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Association of the Pattern of Use of Perioperative β-Blockade and Postoperative Mortality

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ABSTRACT

Background: The 1996 atenolol study provided evidence that perioperative β-adrenergic receptor blockade (β-blockade) reduced postsurgical mortality. In 1998, the indications for perioperative β-blockade were codified as the Perioperative Cardiac Risk Reduction protocol and implemented at the San Francisco Veterans Administration Medical Center, San Francisco, California. The present study analyzed the association of the pattern of use of perioperative β-blockade with perioperative mortality since introduction of the Perioperative Cardiac Risk Reduction protocol.

Methods: Epidemiologic analysis of the operations undertaken since 1996 at the San Francisco Veterans Administration Medical Center was performed. The pattern of use of perioperative β-blockade was divided into four groups: *None*, *Addition*, *Withdrawal*, and *Continuous*. Logistic regression, survival analysis, and propensity analysis were performed.

Results: A total of 38,779 operations were performed between 1996 and 2008. In patients meeting Perioperative Cardiac Risk Reduction indications for perioperative β-blockade, *Addition* is associated with a reduction in 30-day (odds ratio [OR], 0.52; 95% confidence interval [CI], 0.33 to 0.83; $P = 0.006$) and 1-yr mortality (OR, 0.64; 95%, CI 0.51 to 0.79; $P < 0.0001$). *Continuous* is associated with a reduction in 30-day (OR, 0.68; 95% CI, 0.47 to 0.98; $P = 0.04$) and 1-yr mortality (OR, 0.82; 95% CI, 0.67 to 1.0; $P = 0.05$). *Withdrawal* is associated with an increase in 30-day (OR 3.93, 95% CI, 2.57 to 6.01; P less than 0.0001) and 1-yr mortality (OR, 1.96; 95% CI, 1.49 to 2.58; $P < 0.0001$).

Conclusion: Perioperative β-blockade administered according to the Perioperative Cardiac Risk Reduction protocol is associated with a reduction in 30-day and 1-yr mortality. Perioperative withdrawal of β-blockers is associated with increased mortality.

What We Already Know about This Topic

- Perioperative β-blockade is associated with a significant decrease in mortality in patients at high risk for myocardial ischemia and infarction.

What This Article Tells Us That Is New

- Withdrawal of β-blockers in the perioperative period is associated with an increase in mortality, in both the short (30 days) and long (1 yr) terms.
- In actual clinical use, perioperative β-blockade reduces perioperative mortality.

IN 1996, Mangano *et al.*[1,2] published the results of a prospective, randomized, clinical trial of perioperative atenolol in patients at risk for myocardial ischemia and infarction. The patient population studied included patients with known coronary artery disease, known peripheral vascular

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◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

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disease or two risk factors for coronary artery disease: age 65 yr or older, smoking, diabetes, hypertension, or cholesterol of 240 mg/dl or higher. This study showed a reduction in 2-yr mortality. In 1996, the American Heart Association and American College of Cardiology issued guidelines,[3] subsequently updated,[4–6] which made appropriate perioperative β-adrenergic receptor blockade (β-blockade) a standard of care. Additional evidence for the importance of appropriate perioperative β-blockade was provided in randomized trials by Poldermans *et al.* [7,8], which studied the perioperative use of bisoprolol (metoprolol for the intravenous form) and confirmed a reduction in 30-day and 2-yr mortality in high-risk patients. The studies of Mangano *et al.*[1,2] and Poldermans *et al.*[7,8] thus provided the foundation for the adoption of programs of perioperative β-blockade.

A protocol for perioperative β-blockade was developed and implemented at the San Francisco Veterans Affairs Medical Center, San Francisco, California (SF VAMC) in 1998, based on criteria used in the original atenolol study.[1,2] This protocol, entitled Perioperative Cardiac Risk Reduction Therapy (PCRRT), closely adhered to the clinical pathway set out in the original atenolol study with a few exceptions. When intravenous atenolol became difficult to obtain, intravenous metoprolol was substituted. In 2004, with the publication of the clonidine study,[9] a second line agent, clonidine, was added to the PCRRT protocol. Before the introduction of the PCRRT protocol as a local clinical guideline in 1998, only patients in randomized clinical trials received perioperative β-blockade by protocol; patients not enrolled in randomized trials got medications solely based on prescribing physicians' clinical judgment. After the introduction of the PCRRT protocol, patients in the anesthesia preoperative clinic were started on perioperative β-blockers when deemed appropriate by their attending anesthesiologist, and recommendations for continuing β-blockade were made to the responsible surgical teams. Compliance with the protocol was entirely voluntary and was not measured until the introduction of Surgical Care Improvement Project-12 measures in 2007. The SF VAMC Perioperative β-Blocker protocol, PCRRT, has been adopted by a number of hospitals and hospital systems.

Since the introduction of perioperative β-blockade, a number of studies have evaluated its efficacy.[10–17] The Coronary Artery Revascularization Prophylaxis Trial confirmed the value of perioperative β-blockade by demonstrating that medical therapy (which in current practice included β blockade in 86% of patients) was equivalent to either percutaneous coronary intervention or coronary artery revascularization for the reduction in both short- and long-term (3.5 yr) risk after vascular surgery.[10] Two studies failed to show efficacy,[15,16] one study showed the possibility of increased risk in low-risk patients,[12] and one showed increased risk.[13,14] The PeriOperative ISchemic Evaluation (POISE) trial study, the largest β-blocker trial to date, showed that perioperative β-blockade caused a reduction in myocardial infarctions and referrals for cardiologic care, but there was an increase in bradycardia, hypotension, strokes, and all-cause mortality.[13,14] Based in part on these findings, the American Heart Association revised the guidelines[5] for perioperative β-blockade, making them more conservative. The POISE study, however, used inclusion criteria, starting doses of β-blockade, maintenance doses, hold criteria, target heart rates, and a number of other factors substantially different not only from those of the PCRRT protocol but also from the recommendations for metoprolol dosing given in the Physicians' Desk Reference.[13,14] Because of the important questions arising from the POISE publication, it was clear that an analysis of the safety and efficacy of perioperative β-blockade in actual clinical use on a large population of people was necessary. The present study, therefore, is an epidemiologic analysis of the safety, efficacy, and patterns of use of perioperative β-blockade at a single hospital, the San Francisco Veterans Affairs Medical Center. A program for perioperative β-blockade, the PCRRT protocol, had been developed at this hospital and was in wide but nonmandatory use. The present study tested the hypothesis that the pattern of use of perioperative β-blockade was associated with 30-day and 1-yr mortality. The present study also tested the hypothesis that adherence to the PCRRT protocol was associated with reductions in 30-day and 1-yr mortality.

Materials and Methods

After approval from the University of California, San Francisco, Committee on Human Research and SF VAMC Research and Development Committee (San Francisco, California), computerized records for all surgical patients at the SF VAMC from 1996 to September 2008 were extracted into a database. International Classification of Diseases (ICD) Codes, Current Procedural Terminology (CPT) codes, demographic information, problem lists, laboratory data, medication use, hospitalization, and mortality data were extracted from VA VISTA databases.

