Preoperative CYP2D6 metabolism-dependent β-blocker use and mortality after coronary artery bypass grafting surgery

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Objective: Recently, the role of β-blockers (BBs) in reducing perioperative mortality has been challenged. The conflicting results might have resulted from the extent of BB metabolism by the cytochrome P-450 (CYP2D6) isoenzyme. The purpose of the present study was to assess the association between the preoperative use of BBs dependent on metabolism of the CYP2D6 isoenzyme with operative mortality after coronary artery bypass grafting surgery.

Methods: We performed a retrospective study of 5248 patients who had undergone coronary bypass grafting surgery from January 1, 2001 to November 30, 2009 at Duke University Medical Center. The cohorts were defined by the preoperative use of BBs and BB type (non-CYP2D6_BBs, CYP2D6_BBs, or no BBs). Operative mortality was analyzed using inverse probability-weighted estimators with propensity score adjustment.

Results: Of the 5248 patients, 14% received non-CYP2D6_BBs, 43%, CYP2D6_BBs, and 43%, no BBs. The incidence of operative mortality was 0.8%, 2.1%, and 3.7% in the non-CYP2D6_BB, CYP2D6_BB, and no BB groups, respectively. Multivariable inverse probability-weighted–adjusted analyses showed that non-CYP2D6_BBs were associated with a lower incidence of operative mortality (odds ratio, 0.33; 95% confidence interval, 0.13-0.83; $P = .02$) compared with no BB use and a trend toward lower operative mortality (odds ratio, 0.44; 95% confidence interval, 0.16-1.07; $P = .06$) compared with CYP2D6_BBs. No significant decrease occurred in the risk of operative mortality between the CYP2D6_BB and no BB groups (odds ratio, 0.85; 95% confidence interval, 0.54-1.34; $P = .48$).

Conclusions: Among these patients, preoperative non-CYP2D6_BB use, but not CYP2D6_BB use, was associated with a decreased risk of operative mortality. (J Thorac Cardiovasc Surg 2014;147:1368-75)

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The members of the CARE Group are listed in the Appendix.

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Cardiovascular morbidity and mortality are common and costly complications in patients undergoing cardiac and noncardiac surgery.[1] Surgical coronary revascularization has been associated with a mortality rate of 2.3% and a perioperative myocardial infarction rate of ≤17%.[1,2] It is widely believed that heightened sympathetic nervous system activity in response to surgical stress plays a fundamental role in the development of perioperative cardiac complications and that pharmacologic attenuation of this response with β-blockers (BBs) will lead to improved patient outcomes.[3,4]

The benefits of BB therapy have recently been questioned by reports of side effects such as hypotension and bradycardia, which have been associated with a significantly increased incidence of perioperative death and nonfatal stroke in patients undergoing noncardiac surgery.[4] Moreover, accounting for demographic and clinical characteristics, the efficacy and toxicity of BBs in the treatment of hypertension,[5] coronary artery disease,[6] and heart failure have varied significantly,[7] even among nonsurgical patient populations.

A number of genetic variants with a substantial influence on the efficacy and safety of BBs have been characterized. including inherited differences in the metabolism of BBs. One of the most extensively studied and characterized examples of pharmacogenetic variation is the cytochrome

PM

Abbreviations and Acronyms

BB = β-blocker
CABG = coronary artery bypass grafting
CI = confidence interval
EuroSCORE = European System for Cardiac Operative Risk Evaluation score
IPW = inverse probability weighting
OR = odds ratio
PM = poor metabolizer

P-4502D6 isoenzyme or CYP2D6, which is involved in the hepatic elimination of several drugs, including analgesics, anti-arrhythmics, antidepressants, and most of the lipophilic BBs (eg, metoprolol, propranolol, carvedilol, and labetalol). This is in contrast to hydrophilic BBs, such as atenolol and sotalol, which are eliminated largely unchanged by glomerular filtration and, thus, independent of CYP2D6 activity. Metoprolol is the most dependent on this enzyme, with 70% to 80% of its biotransformation directed through this pathway.[7] Clinical studies have observed that subjects characterized as being a CYP2D6 poor metabolizer (PM) had a significantly greater risk of bradycardia,[5,8] hypotension,[5,8] and other adverse effects during metoprolol treatment.[9]

