vascular surgery and found a marked reduction in the risk of myocardial infarction and death during hospitalization and at 30 days postoperatively.

Two recently completed trials have, however, raised questions about the generalizability of the earlier studies. In the first, patients undergoing vascular surgery who were randomly assigned to receive metoprolol had rates of major cardiovascular complications or death from cardiac causes at 30 days that were similar to the rates among those who received placebo.[19] In the second, 921 patients with diabetes who were randomly assigned to receive metoprolol or placebo[20,21] had similar rates of a composite end point of death from any cause or major cardiovascular complications after a median follow-up of 18 months. It is unclear whether the lack of benefit in these recent trials can be explained by differences in treatment protocols or by lower-than-expected rates of events, which would

Table 4. Rates and Risks of In-Hospital Death and the Numbers Needed to Treat and to Harm among Patients in the Entire Study Cohort Who Did Not Receive Perioperative Beta-Blockade, According to the RCRI Score and the Presence of Individual Risk Factors.*

Subgroup	Mortality Rate	Odds Ratio (95% CI)	No. Needed to Treat (95% CI)	No. Needed to Harm (95% CI)
	%			
RCRI score, 0				
All patients	1.4	1.36 (1.27–1.45)	—	208 (276–164)
Patients with hypertension	1.2	0.96 (0.82–1.13)	2349 (496–637)†	
RCRI score, 1				
All patients	2.2	1.09 (1.01–1.19)		504 (4937–256)
Patients with diabetes	1.7	1.28 (1.10–1.50)		209 (583–117)
Patients with ischemic heart disease	2.0	1.12 (0.95–1.31)		408 (975–158)‡
Patients with cerebrovascular disease	9.0	1.03 (0.82–1.23)		410 (67–54)‡
Patients with renal insufficiency	7.2	1.01 (0.76–1.35)		1505 (62–44)‡
Patients undergoing high-risk surgery	2.0	0.94 (0.84–1.05)	864 (323–1039)†	
RCRI score, 2				
All patients	3.9	0.88 (0.80–0.98)	227 (132–1091)	
RCRI score, 3				
All patients	5.8	0.71 (0.63–0.80)	62 (48–92)	
RCRI score, ≥4				
All patients	7.4	0.58 (0.50–0.67)	33 (28–42)	

* Analyses used the primary definition of diabetes. Results using the expanded definition of diabetes are provided in the Supplementary Appendix. The number needed to treat is the number of patients who would need to be treated to prevent one death; the number needed to harm is the number of patients who would need to be treated for one death to occur. CI denotes confidence interval.
† The upper limit of the confidence interval is actually the number needed to harm.
‡ The lower limit of the confidence interval is actually the number needed to treat.

have reduced the statistical power of the studies to detect a moderate effect of treatment.

By evaluating the effect of beta-blocker therapy in a diverse population undergoing a wide variety of surgical procedures at more than 300 hospitals throughout the United States, our results extend the findings from these earlier studies and provide support for the perioperative use of beta-blockers in high-risk patients, while we await the results of a large, ongoing, randomized trial.[22] Yet the lack of benefit of this approach in moderate-risk patients and the potential harm of this approach in the lowest-risk groups suggest that careful patient selection remains necessary.

Our study has some limitations. First, treatment with beta-blockers was not based on random assignment, and results may be confounded by other variables. Although we used rigorous statistical methods to adjust for baseline differences between patients, including propensity-score matching and stratification, the retrospective nature of the study meant that our ability to control for differences was limited to variables for which data were available. Furthermore, because we relied on claims data, the ascertainment of coexisting conditions and potential contraindications to beta-blocker treatment was dependent on physicians' documentation and hospitals' coding practices. Although previous studies have validated the use of administrative data for these purposes,[24,25] they also suggest that we may have underestimated the prevalence of some coexisting conditions. We noted that a substantially greater number of patients were classified as having diabetes when we added insulin use as a diag-

nostic criterion in the absence of an ICD-9-CM code for diabetes. Insofar as we underestimated the prevalence of coexisting conditions, our effect estimates among lower-risk patients may be overly optimistic, whereas the percentage of the population that might actually benefit from beta-blockers could be larger than the 2 to 12 percent we forecast.

An additional limitation was that our study was restricted to the period of hospitalization. We did not have access to information about the use of beta-blockers before admission or after discharge and were unable to report 30-day or 1-year mortality rates. Nevertheless, other trials of perioperative beta-blocker therapy have used protocols in which treatment was begun only hours before surgery and have generally relied on longer-term outcomes because they have been statistically underpowered to detect short-term differences.[10,19-21] Furthermore, we presumed that patients who were treated with a beta-blocker on the first or second hospital day were given the drug for prophylaxis; however, it is likely that some of these patients were actually given beta-blockers for the treatment of postoperative ischemia or infarction. Such misclassification was more likely among the lowest-risk patients, who were least likely to receive prophylaxis. To the extent that we misclassified patients in this way, our results would underestimate the effectiveness of beta-blocker therapy or would incorrectly suggest that beta-blockers were harmful.

Without access to patients' charts, we could not determine the effect of beta-blocker treatment on heart rates before, during, or after surgery. Finally, because administrative data are not a reliable source of information about postoperative cardiovascular complications,[26] we were unable to report the incidence of ischemia or infarction.

We found that perioperative administration of beta-blockers was associated with a reduced risk of death in the hospital among high-risk patients undergoing major noncardiac surgery. Thus, until the results of large randomized trials become available, ongoing national efforts to increase patient safety by increasing the perioperative use of beta-blockers among high-risk patients appear warranted.

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