Before study initiation, definitions and data analysis plans were formalized. Before data analysis, and based upon prior work, the patterns of use of perioperative β-blockade were divided into four groups: *None*, *Addition*, *Withdrawal*, and *Continuous*. The *None* group consisted of patients who did not receive β-blockers before, during, or after surgery. The *Addition* group included patients who did not have β-blockers before surgery but who received at least one dose of β-blocker medication after surgery as either an in-patient or out-patient. The *Withdrawal* group consisted of patients who were receiving β-blockers before surgery but did not receive a single dose after surgery. The *Continuous* group included patients who were receiving β-blockers before surgery and who received at least one dose after surgery. There are many patterns of use of perioperative β-blockade that might be used, including different durations of therapy or dosing in the postoperative period. The definitions for the pattern of use described in the present study were based on prior work and were decided upon before study initiation.

The chosen definitions group patients into a limited number of groups for analysis and concentrate on prophylactic rather than therapeutic use.

Surgical patients were identified by the occurrence of a CPT code consistent with a surgical operation. Surgical procedures were then divided by CPT codes as follows: cardiac surgery, vascular surgery, and all others. Cardiac surgery was defined as CPT codes 33510–33530, 33533–33545, or 33572. Vascular surgery was defined as CPT codes 35500–35907, 35201–35390, 35001–35162, 34001–34490, and 34800–34900. Other surgical procedures were defined as a surgical CPT code not defined as cardiac or vascular surgery.

Demographic information, ICD-9, and CPT codes from the problem list and discharge diagnosis were used to identify risk factors. Coronary artery disease (CAD) was defined by ischemic heart disease ICD9-CM: 410–14, prior or planned coronary artery bypass graft surgery defined by CPT codes 33510–33530, 33533–33545, or 33572, or prior angioplasty by CPT codes 92980, 92981, 92982, 92984, 92995, 92996, G0290, G0291. Peripheral vascular disease (PVD) was defined by ICD-9 CM: 440, 442.84, 443, a CPT code for a past or present operation of 35500–35907, 35201–35390, 35001–35162, 34001–34490, 34800–34900, or a lower extremity amputation 27880–27889, 27590–27598, or 28800–28825. Risk factors for coronary artery disease were defined from prior studies and the PCRRT protocol.[1,2,9,18] If a patient had two risk factors for CAD they were assumed to be at risk. The age risk factor for analysis is based on the PCRRT protocol and was defined as older than 60 yr based on the results of the prior epidemiologic work,[18,19] as well as the atenolol[1,2] and clonidine[9] studies. Diabetes mellitus was defined from any ICD9-CM: 250.0–250.9, which included diabetes mellitus types I and II or unspecified. It excluded gestational diabetes (648.8), hyperglycemia (790.6), neonatal diabetes mellitus (775.1), nonclinical diabetes (790.29), nephrogenic diabetes insipidus (588.1), and diabetes insipidus (253.5). Hyperlipidemia was defined by ICD9-9 code 272, disorders of lipid metabolism. Hypertension was defined as ICD9-CM: 401–05 or an entry on a problem list. Smoking was defined as ICD-9 CM: 305.1 tobacco use disorder, v15.82 history of tobacco use, 989.84 tobacco, or a problem list entry. Smoking excluded e869.4 second-hand tobacco smoke.

Preoperative outpatient medications, in-hospital medication, and postdischarge outpatient medications were identified by time of prescription relative to the date of surgery. β-blockers included: acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol, or a drug listed by VA formulary as a β-blocker. Only oral or intravenous β-blockers were considered. Appropriate use of β-blockers was defined as the percentage of patients actually receiving β-blockers who were candidates, on the basis of the PCRRT protocol (fig. 1), for β-blocker therapy. The numerator was defined as patients actually receiving perioperative β-blockers. The denominator consisted of all patients who qualified for β-blockers based on the PCRRT protocol. Those patients include all patients with known CAD, all patients with known PVD, and any patient with two risk factors: diabetes, hypertension, smoking, cholesterol greater than 240 mg/dl, or age greater than 60 yr.

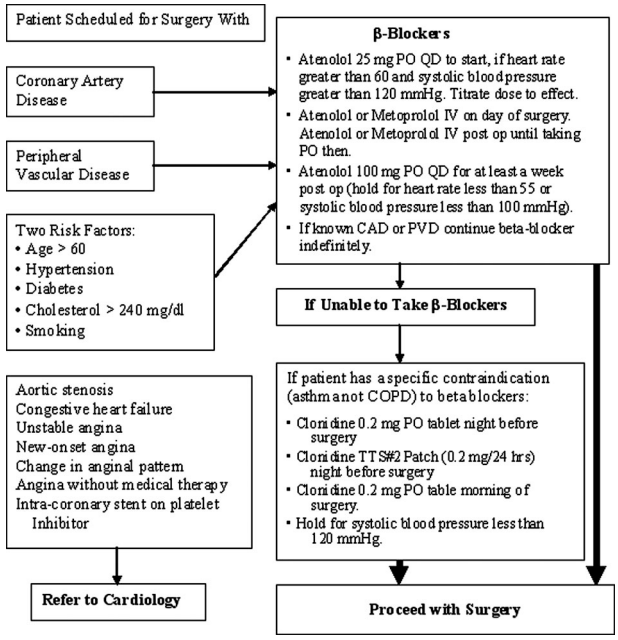


Fig. 1. The Perioperative Cardiac Risk Reduction Therapy (PCRRT) Protocol has been used by the San Francisco Veterans Affairs Medical Center since 1998. It has been adopted by a larger number of hospitals as well as hospital systems as a basis for perioperative β-blocker programs. Full information is available on the web at http://www.betablockerprotocol.com. β-blocker = β-adrenergic receptor blocker; COPD = chronic obstructive pulmonary disease; PO = by mouth; IV = intravenous; CAD = Coronary artery disease; Post op = Post operatively; PVD = peripheral vascular disease; QD = daily.

Statistical Analysis

The risk of in-hospital, 30-day, and 1-yr mortality among patients with the predictor *versus* those without the predictor was compared using the chi-square test or Fisher exact test, as appropriate. For these analyses, the odds ratio and its 95% CI were calculated with associated *P* value. Multivariable logistic regression was used to evaluate the effects of patient risk factors and of drug usage patterns on outcome variables (death, in-hospital death, 30-day mortality, and 1-yr morbidity and mortality) and to examine the effects of confounding variables such as preexisting medical conditions (age, sex, presence of known coronary artery disease, presence of known vascular disease, diabetes, hypertension, smoking, hypercholesterolemia, class of operation, medication use, revised cardiac risk index[12,20] [RCRI], *etc.*). RCRI[20] was calculated according to the methodology of Lindenauer *et al.*[12] Logistic regression analysis with repeated measures was used to correct for patients with multiple surgeries and changes in cardiac risk factors. An independent correlation structure was used to model the correlation of surgeries within a pa-