In addition, BBs have a broad therapeutic index, and the effect of PM status on the therapeutic safety of BBs metabolized by way of CYP2D6 might become clinically apparent only in patients at an increased risk of β-blockade, such as patients with poor left ventricular function.[3,9] Although there is a noticeable lack of studies examining the contribution of CYP2D6 genetic variations on the efficacy and safety of BBs in the perioperative setting is noticeable, Badgett and colleagues[10] conducted a meta-analysis of existing trials of perioperative BB use in the setting of noncardiac surgery and found that increased mortality was confined to trials that had used BBs that were dependent on the CYP2D6 metabolism. This was recently re-emphasized in a large retrospective cohort analysis of patients undergoing major noncardiac surgery.[11] They identified stronger associations with perioperative mortality among patients treated with metoprolol rather than with atenolol.[11] To date, however, no randomized or observational studies have evaluated the association between preoperative use of BBs dependent on CYP2D6 metabolism and operative mortality after cardiac surgery. Therefore, using a large observational cohort of patients who had undergone CABG surgery, we sought to determine whether the operative mortality rates differed for patients treated with BBs dependent on the CYP2D6 metabolism (CYP2D6_BBs), patients treated BBs that were independent of CYP2D6 metabolism (non-CYP2D6_BBs), and patients without BB use.

METHODS

Study Population

For the present retrospective observational study, we evaluated 5340 patients who had undergone off-pump or on pump CABG from January 1, 2001 to November 30, 2009 at Duke University Medical Center (Durham, NC).

Data Collection

After obtaining approval from the institutional review board, the perioperative variables were collected from the Duke University Medical Center databases, including the Automated Anesthesia Recordkeeping Database (intraoperative BB and other cardiovascular drug use), Cardiac Surgery Quality Assurance Database, Duke Databank for Cardiovascular Diseases, and the patients' electronic medical records. Two independent investigators (M.D.K. and S.A.E.) ascertained the data quality by performing regular crosschecks for completeness and inconsistencies between the data set assembled and the medical records.

Clinical Risk Factor Definitions

The potential clinical determinants of all-cause mortality collected for the present study included patient characteristics, preoperative and intraoperative medication use, preoperative laboratory values (serum creatinine), the European System for Cardiac Operative Risk Evaluation score (EuroSCORE; definitions of the EuroSCORE are provided in Table E1),[12] and the cardiopulmonary bypass and aortic crossclamping times. The intraoperative use and type of BBs, inotropes, vasopressors, and vasodilators were also recorded.

Cardiac Medication Use

For patients with acute coronary syndromes, cardiac medication use was noted on arrival at the hospital. For electively treated patients, this medication information was obtained routinely during the outpatient clinic visit before hospital admission for cardiac surgery. A history of cardiac medication use (α-receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, BBs, calcium channel blockers, clopidogrel, diuretics, nitrate, statins, and warfarin) was established if the patient had taken the medicine within 24 hours before cardiac surgery. According to institutional practice, the patients continued to take their medication on the evening before surgery and, absent contraindications, resumed oral medications on postoperative day 1. Aspirin was not discontinued, but clopidogrel was discontinued for ≥7 days before surgery. Warfarin was discontinued 4 days preoperatively and "bridged" with intravenous heparin infusion.

The treatment groups in the present study were determined by preoperative BB use and the BB type. Patients with a history of preoperative use of carvedilol (n = 254), labetalol (n = 25), metoprolol (n = 1936), nebivolol (n = 6), or propranolol (n = 25) were assigned to the CYP2D6_BB group. Patients with a history of preoperative use of acebutolol (n = 5), atenolol (n = 695), bisoprolol (n = 24), nadolol (n = 12), or sotalolol (n = 20) were assigned to the non-CYP2D6_BB group. Patients with no history of preoperative BB use were assigned to the no BB group. Those who had received both types of BBs preoperatively—with and without CYP2D6-dependent metabolism—were excluded from the present study. Of the initial 5340 patients evaluated, 5248 had information available on the preoperative BB type used, and their data were included in our analyses.

Outcome Classification

The outcome chosen for the present study was all-cause operative mortality, defined as deaths occurring during the same hospitalization as surgery, regardless of timing, or within 30 days of surgery, regardless of venue, unless the cause of death was clearly unrelated to the operation, such as trauma.[3] For patients who died at Duke University Medical Center, the hospital records and autopsy results, when available, were retrieved and

reviewed. In addition, the National Death Index (available at: http://www.cdc.gov/nchs/ndi.htm) was accessed to ascertain the vital status of patients discharged alive within 30 days of surgery.

Statistical Analysis

The baseline characteristics are presented as the mean ± standard deviation for continuous variables and as percentages and frequencies for categorical variables. Differences between groups with a specific treatment were assessed using the *t* test, analysis of variance, Kruskal-Wallis test, or chi-square test, as appropriate.

Because the treatment assignment to preoperative BB administration was not random, a propensity score-based approach involving inverse probability weighting (IPW) was used to control for treatment selection (see Supplemental methods). The effects of specific variables on mortality (eg, non-CYP2D6_BBs or CYP2D6_BBs compared with no BBs, or a difference between the 2 groups of BBs) were subsequently studied in multivariable logistic regression analyses with and without weights and, thus, providing results adjusted for treatment selection.

The discriminatory power of the final multivariable model of operative mortality was quantified by the c-index, corresponding to the area under the receiver operating characteristics curve, ranging from 0.5 (performance at chance) to 1.0 (optimal performance; see Supplemental Methods). The model fit of the final multivariable model was further assessed using the Hosmer-Lemeshow goodness-of-fit test. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) are reported. The analyses were performed using Statistical Analysis Systems, version 9.2 (SAS Institute, Inc, Cary, NC); $P < .05$ was considered significant.

RESULTS

The clinical characteristics of the 3 treatment groups in the study population are listed in Table 1. Of the 5248 patients, 43% had received a CYP2D6_BB, 14%, a non-CYP2D6_BB, and 43%, no BBs preoperatively. Of the 5248 patients, 137 died perioperatively. Of these, 74 were cardiac deaths. Death was attributed to multiorgan failure in 27 patients, stroke in 11 patients, and respiratory failure in 9 patients. In the remaining 16 patients, the cause of death was bleeding, intestinal necrosis, or vascular thrombosis.

The data listed in Table 1 revealed statistically significant differences among the groups for many clinical characteristics, including age, race, medical history, concomitant comorbidities, previous medications, and intraoperative characteristics. After propensity score adjustment, no significant imbalance was observed in the patient characteristics among the groups (Table E2).

Several preoperative and intraoperative variables were found in the univariable analysis to be significantly associated with an increased risk of operative mortality. However, the use of aspirin, α-receptor blockers, angiotensin-converting enzyme inhibitors, statins, and intraoperative esmolol and metoprolol were associated with significant reductions in mortality risk (Table 2). In addition, patients receiving a non-CYP2D6_BB or a CYP2D6_BB preoperatively had a lower incidence of operative mortality than the patients who did not receive a BB preoperatively (0.8% and 2.1% vs 3.7%, respectively; $P < .0001$).

TABLE 1. Baseline characteristics of study population (n = 5248)

Characteristic	BBs: No BB group (n = 2246)	BBs: CYP2D6 group (n = 2246)	BBs: Non-CYP2D6 group (n = 756)	*P* value
Demographics				
Age range (y)				.017
<55	495 (22.0)	464 (20.7)	125 (16.5)	
55-64	648 (28.9)	669 (29.8)	242 (32.0)	
65-74	683 (30.4)	730 (32.5)	258 (34.1)	
75-84	392 (17.4)	344 (15.3)	118 (15.6)	
≥ 85	28 (1.2)	39 (1.7)	13 (1.7)	
Race				.017
White	1755 (78.1)	1707 (76.0)	595 (78.7)	
Black	368 (16.4)	435 (19.4)	132 (17.5)	
Hispanic	11 (0.5)	15 (0.7)	2 (0.3)	
Asian	19 (0.8)	19 (0.8)	6 (0.8)	
Native American	91 (4.1)	68 (3.0)	21 (2.8)	
Other	2 (0.1)	2 (0.1)	0	
Female gender	643 (28.6)	655 (29.2)	230 (30.4)	.641
Medical history*				
EuroSCORE-related variables				
COPD	358 (15.9)	338 (15.0)	74 (9.8)	.0002
PVD	324 (14.4)	415 (18.5)	122 (16.1)	.001
CVA	192 (8.5)	214 (9.5)	93 (12.3)	.01
Previous cardiac surgery	24 (1.1)	22 (1.0)	6 (0.8)	.802
Chronic renal insufficiency	173 (7.7)	267 (11.9)	50 (6.6)	<.0001
Critical preoperative state	92 (4.1)	41 (1.9)	13 (1.7)	<.0001
Unstable angina pectoris	305 (13.6)	264 (11.8)	121 (16.0)	.008
Left ventricular function				<.0001
Normal	1112 (49.5)	1066 (47.5)	441 (58.3)	
Moderate dysfunction	908 (40.4)	917 (40.8)	273 (36.1)	
Severe dysfunction	226 (10.1)	263 (11.7)	42 (5.6)	
Recent MI	723 (32.2)	485 (21.6)	146 (19.3)	<.0001
Pulmonary hypertension	14 (0.6)	16 (0.7)	3 (0.4)	.64
Emergency cardiac surgery	194 (8.6)	95 (4.2)	40 (5.3)	<.0001
Postinfarct septal rupture	10 (0.4)	1 (0.04)	1 (0.1)	.016
Average logistic EuroSCORE	3.5 (1.8-7.0)	3.3 (1.8-6.8)	3.1 (1.7-6.0)	.012
Diabetes mellitus	763 (34.0)	841 (37.4)	276 (36.5)	.048
Preoperative medications				
Acetylsalicylic acid	1012 (45.1)	1758 (78.3)	570 (75.4)	<.0001
α-Receptor blockers	113 (5.0)	132 (5.9)	50 (6.6)	.21
ACE inhibitors	609 (27.1)	1200 (53.4)	360 (47.6)	<.0001