Table 1. Characteristics of the Patients

Characteristics	Female (%)	Male (%)	*P* Value	Outpatients (%)	Inpatients (%)	*P* Value	All Patients (%)
n	1,949 (5)	36,830 (95)	<0.0001	14,040 (36)	24,739 (64)	<0.0001	38,779 (100)
Age, yr	57 ± 15	63 ± 13	<0.0001	62 ± 14	63 ± 12	<0.0001	63 ± 13
Age ≥60 yr	727 (37)	21,270 (58)	<0.0001	7,671 (55)	14,326 (58)	<0.0001	21,997 (57)
Known PVD	219 (11)	7,311 (20)	<0.0001	1,613 (11)	5,917 (24)	<0.0001	7,530 (19)
Known CAD	228 (12)	9,274 (25)	<0.0001	2,649 (19)	6,853 (28)	<0.0001	9,502 (25)
Prior MI	29 (1)	1,082 (3)	0.0002	262 (2)	849 (3)	<0.0001	1,111 (3)
Two or More Risk Factors	671 (34)	15,896 (43)	<0.0001	6,931 (49)	9,636 (39)	<0.0001	16,567 (43)
Diabetes	237 (12)	6,552 (18)	<0.0001	2,511 (18)	4,278 (17)	0.14	6,789 (18)
Hypertension	699 (36)	14,475 (39)	0.0024	6,419 (46)	8,755 (35)	<0.0001	15,174 (39)
Smoking	255 (13)	4,984 (14)	0.57	2,247 (16)	2,992 (12)	<0.0001	5,239 (14)
Hyperlipidemia	345 (18)	9,218 (25)	<0.0001	4,290 (31)	5,273 (21)	<0.0001	9,563 (25)
CAD, PVD, or Two Risk Factors	776 (40)	20,406 (55)	<0.001	7,549 (54)	13,633 (55)	0.01	21,182 (55)
Postop Deaths within 30 days	14 (1)	637 (2)	0.0007	17 (0)	634 (3)	<0.0001	651 (2)
Postop Deaths within 1 yr	80 (4)	3,146 (9)	<0.0001	481 (3)	2,745 (11)	<0.0001	3,226 (8)

Data are expressed as a number (percentage) or mean ± S.D.

CAD = coronary artery disease; MI = myocardial infarction; Postop = postoperative; PVD = peripheral vascular disease; Two or More Risk Factors = presence of two or more cardiac risk factors, including diabetes, smoking, hypertension, age ≥60 yr, hyperlipidemia; CAD, PVD, or Two Risk Factors = presence of Perioperative Cardiac Risk Reduction Therapy risk factors of coronary artery disease, peripheral vascular disease, or two or more cardiac risk factors.

tient. Both Kaplan–Meier regression and Cox Proportional Hazard Model analysis were performed for survival analysis. Because some patients had multiple surgical procedures during the study period, for purposes of survival analysis, the last surgical procedure on each high-risk patient (CAD, or PVD, or two risk factors) was determined, and survival was measured from the date of that procedure. Multiple surgeries on the same day were excluded from survival analysis.

Propensity scores were developed using multinomial regression, using proc logistic of SAS 9.2 (SAS Institute Inc., Cary, NC), based on cardiac risk factors. Patient matching was based on propensity score. Group assignment was by β-blocker usage pattern. The population used for the propensity analysis consisted of high-risk patients (CAD, PVD, or two risk factors) having inpatient procedures. The predictors used to develop the score were age of the patient at the time of surgery, CAD, PVD, diabetes, high cholesterol, history of heart attack, age over 60 yr, and smoking. To get as much diverse scoring as possible, all predictors were used regardless of the predictor's significance. Because there are four predicted scores to choose from (*None*,

Table 2. Comparison of Characteristics of the Patients Treated or Not with β-Blockers

Characteristics	No β-Blocker (%)	β-Blocker (%)	RR [95% CI]	*P* Value
n = 38,779 (%)	18,476 (48)	20,303 (52)	—	—
Age, yr	60 ± 14	66 ± 11	—	<0.0001
Age ≥60 yr	8,622 (47)	13,375 (66)	1.4 [1.4–1.4]	<0.0001
Known PVD	1,853 (10)	5,675 (28)	2.8 [2.7–2.9]	<0.0001
Known CAD	1,342 (7)	8,160 (40)	5.5 [5.2–5.8]	<0.0001
Prior MI	99 (0.5)	1,012 (5)	9.3 [7.6–11.4]	<0.0001
Two or More Risk Factors	4,990 (27)	11,577 (57)	2.1 [2.1–2.2]	<0.0001
Diabetes	1,890 (10)	4,899 (24)	2.4 [2.2–2.5]	<0.0001
Hypertension	4,113 (22)	11,061 (55)	2.4 [2.4–2.5]	<0.0001
Smoking	2,251 (12)	2,988 (15)	1.2 [1.1–1.3]	<0.0001
Hyperlipidemia	2,802 (15)	6,761 (33)	2.2 [2.1–2.3]	<0.0001
CAD, PVD, or Two Risk Factors	6,166 (33)	15,016 (74)	2.2 [2.2–2.3]	<0.001
Postop Deaths within 30 days	204 (1)	447 (2)	2 [1.7–2.4]	<0.0001
Postop Deaths within 1 yr	1,255 (7)	1,971 (10)	1.4 [1.3–1.5]	<0.0001

Data are presented as mean ± S.D. or number (percentage).

β-blocker = β-adrenergic receptor blocker; CAD = coronary artery disease; 95% CI = 95% confidence interval; MI = myocardial infarction; Postop = postoperative; PVD = peripheral vascular disease; RR = relative risk; Two or More Risk Factors = presence of two or more cardiac risk factors, including diabetes, smoking, hypertension, age ≥60 yr, hyperlipidemia; CAD, PVD, or Two Risk Factors = presence of Perioperative Cardiac Risk Reduction Therapy risk factors of coronary artery disease, peripheral vascular disease, or two or more cardiac risk factors.

Table 3. Dosage Patterns for Perioperative β-Blockers in In-patients and Out-patients

	Inpatients (n = 24,739)				Outpatients (n = 14,040)			
Drug	No. of Prescriptions (%)	Median Drug Dose, mg	Median Times Per Day Administered	Median No. of Days Administered	No. of Prescriptions (%)	Median Drug Dose, mg	Median Times Per Day Administered	Median Days Prescribed
Acebutolol	28 (0)	400 [200–400]	1 [1–2]	3 [2–3.5]	540 (0)	200 [200–400]	1 [1–1]	90 [90–90]
Atenolol	10,781 (16)	50 [25–50]	1 [1–1]	2 [2–4]	64,617 (54)	50 [25–50]	1 [1–1]	90 [60–90]
Betaxolol	2 (0)	10 [10–10]	1 [1–1]	2 [2–2]	24 (0)	10 [10–10]	1 [1–1]	90 [90–90]
Carvedilol	2,054 (3)	6.2 [3.1–18.8]	2 [2–2]	2 [2–4]	6,043 (5)	25 [6.25–25]	2 [2–2]	30 [30–60]
Esmolol	1,188 (2)	2,500 [2,500–2,500]	1 [1–1]	2 [1–4]	—	—	—	—
Labetalol	2,076 (75)	20 [10–200]	2 [1–2]	2 [1–3]	1,030 (1)	200 [100–200]	2 [2–2]	30 [30–50]
Metoprolol	51,597 (75)	25 [12.5–50]	2 [2–2]	2 [1–3]	39,296 (33)	50 [50–50]	2 [2–2]	90 [30–90]
Nadolol	70 (0)	40 [20–40]	1 [1–1]	3.5 [2–8]	869 (1)	40 [40–80]	1 [1–1]	30 [30–60]
Pindolol	31 (0)	5 [5–10]	2 [2–2]	3 [1–7]	425 (0)	5 [5–10]	2 [2–2]	30 [30–30]
Propranolol	624 (1)	20 [10–40]	2 [2–2]	2 [2–5]	5,667 (5)	20 [20–40]	2 [2–2]	50 [30–90]
Sotalol	194 (0)	120 [80–160]	2 [2–2]	2 [2–4]	1,091 (1)	80 [80–120]	2 [2–2]	30 [30–30]
Timolol	—	—	—		4 (0)	5 [5–5]	2 [2–2]	30 [30–30]

Data are presented as number (%) or median [25–75 interquartile range].
β-blocker = β-adrenergic receptor blocker.