(Continued)

TABLE 1. Continued

Characteristic	BBs: No BB group (n = 2246)	BBs: CYP2D6 group (n = 2246)	BBs: Non-CYP2D6 group (n = 756)	*P* value
Angiotensin II receptor antagonist	188 (8.4)	209 (9.3)	69 (9.1)	.527
Calcium channel blockers	381 (17.0)	412 (18.3)	169 (22.4)	.004
Clopidogrel	145 (6.5)	432 (19.2)	123 (16.3)	<.0001
Diuretics	524 (23.3)	752 (33.5)	264 (34.9)	<.0001
Nitrates	334 (14.9)	957 (42.6)	311 (41.1)	<.0001
Statins	734 (32.7)	1461 (65.0)	432 (57.1)	<.0001
Warfarin	74 (3.3)	97 (4.3)	33 (4.4)	.16
Intraoperative characteristics				
Year of surgery				<.0001
2001	435 (19.4)	365 (16.3)	182 (24.1)	
2002	422 (18.8)	338 (15.0)	143 (18.9)	
2003	303 (13.5)	267 (11.9)	108 (14.3)	
2004	227 (10.1)	208 (9.3)	85 (11.2)	
2005	212 (9.4)	208 (9.3)	62 (8.2)	
2006	210 (9.3)	198 (8.8)	54 (7.1)	
2007	187 (8.3)	182 (8.1)	52 (6.9)	
2008	154 (6.9)	222 (9.9)	34 (4.5)	
2009	96 (4.3)	258 (11.5)	36 (4.8)	
Surgery type				.37
On-pump CABG	1921 (85.5)	1944 (86.6)	640 (84.7)	
Off-pump CABG	325 (14.5)	302 (13.4)	116 (15.3)	
Duration of CPB (min)	107.7 ± 59.9	109.9 ± 60.6	103.9 ± 56.4	.05
Aortic crossclamp time (min)	59.0 ± 36.7	59.4 ± 35.4	56.9 ± 34.2	.25
Intraoperative medication				
Epinephrine	1054 (46.9)	1118 (49.8)	291 (38.5)	<.0001
Norepinephrine	300 (13.4)	265 (11.8)	81 (10.7)	.10
Vasopressin	252 (11.2)	289 (12.9)	58 (7.7)	.0001
Nitroprusside	839 (37.4)	839 (37.4)	326 (43.1)	.01
Nitroglycerin	1630 (72.6)	1637 (72.9)	558 (73.8)	.80
Esmolol	78 (3.5)	72 (3.2)	24 (3.2)	.86
Metoprolol	1497 (66.7)	1427 (63.5)	482 (63.8)	.071

Data presented as mean ± standard deviation, median (interquartile range), or n (%). *BB,* β-Blocker; *EuroSCORE,* European System for Cardiac Operative Risk Evaluation score; *COPD,* chronic obstructive pulmonary disease; *PVD,* peripheral vascular disease; *CVA,* cerebrovascular accident; *MI,* myocardial infarction; *ACE,* angiotensin-converting enzyme; *CABG,* coronary artery bypass grafting; *CPB,* cardiopulmonary bypass. *The definitions of these risk factors were determined from the definitions (Table E1) used by the EuroSCORE scoring system.[12]

In multivariable analysis, a higher logistic EuroSCORE, intraoperative administration of epinephrine and norepinephrine, and an increased duration of cardiopulmonary bypass remained significant predictors of operative mortality (Table 2). Preoperative aspirin and statin use and intraoperative administration of metoprolol were associated with decreased operative mortality. After correcting for differences in the preoperative and intraoperative characteristics, only preoperative non-CYP2D6_BB use was significantly associated with a lower incidence of operative mortality compared with patients who did not take BBs (OR, 0.34; 95% CI, 0.14-0.81; $P = .015$; Table 2).

After IPW-adjusted multivariable analysis, the association between preoperative non-CYP2D6_BB use and a lower incidence of operative mortality compared with no BB use remained significant (OR, 0.33; 95% CI, 0.14-0.86; $P = .02$; Table 2). The final IPW-adjusted multivariable logistic regression model for all-cause operative mortality showed good discriminative ability and good fit (c-index, 0.775; overall goodness-of-fit Hosmer-Lemeshow test, chi-square = 6.91; $P = .55$). The degree of overoptimism was minimal at 0.004, which resulted in an adjusted c-index of 0.779.

In a secondary analysis, we also tested a hypothesis of whether the type of BB use was associated with mortality by directly comparing CYP2D6_BBs and non-CYP2D6_BBs and found a trend toward lower all-cause operative mortality for non-CYP2D6_BB treatment on IPW-adjusted multivariable analysis (OR, 0.44; 95% CI, 0.16-1.07; $P = .06$).

DISCUSSION

To our knowledge, this is the first study to compare the risk of operative mortality among CYP2D6_BB, non-CYP2D6_BB, and no BB use groups in a large population undergoing CABG surgery. The operative mortality was lower for the patients who had received non-CYP2D6_BBs preoperatively than for the patients who had received no preoperative BBs. We found, however, no difference in operative mortality between patients taking CYP2D6_BBs and those without preoperative BB therapy.

Our finding that metabolism by way of the CYP2D6 pathway might be associated with the efficacy of BBs has been supported by previous pharmacogenomic studies,[13-15] which have demonstrated an association between CYP2D6 genotype and the pharmacokinetics of BBs, particularly metoprolol. The effect of the CYP2D6 genotype appears to be large. According to clinical studies, CYP2D6 PMs had 3- to 10-fold greater plasma concentrations of metoprolol than did subjects who were extensive metabolizers with normal CYP2D6 activity.[13,16] Furthermore, the elimination half-life of metoprolol was found to be 7.5 hours in PMs versus 2.8 hours in extensive metabolizers.[13] In a recent prospective trial, the plasma concentrations of metoprolol were 4.9-fold higher in the PMs than in the non-PMs, although the dosing was similar.[5] This difference in the plasma concentrations of metoprolol was associated with significantly and persistently increased drug effects in the PMs, resulting in greater reductions in heart rate, diastolic blood pressure, and mean arterial pressure than in the non-PMs. The more pronounced heart rate-lowering effect in PMs was also supported by a study by Wuttke and

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TABLE 2. Univariable and multivariable predictors of operative mortality

Variable	Univariable analysis		Multivariable analysis		Multivariable analysis, propensity adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Demographics						
Race						
White	1.0					
Black	0.78 (0.48-1.27)	.32				
Hispanic	<0.001 (<0.001->999.99)	.99				
Asian	0.83 (0.11-6.12)	.86				
Native American	1.24 (0.54-2.85)	.62				
Other	<0.001 (<0.001->999.99)	.99				
Patient characteristics						
Diabetes mellitus	0.87 (0.61-1.25)	.46				
Logistic EuroSCORE per 1% increase	1.07 (1.06-1.08)	<.0001	1.06 (1.05-1.07)	<.0001	1.05 (1.04-1.07)	<.0001
Preoperative medication						
Acetylsalicylic acid	0.41 (0.29-0.58)	<.0001	0.60 (0.41-0.87)	.008	0.57 (0.35-0.92)	.021
α-Receptor blockers	0.37 (0.12-1.17)	.09				
ACE inhibitors	0.69 (0.48-0.98)	.04				
Angiotensin II receptor antagonists	0.46 (0.20-1.06)	.07				
BB use						
No BB group	1.0		1.0		1.0	
CYP2D6 group	0.56 (0.39-0.82)	.002	0.86 (0.59-1.23)	.40	0.85 (0.54-1.34)	.48
Non-CYP2D6 group	0.21 (0.09-0.48)	<.0001	0.34 (0.14-0.81)	.015	0.33 (0.13-0.83)	.02
Calcium channel blockers	0.85 (0.54-1.35)	.49				
Clopidogrel	0.98 (0.59-1.62)	.94				
Diuretics	0.89 (0.61-1.30)	.54				
Nitrates	0.87 (0.60-1.27)	.47				
Statins	0.46 (0.32-0.67)	<.0001	0.61 (0.42-0.90)	.012	0.55 (0.33-0.90)	.02
Warfarin	1.34 (0.62-2.91)	.46				
Intraoperative characteristics						
Year of surgery per year	0.99 (0.93-1.06)	.72				
CPB time per 10 min	1.06 (1.04-1.09)	<.0001	1.05 (1.02-1.08)	.0003	1.05 (1.01-1.08)	.01
Epinephrine	2.53 (1.76-3.65)	<.0001	1.57 (1.05-2.34)	.028	1.96 (1.21-3.19)	.007
Esmolol	0.65 (0.20-2.05)	.46				
Metoprolol	0.54 (0.38-0.76)	<.0001	0.62 (0.43-0.89)	.009	0.60 (0.38-0.95)	.03
Norepinephrine	1.70 (1.10-2.62)	.02	1.62 (1.01-2.62)	.048	1.62 (0.88-2.98)	.12
Vasopressin	2.14 (1.41-3.25)	<.0001				
Nitroprusside	0.96 (0.68-1.36)	.82				
Nitroglycerin	0.90 (0.62-1.31)	.58				

OR, Odds ratio; *CI,* confidence interval; *EuroSCORE,* European System for Cardiac Operative Risk Evaluation score; *ACE,* angiotensin-converting enzyme; *BB,* β-blocker; *CPB,* cardiopulmonary bypass.