Addition, *Continuous*, and *Withdrawal*) the *None* category was used to start the propensity matching. For an observation to be selected for the propensity analysis, the observation could not be the only observation with the score. This approach is used to discard outliers. Matching used exact matching of 12 digits of the propensity score. Because the model used was a multinomial regression, the c test or Hosmer–Lemeshow test for goodness of fit are unavailable.

For all analyses, a two-tailed nominal *P* value of 0.05 or less was considered statistically significant. Data are presented as mean ± SD. Data are presented by procedure. Some patients had more than one procedure so the number of patients is less than the number of procedures. All statistical analysis was performed using SAS 9.2 (SAS Institute Inc.).

Results

Patient Characteristics

There were 38,779 surgical operations in 20,937 different patients. Table 1 lists the characteristics of the patients undergoing procedures. The majority of procedures were in men with an average age of 63 ± 13 yr. Procedures in women were less common, and women were slightly younger than men, on average ($P < 0.001$). Inpatient procedures predominated over outpatient procedures ($P < 0.001$). Inpatient procedures had a higher 1-month ($P < 0.001$) and 1-yr ($P < 0.001$) mortality than outpatient procedures.

Table 2 compares the characteristics of the patients who were administered a β-blocker at any time with those who were never administered a β-blocker. Patients who received

Table 4. Pattern of Use of Perioperative β-Blockers

	Addition			*Continuous*		
	Outpatient	Inpatient	Both	Outpatient	Inpatient	Both
Total	1,262 (3)	4,570 (12)	5,832 (15)	3,901 (10)	8,779 (23)	12,680 (33)
Known PVD	120 (10)	1,047 (23)	1,167 (20)	829 (21)	3,272 (37)	4,101 (32)
Known CAD	211 (17)	1,013 (22)	1,224 (21)	1,656 (42)	4,660 (53)	6,316 (50)
Two or More Risk Factors	635 (50)	1,632 (36)	2,267 (39)	3,096 (79)	5,141 (59)	8,237 (65)
Diabetes	244 (19)	708 (15)	952 (16)	1,163 (30)	2,365 (27)	3,528 (28)
Hypertension	594 (47)	1,489 (33)	2,083 (36)	3,103 (80)	4,852 (55)	7,955 (63)
Smoking	175 (14)	512 (11)	687 (12)	730 (19)	1,310 (15)	2,040 (16)
Prior MI	12 (1)	80 (2)	92 (2)	195 (5)	657 (7)	852 (7)
Hyperlipidemia	358 (28)	844 (18)	1,202 (21)	1,928 (49)	3,016 (34)	4,944 (39)
Age ≥60 yr	758 (60)	2,786 (61)	3,544 (61)	2,688 (69)	5,984 (68)	8,672 (68)
CAD, PVD, or Two or More Risk Factors	702 (56)	2,422 (53)	3,124 (54)	3,296 (84)	7,278 (83)	10,574 (83)
Postop Deaths within 30 days	0 (0)	88 (2)	88 (2)	2 (0)	252 (3)	254 (2)
Postop Deaths within 1 yr	29 (2)	389 (9)	418 (7)	158 (40	1,124 (13)	1,282 (10)

Data are presented as number (%).
Addition = addition of β blocker; β-blocker = β-adrenergic receptor blocker; CAD = coronary artery disease; *Continuous* = continuous use of β-blocker; MI = myocardial infarction; *None* = no β-blockers before, during, or after surgery; Postop = postoperative; PVD = peripheral vascular disease; Two or More Risk Factors = presence of two or more cardiac risk factors, including diabetes, smoking, hypertension, age ≥60 yr, hyperlipidemia; CAD, PVD, or Two Risk Factors = presence of Perioperative Cardiac Risk Reduction Therapy risk factors of coronary artery disease, peripheral vascular disease, or two or more cardiac risk factors; *Withdrawal* = withdrawal of β-blocker.

β-blockade at any time were older ($P > 0.0001$) and had more coexisting disease than those who were not. Patients given a β-blocker at any time had a higher incidence of vascular disease ($P < 0.0001$), coronary artery disease ($P < 0.0001$), prior myocardial infarction ($P < 0.0001$), diabetes ($P < 0.0001$), hypertension ($P < 0.0001$), smoking ($P < 0.0001$), hyperlipidemia ($P < 0.0001$), and age more than 60 yr ($P < 0.0001$). Patients receiving β-blockers at any time are, as a group, at higher risk, as shown by the higher 30-day ($P < 0.0001$) and 1-yr ($P < 0.0001$) raw mortalities.

Patterns of Perioperative β-Blockade Use

Table 3 lists the inpatient and outpatient β-blocker prescriptions, including the number of prescriptions, percentage of prescriptions for a given β-blocker, the median dose, the median number of doses per day, and the median number of days β-blockers were given. Metoprolol was by far the most common inpatient drug (75%), because of its availability in intravenous formulations. Atenolol was the most common outpatient drug (54%). Table 4 details the patterns of use of perioperative β-blockade. β-blocker use was divided into four groups: *Addition*, *Continuous*, *None*, and *Withdrawal*. In the *Addition* group, 15% of all surgical patients had a β-blocker added to their medications on the day of surgery. In the *Continuous* group, 33% were receiving a β-blocker continuously (before admission and at least one dose after surgery). In the *None* group, 48% of all surgical patients received no β-blocker in the perioperative period. This group included 25% of all vascular surgery patients and 14% of all patients with known CAD who were not receiving a β-blocker perioperatively. Thirty (30%) percent of all patients with two or more risk factors received no β-blocker. In the *Withdrawal* group, 5% of surgical patients were withdrawn from β-blockers in the postoperative period.

Table 5. Logistic Regression Model for Perioperative β-Blockade for 30-day and 1-yr Mortality

Variable	OR [95% CI]	*P* Value
30-day mortality		
Age	1.03 [1.01–1.04]	0.0003
Addition	0.52 [0.33–0.83]	0.006
Continuous	0.68 [0.47–0.98]	0.04
Withdrawal	3.93 [2.57–6.01]	<0.0001
Presence of CAD	1.87 [1.38–2.53]	<0.0001
Presence of PVD	1.68 [1.30–2.17]	<0.0001
1-year mortality		
Age	1.03 [1.02–1.04]	<0.0001
Addition	0.64 [0.51–0.79]	<0.0001
Continuous	0.82 [0.67–1.00]	0.05
Withdrawal	1.96 [1.49–2.58]	<0.0001
Presence of CAD	1.27 [1.06–1.51]	0.008
Presence of PVD	1.61 [1.37–1.88]	<0.0001

Population consisted of 13,629 patients with cardiac risk, or coronary artery disease, or peripheral vascular disease, who had inpatient surgery. The fit of the logistic regression model was tested with the Hosmer and Lemeshow Goodness-of-Fit Test: for 30-day analysis, chi square = 8.63, $P = 0.37$, c statistic = 0.709; for 1-yr analysis, chi-square = 3.97, p value = 0.86, c statistic = 0.657.