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colleagues.[9] They found an overrepresentation of patients with the PM genotype among patients with metoprolol-associated adverse effects such as bradycardia. In a study by Kirchheiner and colleagues,[17] metoprolol use in PMs was associated with a more pronounced lowering of exercise-induced tachycardia. Because the plasma concentration of metoprolol is determined largely by CYP2D6 activity, the observed reduction in exercise-induced tachycardia was an indication of the effect of CYP2D6 PM status.[18]

In a recent meta-analysis, Badgett and colleagues[10] observed that the benefit of BBs in patients undergoing noncardiac surgery was reduced for BBs with the CYP2D6 metabolism. Increased mortality from perioperative BBs was confined to trials that had used BBs with the CYP2D6 metabolism. These findings also indicated that patients using BBs with the CYP2D6 metabolism were more susceptible to bradycardia, likely caused by lower functioning genetic polymorphisms. Of importance, patients who are ultrarapid metabolizers might be at greater risk of operative mortality, because increased activity of the CYP2D6 isoenzyme has been associated with insufficient CYP2D6_BB exposure[19] compared with extensive metabolizers (normal phenotype) who will have sufficient CYP2D6_BB exposure. However, patients who are PMs might be at high risk of operative mortality because of excessive CYP2D6_BB exposure. Our observation of increased intraoperative requirements for both epinephrine

and vasopressin in the CYP2D6_BB group compared with the non-CYP2D6_BB group (Table 1) is consistent with this mechanism. Given that the prevalence of ultra-rapid metabolizers is low (2%-3% in whites), the lack of efficacy of CYP2D6_BBs compared with no BB use observed in our study was likely a result of the combined effect of sufficient exposure and too much exposure to CYP2D6_BBs.

BBs are known to differ in their pharmacokinetic and pharmacodynamic properties. The assumption that the potential benefits in patients with different cardiovascular conditions relate to a class effect might be incorrect. Differences in half life, volume of distribution, protein binding, and route of elimination could result in differences in the duration, side effects, and efficacy of BBs. Several large studies have investigated the relationship between BB therapy and perioperative ischemic outcomes. In a group of 37,151 patients who had undergone orthopedic and abdominal surgery, Redelmeier and colleagues[20] found that the risk of myocardial infarction and mortality was lower in patients who had received atenolol than in those who had received metoprolol. Wallace and colleagues[21] studied a group of 6563 patients who had undergone noncardiac surgery and found that perioperative β-blockade with atenolol was associated with reduced short- and long-term mortality compared with metoprolol. In a recent study, London and colleagues[11] also studied a group of 75,610 propensity-matched patients who had undergone noncardiac surgery and found that perioperative exposure to atenolol was associated with a significantly lower incidence of mortality and stroke than was metoprolol. Such anti-ischemic effects and differences in specific BB type appear to be linked to adequate heart rate control. According to results of a meta-analysis of randomized trials of BB in noncardiac surgery by Beattie and colleagues,[22] *effective* control of the heart rate was associated with the greatest reduction in the incidence of postoperative myocardial infarction. Importantly, BBs other than metoprolol resulted in more effective control of the heart rate and less variability in the heart rate response. The reasons for inadequate heart rate response to BBs such as metoprolol could be multifactorial; however, pharamacokinetic properties, including the metabolic pathway, might significantly influence the efficacy of BBs. Nevertheless, several other genetic and nongenetic factors are also likely to contribute to the response and efficacy of BBs. Such genetic factors include polymorphisms in the adrenergic signaling pathway, introducing pharmacodynamic variability,[10] and nongenetic factors, such as drug–drug interactions, release or dissolution, absorption, and intestinal first-pass extraction.[23] Furthermore, the β_1-adrenergic receptor selectivity of atenolol (the typical non-CYP2D6_BB in our cohort) is twice superior to that of metoprolol (the typical CYP2D6_BB).[10] Given the retrospective nature of our study, we were unable to explore all the genetic and nongenetic factors that might influence the efficacy of BBs.