Addition = addition of β blocker; CAD = coronary artery disease; *Continuous* = continuous use of β-blocker; 95% CI = 95% confidence interval; *None* = no β-blockers before, during, or after surgery; OR = odds ratio; PVD = peripheral vascular disease; *Withdrawal* = withdrawal of β-blocker.

Effects on Mortality

Based on the PCRRT criteria, including presence of CAD, PVD, or two risk factors (diabetes, hypertension, age more

Table 4. Continued

None			*Withdrawal*			Total
Outpatient	Inpatient	Both	Outpatient	Inpatient	Both	Both
8,037 (21)	10,439 (27)	18,476 (48)	840 (2)	951 (2)	1,791 (5)	38,779 (100)
495 (6)	1,358 (13)	1,853 (10)	169 (20)	238 (25)	407 (23)	7,528 (19)
508 (6)	834 (8)	1,342 (7)	274 (33)	346 (36)	620 (35)	9,502 (25)
2,596 (32)	2,394 (23)	4,990 (27)	604 (72)	469 (49)	1,073 (60)	16,567 (43)
878 (11)	1,012 (10)	1,890 (10)	226 (27)	193 (20)	419 (23)	6,789 (18)
2,131 (27)	1,982 (19)	4,113 (22)	591 (70)	432 (45)	1,023 (57)	15,174 (39)
1,184 (15)	1,067 (10)	2,251 (12)	158 (19)	103 (11)	261 (15)	5,239 (14)
21 (0)	78 (1)	99 (1)	34 (4)	34 (4)	68 (4)	1,111 (3)
1,628 (20)	1,174 (11)	2,802 (15)	376 (45)	239 (25)	615 (34)	<9,563 (25)
3,676 (46)	4,946 (47)	8,622 (47)	549 (65)	610 (64)	1,159 (65)	21,997 (57)
2,892 (36)	3,274 (31)	6,166 (33)	659 (78)	659 (69)	1,318 (74)	21,182 (55)
13 (0)	191 (2)	204 (1)	2 (0)	103 (11)	105 (6)	651 (20
237 (3)	1,018 (10)	1,255 (7)	57 (7)	214 (23)	271 (15)	3,226 (8)

Table 6. Summary of Logistic Regression and Propensity Analysis for 30-day and 1-yr Mortality by Type of Surgery

Outcome Variable & Population	No. of Patients	*Addition* OR [95% CI]	*P* Value	*Continuous* OR [95% CI]	*P* Value
30-Day					
All Surgery	13,629	0.52 [0.33–0.83]	0.006	0.68 [0.47–0.98]	0.04
Last Surgery Only	6,731	0.38 [0.24–0.61]	<0.0001	0.57 [0.42–0.78]	0.0004
Propensity Score	12,953	0.53 [0.33–0.85]	0.009	0.70 [0.48–1.01]	0.06
All Patients + RCRI	13,629	0.51 [0.33–0.81]	0.004	0.60 [0.42–0.85]	0.004
RCRI					
0–1	7,422	1.22 [0.67–2.25]	0.52	1.41 [0.88–2.26]	0.15
2–6	6,207	0.24 [0.13–0.46]	<0.0001	0.39 [0.26–0.59]	<0.0001
Cardiac Surgery	1,527	0.08 [0.01–0.82]	0.03	0.29 [0.08–0.99]	0.05
Vascular Surgery	2,117	0.38 [0.14–1.03]	0.06	0.46 [0.21–1.01]	0.05
Noncardiac Surgery	12,105	0.58 [0.37–0.92]	0.02	0.74 [0.51–1.05]	0.09
Noncardiac, Nonvascular Surgery	9,988	0.66 [0.40–1.08]	0.10	0.82 [0.57–1.2]	0.31
1-Year					
All Surgery	13,629	0.64 [0.51–0.79]	<0.0001	0.82 [0.67–1.00]	0.05
Last Surgery Only	6,731	0.51 [0.40–0.65]	<0.0001	0.72 [0.60–0.86]	0.0002
Propensity Score	12,953	0.65 [0.52–0.81]	0.0001	0.84 [0.68–1.03]	0.09
All Patients + RCRI	13,629	0.79 [0.63–0.99]	0.04	0.80 [0.66–0.97]	0.02
RCRI					
0–1	7,422	0.89 [0.69–1.16]	0.40	1.08 [0.86–1.36]	0.51
2–6	6,207	0.37 [0.26–0.51]	<0.0001	0.48 [0.36–0.64]	<0.0001
Cardiac Surgery	1,527	0.50 [0.14–1.80]	0.29	0.59 [0.21–1.69]	0.33
Vascular Surgery	2,117	0.76 [0.47–1.24]	0.28	0.73 [0.46–1.15]	0.17
Noncardiac Surgery	12,105	0.67 [0.54–0.83]	0.0002	0.89 [0.73–1.08]	0.23
Noncardiac, Nonvascular Surgery	9,988	0.70 [0.55–0.88]	0.002	0.96 [0.78–1.17]	0.66

Addition = addition of β blocker; All Patients + RCRI = population of model was all inpatient surgery with patients with cardiac risk with RCRI index added to logistic regression; All Surgery = all inpatient surgery with patients with cardiac risk; β-blocker, β-adrenergic receptor blocker; CAD = coronary artery disease; 95% CI = 95% confidence interval; *Continuous* = continuous use of β-blocker; Last Surgery Only = to avoid difficulties with repeated measures analysis, only last surgical operation was used in patients with multiple surgical procedures; propensity score = patients matched by propensity score; PVD = peripheral vascular disease; RCRI = revised cardiac risk index; RCRI 0–1 = only patients with RCRI of 0 or 1 included; RCRI 2–6 = only patients with RCRI of 2–6 included; *Withdrawal* = withdrawal of β-blocker.

than 60 yr, smoking, and hyperlipidemia), 21,272 patient procedures (54.9%) qualified for perioperative β-blockade under the PCRRT protocol. 13,629 of these procedures were on high-risk inpatients. In this inpatient group, multivariate logistic regression analysis demonstrates that the pattern of use of β-blockers is associated with 30-day and 1-yr mortality (table 5). *Addition* of β-blockers is associated with a reduction in 30-day mortality (Odds Ratio [OR], 0.52; 95% CI, 0.33 to 0.83; $P = 0.006$) and 1-yr mortality (OR, 0.64; 95% CI, 0.51 to 0.79; $P < 0.0001$) compared with *None*. *Continuous* use of β-blockers is associated with a reduction in 30-day mortality (OR, 0.68; 95% CI, 0.47 to 0.98; $P = 0.04$) and 1-yr mortality (OR, 0.82; 95% CI, 0.67 to 1.0; $P = 0.05$) compared with *None*. *Withdrawal* of β-blockers is associated with an increase in 30-day mortality (OR, 3.93; 95% CI, 2.57 to 6.01; $P < 0.0001$) and 1-yr mortality (OR, 1.96; 95% CI, 1.49 to 2.58; $P < 0.0001$) compared with *None*. The presence of coronary artery disease (30-day OR, 1.87; 95% CI, 1.38 to 2.53; $P < 0.0001$ and 1-yr OR, 1.27; 95% CI, 1.06 to 1.51; $P < 0.008$) and peripheral vascular disease (30-day OR, 1.68; 95% CI, 1.30 to 2.17; $P < 0.0001$ and 1-yr OR, 1.61; 95% CI, 1.37 to 1.88; $P < 0.0001$) increase the risk of postoperative mortality. The discrimination of the logistic regression model was evaluated using the c-statistic, with c = 0.709 for 30-day analysis and c = 0.657 for 1-yr analysis. The calibration of the model was tested using the Hosmer–Lemeshow Goodness-of-Fit test, showing in the 30-day analysis (Pr > chi-square = 0.3744) and (Pr > chi-square = 0.8602) for the 1-yr analysis.