Study Limitations

As is common with retrospective study designs, our study had several limitations. Information on some important predictors of operative mortality was not prospectively collected. We used electronic medical records and physician documentation to collect additional data on the clinical risk factors and medication use, including type of preoperative BBs. Thus, the effect of some risk factors and medication use might have been biased. However, their predictive values were similar to those reported by others and in current guidelines.[1]

Although the propensity score analysis adjusted for known confounders, other unmeasured confounders could not be accounted for and the possibility of residual confounding by indication could not be completely ruled out. In addition, we defined the type of preoperative BB as treatment received at any dose within 24 hours before surgery. Therefore, BB therapy might not have been optimized for all patients and the observed differences in outcomes might have been altered if a standardized treatment regimen had been used. Finally, our analysis was restricted to the preoperative administration of BBs and, given the retrospective design of our study, we could not account for the continuation and type of BB therapy after surgery. The potential mechanisms by which preoperatively administered BBs might have the influenced surgical outcome after CABG in our study are unknown; however, factors such as a more pronounced sympathetic rebound with the shorter half-life of preoperatively administered metoprolol,[20] the extent of BB metabolism by CYP2D6 resulting in inconsistent sympatholysis, or variations in BB selectivity for the β_1-adrenergic receptor associated with reduced cerebral and renal protection could all have contributed to an increased risk of postoperative mortality.[10]

Within the P-450 superfamily of drug-metabolizing enzymes, CYP2D6 accounts for the metabolism of 25% of marketed drugs including BBs, antidepressants, opioids, anti-arrhythmics, and antihistamines. Many of these drugs are substrates, inhibitors, or inducers of the CYP2D6 enzyme, and concomitant administration of a substrate with an inhibitor or an inducer can lead to unwanted drug–drug interactions, with implications for patient safety in the clinical setting.[24] Given the retrospective nature of our study, we could not account for the list of medications that would potentially be associated with drug–drug interactions with CYP2D6_BBs and operative mortality. However, the administration of a potent CYP2D6 inhibitor would not be expected to cause a marked CYP2D6 drug–drug interaction for those exhibiting the PM phenotype. In contrast, CYP2D6-mediated drug–drug

interactions might be observed in those who exhibit the ultrarapid, extensive, or intermediate metabolizer phenotype.[19,25] Finally, we used all-cause operative mortality, rather than cardiac mortality, as our endpoint, which could have resulted in a spurious association between non-CYP2D6_BB use and outcome.

CONCLUSIONS

In patients undergoing CABG surgery, preoperative non-CYP2D6_BB use was associated with lower operative mortality after CABG surgery. However, preoperative CYP2D6_BB use was not associated with lower short-term mortality.

Our findings and those from former pharmacogenomic studies represent a step forward toward personalizing the clinical strategies to minimize perioperative cardiac complications and lower operative mortality according to genotype. The robust association between the CYP2D6 genotype and pharmacokinetics of CYP2D6-dependent BBs has provided strong evidence that the CYP2D6 genotype might influence the efficacy of BBs such as metoprolol.[5,9,10] An obvious clinical implication of the personalized perioperative BB use could be genetic testing for CYP2D6 variant alleles, especially in patients with a history of side effects from BB use or in patients starting to use CYP2D6-dependent BBs. The results of such genetic testing could lead physicians in the perioperative setting to consider lowering the dose of CYP2D6-dependent BBs in PMs[5,9,10] or increasing the dose in ultrarapid metabolizers[19] or to consider alternative therapy using CYP2D6-independent BBs such as atenolol or bisoprolol.[10] Information on the CYP2D6 genotype could also help individualize the titration of perioperative analgesic, antiarrhythmic, and antiemetic drugs that depend on the CYP2D6 metabolism, thereby preventing adverse effects.[25]

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APPENDIX

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SUPPLEMENTAL METHODS

Statistical Analysis

Inverse probability weighting and treatment model. We used the inverse probability weighting (IPW) estimators to control for treatment selection.[E1] The IPW creates a pseudopopulation in which each predictor of treatment, including demographic characteristics, medical history characteristics, and baseline medications, becomes balanced among the 3 groups. Three steps in this modeling include estimation of a treatment model, calculation of individual weights, and analysis of the outcome of interest for weighted observations.