Table 6 shows subgroup analysis by type of surgery as well as by cardiac risk stratum as measured by the RCRI.[12,20] Surgical cases are divided as follows: *All*, *Cardiac*, *Vascular*, *Noncardiac*, and *Noncardiac-Nonvascular*. Perioperative β-blockade *Withdrawal* was associated with significantly increased 30-day and 1-yr mortality in all classes of surgery. *Withdrawal* was furthermore associated with increased 30-day mortality (OR, 3.78; $P = 0.0001$) even in lowest risk (RCRI 0 and 1) patients, though this effect was not significant at 1 yr. *Addition* of β-blockade was associated with reduced 30-day mortality in the *All* group, and in the subgroups of *Cardiac* and *Noncardiac* patients. *Addition* furthermore was associated with a strong trend to reduced mortality in *Vascular* patients and in *Noncardiac-Nonvascular* surgery. *Addition* did not significantly reduce mortality at 1 yr for *Vascular* or *Cardiac* surgery. Neither *Addition* nor *Continuous* use of β-blockade significantlty affected mortality in pa-

Table 6. Continued

Withdrawal OR [95% CI]	*P* Value	CAD OR [95% CI]	*P* Value	PVD OR [95% CI]	*P* Value
3.93 [2.57–6.01]	<0.0001	1.87 [1.38–2.53]	<0.0001	1.68 [1.30–2.17]	<0.0001
3.46 [2.36–5.08]	<0.0001	1.73 [1.33–2.25]	<0.0001	2.46 [1.93–3.15]	<0.0001
4.05 [2.61–6.27]	<0.0001	1.93 [1.41–2.62]	<0.0001	1.73 [1.33–2.25]	<0.0001
3.68 [2.41–5.62]	<0.0001	—	—	1.34 [1.02–1.76]	0.04
3.78 [1.90–7.50]	0.0001	—	—	1.93 [1.30–2.88]	0.001
3.29 [1.97–5.50]	<0.0001	—	—	1.30 [0.94–1.79]	0.11
5.91 [1.48–23.5]	0.01	—	—	2.07 [0.94–4.56]	0.07
3.97 [1.42–11.1]	0.009	1.12 [0.56–2.22]	0.75	—	—
3.57 [2.31–5.52]	<0.0001	1.90 [1.40–2.58]	<0.0001	1.57 [1.20–2.07]	0.001
3.60 [2.28–5.69]	<0.0001	2.04 [1.47–2.83]	<0.0001	1.80 [1.34–2.41]	<0.0001
1.96 [1.49–2.58]	<0.0001	1.27 [1.06–1.51]	0.008	1.61[1.37–1.88]	<0.0001
1.93 [1.46–2.55]	<0.0001	1.09 [0.94–1.27]	0.23	1.66 [1.44–1.91]	<0.0001
1.96 [1.47–2.61]	<0.0001	1.27 [1.06–1.53]	0.009	1.64 [1.39–1.93]	<0.0001
1.22 [0.95–1.56]	0.12	—	—	1.40 [1.20–1.64]	<0.0001
1.41 [0.92–2.15]	0.12	—	—	1.30 [1.05–1.60]	0.02
1.94 [1.32–2.85]	0.0007	—	—	1.72 [1.39–2.13]	<0.0001
6.21 [1.83–21.1]	0.003	—	—	1.91 [1.13–3.21]	0.02
2.34 [1.06–5.13]	0.03	1.66 [1.16–2.38]	0.005	—	—
1.81 [1.37–2.39]	<0.0001	1.42 [1.19–1.69]	0.0001	1.46 [1.24–1.71]	<0.0001
1.76 [1.32–2.36]	0.0001	1.34 [1.12–1.61]	0.002	1.82 [1.53–2.16]	<0.0001

tients with low risk (RCRI 0 and 1). *Continuous* use of β-blockade was associated with reduced 30-day mortality in the *All* group, in the subgroup of *Cardiac* surgery patients, and in patients with higher RCRI of 2–6. *Continuous* use was associated with decreased mortality in patients with high RCRI at 1 yr, but this effect was not seen in the subgroups of *Cardiac*, *Vascular*, *Noncardiac*, or *Noncardiac-Nonvascular*.

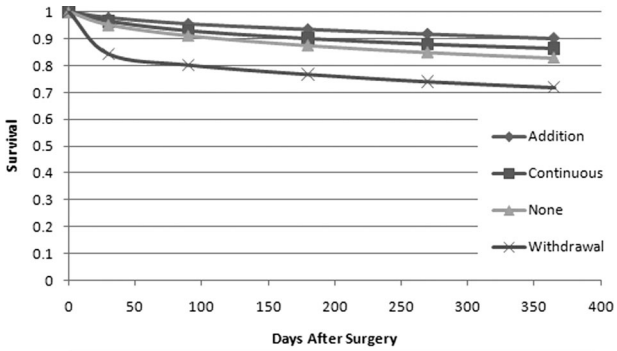
Survival Analysis

Survival analysis was based on the last surgery. Analysis was restricted to high-risk in-patients as defined by presence of CAD, PVD, or two risk factors (n = 6,731). Kaplan–Meier survival analysis, performed on these high-risk patients (fig. 2) demonstrates the association of the patterns of use of perioperative β-blockade with postoperative mortality (Log Rank test $P < 0.0001$). *Addition* of β-blockers improves survival compared with *None* (Log Rank test $P < 0.0001$). *Continuous* β-blocker use is superior to *None* (Log Rank test $P = 0.0004$). *Withdrawal* of β-blockers has the poorest long-term survival *versus None* (Log Rank test $P = 0.0001$).

Cox-Proportional Hazards model survival analysis confirms the association of the pattern of use of β-blockade with postoperative 30-day and 1-yr mortality (Likelihood Ratio test $P < 0.0001$). The Cox-Proportional Hazards model was adjusted for age, blocker group (*Addition*, *Continuous*, *Withdrawal*, or *None*), presence of vascular disease, and presence of coronary artery disease and was compared with the *None* group. The hazard ratio shows a reduction in risk with *Addition* and *Continuous*, and an increase in risk with *Withdrawal*, compared with *None* (*Addition* hazard ratio, 0.71 [95% CI, 0.61–0.82], $P < 0.0001$; *Continuous* hazard ratio, 0.81 [95% CI, 0.72–0.92], $P = 0.0006$; *Withdrawal* hazard ratio, 1.51 [95% CI, 1.25–1.83], $P < 0.0001$).

Propensity Analysis

Propensity analysis matched 12,953 patient procedures based on PCRRT risk factors. Propensity analysis (table 6) confirms the results found with survival and logistic regression analysis for 30-day and 1-yr mortality (30-Day: *Addition* OR, 0.53 [95% CI, 0.33–0.85], $P = 0.009$; *Continuous* OR, 0.70 [95% CI, 0.48–1.01], $P = 0.06$, *Withdrawal* OR, 4.05 [95% CI, 2.62–6.27], $P < 0.0001$; 1 yr: *Addition* OR, 0.65 [95% CI, 0.52–0.81], $P = 0.0001$, *Continuous* OR, 0.84 [95% CI, 0.68–1.03], $P = 0.09$, *Withdrawal* OR, 1.96 [95% CI, 1.47–2.61], $P <$



Number at Risk						
Days After Surgery	0	30	90	180	270	365
Addition	1226	1200	1172	1137	1082	1040
Continuous	3644	3517	3389	3233	3025	2890
None	1517	1444	1383	1309	1225	1167
Withdrawal	344	290	276	258	235	221

Fig. 2. Kaplan-Meier Survival curves for different patterns of use of perioperative β-adrenergic receptor blockade (β-blockade) over time. The *None* group consisted of patients who did not receive β-blockers before, during, or after surgery. The *Addition* group included patients who did not have β-blockers before surgery but who received at least one dose of β-blockers after surgery as either an inpatient or outpatient. The *Withdrawal* group consisted of patients who were receiving β-blockers before surgery but did not receive a single dose after surgery. The *Continuous* group included patients who were receiving β-blockers before surgery and who received at least one dose after surgery.

0.0001). The propensity model was statistically significant ($P < 0.0001$).

Changes in Patterns of Perioperative β-Blockade over Time

There have been changes in the pattern of use of perioperative β-blockade over time. Figure 3A shows the time course of the pattern of use of β-blockers for all patients from 1996 to 2008 at the SF VAMC. There has been an increase in the percentage of *Continuous* use (Logistic regression $P < 0.0001$) and a decrease in the patients who receive *None* (Logistic regression $P < 0.0001$). There has been no significant change in the *Addition* of β-blockers over time (Logistic regression P value = 0.60). There has been an increase in the percentage *Withdrawal* use (Logistic regression P value < 0.0001). Logistic regression analysis demonstrates that 30-day ($P = 0.0001$) and 1-yr ($P = 0.00003$) mortality have decreased over the time period (fig. 3B).

Discussion

In patients with PCRRT indications for perioperative β- blockade, the pattern of use of perioperative β-blockers has a significant association with postoperative survival. The perioperative *Addition* of a β-blocker to the medical regimen of patients with CAD, PVD, or two risk factors is associated with improved 30-day and 1-yr survival. *Continuous* use of β-blockers in the perioperative period, in patients at risk, is associated with improved 30-day and 1-yr survival compared with patients receiving *None*. *Withdrawal* from β-blockers in the perioperative period increases the risk for 30-day and 1-yr mortality.

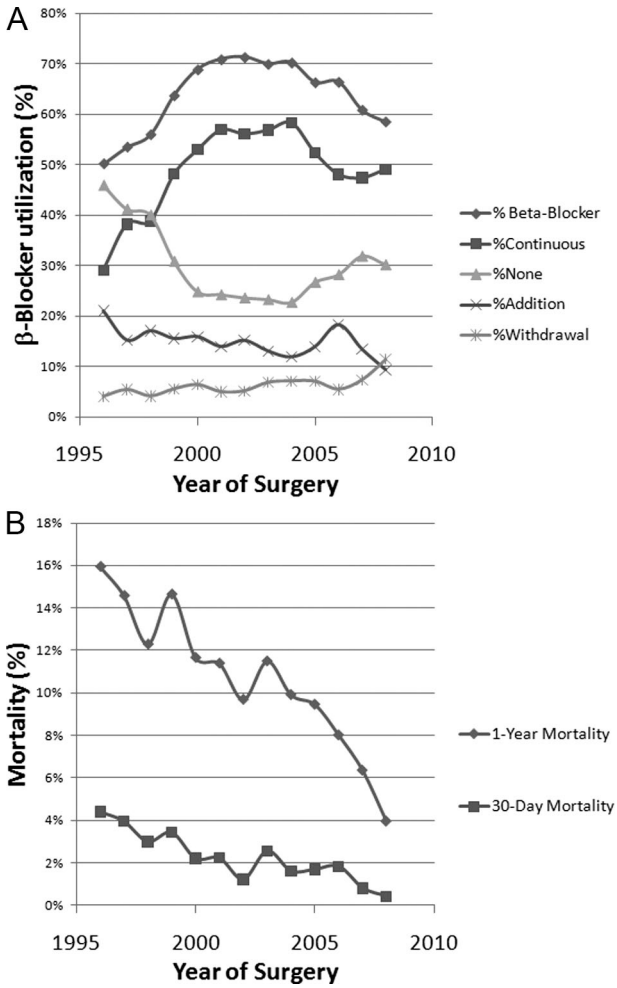


Fig. 3. (*A*) Percentage of use of β-adrenergic receptor blockers (β-blockers) over time. The β-blocker group consists of patients who were in either the *Addition* or *Continuous* groups. The *None* group consisted of patients who did not receive β-blockers before, during, or after surgery. The *Addition* group included patients who did not have β-blockers before surgery but who received at least one dose of β-blockers after surgery as either an inpatient or outpatient. The *Withdrawal* group consisted of patients who were receiving β-blockers before surgery but did not receive a single dose after surgery. The *Continuous* group included patients who were receiving β-blockers before surgery and who received at least one dose after surgery. (*B*) Percentage of 30-day and 1-year mortality over time.

In the present study, 5% of patients were withdrawn from β-blockers in the perioperative period, which in absence of newly developed contraindications would violate a level 1 standard of care.[4–6,21,22] This 5% withdrawal rate seems high but is lower than those of prior studies of hospital prescribing errors, which show that 10–61% of the time, a drug deletion error, often significant, is made at the time of admission.[23] The high prevalence of medication errors has been recognized as a significant patient safety problem, a concept supported by the current investigation.

Patients who are administered β-blockers have more preoperative cardiac risk factors than those who do not receive β-blockers (table 2). A prescription for a β-blocker is a surrogate marker for cardiac risk. Patients administered β-blockers are older, have more risk factors, and have a higher incidence of known coronary artery and peripheral vascular disease. Any analysis of the association of perioperative β-blocker use with perioperative mortality must correct for the simple fact that patients coming to surgery who are treated with β-blockers are older and have significantly more perioperative risk factors than those not treated with β-blockers. For this reason, careful risk adjustment strategies are necessary in studying the efficacy of perioperative β-blockade.

Epidemiologic studies can be quite large; the present study has 38,779 surgical procedures and can therefore identify rare or infrequent events. They reflect the actual practice of medicine but can only identify associations, not causality. The present study, using multivariate risk adjustment, demonstrates a strong association between the *Addition* or *Continuation* of perioperative β-blockers and an improved survival in patients with risk factors defined by the PCRRT protocol. The present study also identifies the average doses used in actual clinical practice. In the current study, the most commonly prescribed inpatient β-blocker drug was metoprolol, in doses of 25–50 mg twice daily (mean 78 mg/day) For outpatients, atenolol was most commonly given, with a mean dose of 51 mg daily. Such regimens are pharmacodynamically very similar to the dosage regimens found in the atenolol[1,2] and the bisoprolol[7,8] trials, but stand in stark contrast to the drug dosing used in the POISE study.[13,14] The POISE study used a starting dose of metoprolol XL of 400 mg on the day of surgery and then 200 mg orally for 30 days.[13,14] The recommended starting dose of atenolol or metoprolol XL is 25 mg orally daily.[24] The maximum recommended starting dose of metoprolol XL is 100 mg orally daily.[24] In contrast, the PCRRT protocol recommends a starting dose of atenolol of 25 mg orally daily. The present study found an improved 30-day and 1-yr mortality when perioperative β-blockade was *Added* or C*ontinued*, on the basis of the PCRRT risk assessment protocol. POISE, using much higher doses of β-blockade drugs, found decreased survival, increased strokes, and significant hypotension and bradycardia.[13,14] The results of POISE study should be evaluated very carefully given the choice of dose, hold orders, and the limitations of the study conduct.

Lindenauer *et al.*[11] analyzed the pattern of use of perioperative β-blockade by review of medical records of patients who developed postoperative myocardial infarctions in a single hospital. Of 58 patients who were found retrospectively to have been "ideal" candidates for perioperative β-blockade, only 30 (52%) actually received this treatment—a figure quite similar to the findings in the current study (*Addition* + *Continuation* groups = 48%).[11] This finding suggests that undertreatment is still common, and prospective identification and treatment could potentially decrease perioperative mortality further still. Lindenauer *et al.*[11] found that treatment with β-blockers before infarction was associated with reduced mortality (OR, 0.19; 95% CI, 0.04–0.87). Subsequently, Lindenauer *et al.*[12] refined their findings in a multihospital epidemiologic analysis in 329 US hospitals in 782,969 patients. The association between perioperative β-blocker treatment and the risk of death varied with cardiac risk.[12] Patients without identifiable cardiac risk had no benefit and possible harm.[12] The present study analysis, which used an RCRI,[20] shows improved survival with *Addition* and *Continuous* patterns of β-blockade in patients with RCRI 2–6. We found decreased survival when the pattern is perioperative *Withdrawal. Withdrawal* of β blockers in the perioperative period is associated with increased mortality, even in low-risk (RCRI 0–1) patients. The current study does not demonstrate a problem with appropriate administration of β-blockers to low-risk patients. In Lindenauer *et al.*,[12] patients with cardiac risk treated with β-blockers had an improved in-hospital survival. Unfortunately, the analysis was limited by an inability to identify the exact relationship between the timing of the β-blocker administration, the day of the operation, and the observed morbidity.[12] Separating patients who received prophylactic β-blockers from those who received them for therapy of a complication is a difficult problem in epidemiologic studies. The present study used the pattern of administration of the medication relative to surgery as the independent variable and 30-day and 1-yr mortality as the outcome to identify the effects of prophylactic (before a complication) rather than therapeutic (after a complication) use of β-blockade. The atenolol[1,2] and the clonidine studies[9] showed short- and long-term effects of short-term perioperative use of medications. Short- and long-term mortality was influenced by a single week of perioperative medication. Poldermans *et al.*[7,8] has shown similar long-term effects of short-term therapy. Van Klei *et al.*,[25] in an epidemiologic analysis of low- and intermediate-risk patients, showed similar adverse effects of withdrawal of β-blockers to the current study. The present study demonstrates that use of perioperative β-blockers is associated with a reduction in both short-term (30-day) and long-term (1-yr mortality) in patients with cardiac risk.

This study has several limitations. The present study evaluates the results of the implementation of a protocol (PCRRT) for perioperative β-blockade that was developed and implemented at a single hospital from 1996 to 2008. There was a persistent effort during this period to increase utilization of the protocol with educational sessions, laminated protocols, a web site,§ academic detailing, computerized reminders in the hospital computer system, and feedback of medication compliance based on Surgical Quality Improvement Project measures. Compliance with the protocol was voluntary, not mandatory, as demonstrated by the large number of patients in the *None* group. Because use of the protocol was up to the individual physician caring for each patient, we cannot exclude the possi-

§Beta-blocker and clonidine protocol. Available at: http://www.betablockerprotocol.com. Accessed January 1, 2010.

bility that selection bias, perhaps based upon unmeasured patient risk factors, played a role in decisions to use perioperative β-blockade in individual patients. The results of our propensity matching analysis, however, suggest that this confounding bias is unlikely.

This study used retrospective epidemiologic analysis of computerized medical records. The data used for cardiac risk were derived from problem lists, discharge diagnosis, CPT codes, and ICD-9 codes. Some patients may not have problem lists completed fully, so some risk factors were probably missed.[26] The quality of risk factor data probably improved over the course of the study. The outcome variable, death, is carefully identified by the Department of Veterans Affairs and has a high accuracy.[27] The analysis attempted to review the effects of β-blocker use on stroke to address issued raised by the POISE study.[13,14,28] Unfortunately, the stroke rates recorded in the medical record were too low to allow analysis. The present study did not examine the interaction of anemia on the effects of β-blockers.[29]

Clonidine was added to the PCRRT protocol in 2004 with the publication of the clonidine study.[9] Clonidine is a second-line agent reserved for patients intolerant to β-blockers. Perioperative clonidine is used infrequently, and little can be said, with this present data base, about its efficacy.

This study reviewed the use of β-blockers but did not evaluate the effects of other cardiovascular medications or their interactions with β-blockers. Future research may be able to evaluate the efficacy of other antiischemic medications. The mortality analysis was limited to inpatients only because the mortality rate for outpatient surgery was too low to allow for analysis (0.1%). This study used retrospective epidemiologic analysis of medical records, and exact cause of death cannot be established without reviewing every chart by hand. Even with chart review, exact cause of death is frequently difficult or impossible to establish. This study reports mortality and did not try to establish cause of death; the causes of death remain undetermined. This study is observational, and thus a causal link cannot be definitely inferred, even after sophisticated statistical analysis.[30] A large cohort was obtained using computerized medical record data that could not be accurately verified as would be in a randomized study.[31]

Appropriate perioperative β-blockade in high-risk patients has been a level 1 standard of care since 1996, although guidelines for implementation have been updated several times and continue to evolve.[3–6] The PCRRT protocol is a guideline for implementation that has been adopted by a large number of hospitals and hospital systems. There are very few studies in the medical literature in which a standard of care has been proposed and implemented, adherence to the standard of care is evaluated, and the efficacy of that implementation on a hard outcome, such as mortality, is completed. The present study attempts to evaluate the entire process from adoption of a standard of care, through implementation, to a hard outcome. Appropriate use of the PCRRT protocol is clearly associated with a reduction in 30-day and 1-yr mortality.

In conclusion, the *Addition* or *Continuation* of perioperative β-blockade based on PCRRT protocol indications (patients with known coronary artery disease, peripheral vascular disease, or two risk factors for coronary artery disease including age greater than 60 yr, diabetes, hypertension, hyperlipidemia, or smoking) is associated with a reduction in 30-day and 1-yr mortality. *Withdrawal* of β-blockers in the perioperative period is associated with an increase in 30-day and 1-yr mortality.

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