Because the response variable (treatment group) is nominal, we used the multinomial (or generalized) logistic model to represent the treatment in terms of the predictors of treatment:

$$\log\left(\frac{\Pr(T=i|x_1,\ldots,x_K)}{\Pr(T=0|x_1,\ldots,x_K)}\right)=\alpha_i+\sum_{k=1}^{K}\beta_{ik}x_k,\quad i=0,1,2$$

where α_i are the 3 intercept parameters and β_{ik} are $3K$ slope parameters. The following variables were used as predictors: age, race, female gender, chronic obstructive pulmonary disease, peripheral vascular disease, cerebrovascular accident, previous cardiac surgery, chronic renal insufficiency, critical preoperative state, unstable angina pectoris, left ventricular function, recent myocardial infarction, pulmonary hypertension, emergency cardiac surgery, postinfarct septal rupture, diabetes mellitus, preoperative acetylsalicylic acid use, preoperative α-receptor blocker use, preoperative angiotensin-converting enzyme inhibitor use, preoperative angiotensin II receptor antagonist use, preoperative calcium channel blocker use, preoperative clopidogrel, preoperative diuretic use, preoperative nitrate use, preoperative statin use, preoperative warfarin use, and year of surgery.

The model parameters were estimated by the method of maximum likelihood using SAS Proc LOGISTIC. The estimated parameters allowed for estimating the linear predictors $\eta_i=\alpha_i+\sum_{k=1}^{K}\beta_{ik}x_k$ and the individual probabilities π_i for obtaining the response value i as follows:

$$\pi_0=\frac{1}{1+\sum_{i=1}^{2}\exp(\eta_i)}$$

for referent treatment ($i=0$) and

$$\pi_i=\pi_0\exp(\eta_i)$$

for $i=1$ or 2. As one can see, $\pi_0+\pi_1+\pi_2=1$. The estimated probabilities were used to estimate the individual weights w as reciprocal of the probability to have the actually observed treatment (ie, $w=1/\pi_{\bar{i}}$), where $\bar{i}$ ($\bar{i}$ could be 0, 1, or 2) is the treatment observed for the given patient.

Discriminatory Power

To further evaluate the discriminatory power of the final multivariable model, the bootstrap method using 1000 bootstrap samples of the size of the original cohort was used to assess the degree of overoptimism. Overoptimization occurs when application of the statistical modeling techniques results in models that inaccurately predict the outcomes on subsequent data sets. A bootstrapping procedure is 1 method that can be used to try to correct for this overoptimism.[E2] The distribution of the c-index statistics was evaluated and compared for the calculations with and without the weights adjusting the results of treatment selection.

E-References

E1. Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat Med*. 2010;29:2137-48.

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TABLE E1. Definition of variables in the EuroSCORE risk model

Risk factor	STS definition match
1. Age	Per 5 y or part thereof >60 y
2. Gender	Female
3. Chronic pulmonary disease	Patient requires pharmacologic therapy for treatment of chronic pulmonary compromise or patient had FEV_1 < 75% of predicted value
4. Extracardiac arteriopathy	Patient has peripheral vascular disease as indicated by claudication with either exertion or rest; amputation for arterial insufficiency; aortoiliac occlusive disease reconstruction; peripheral vascular bypass surgery; angioplasty or stent; documented abdominal aortic aneurysm, abdominal aortic aneurysm repair, or stent; positive noninvasive testing documented—or—patient has cerebrovascular disease, documented by any 1 of the following: unresponsive coma for >24 h; CVA (symptoms for >72 h after onset); RIND (recovery within 72 h); TIA (recovery within 24 h); or noninvasive carotid test results with 75% occlusion
5. Neurologic dysfunction disease	A central neurologic deficit persisting >24 h
6. Previous cardiac surgery	Previous cardiac surgical operations with or without CPB
7. Serum creatinine	>200 mmol/L preoperatively
9. Critical preoperative state	Any ≥1 of the following: sustained ventricular tachycardia or ventricular fibrillation requiring cardioversion and/or intravenous amiodarone, preoperative inotropic support, preoperative intra-aortic balloon pump, or patient required cardiopulmonary resuscitation within 1 h before the start of the operative procedure
10. Unstable angina	Preoperative use of intravenous nitrates
11. Left ventricular dysfunction	Normal, LVEF > 50%; moderate, LVEF 30%-50%; severe, LVEF < 30%
12. Recent MI	<21 d
13. Pulmonary hypertension	Systolic pulmonary artery pressure > 30 mm Hg
14. Emergency	Procedure status is emergent or salvage. Emergent: the patient's clinical status includes any of the following: (1) ischemic dysfunction (any of the following): (a) ongoing ischemia, including ret angina despite maximal medical therapy (medical and/or IABP); (b) acute evoking myocardial infarction within 24 h before surgery; and/or (c) pulmonary edema requiring intubation; (2) mechanical dysfunction (either of the following): (a) shock with circulatory support; or (b) shock without circulatory support. Salvage: the patient is undergoing CPR en route to the OR or before anesthesia induction
15. Other than isolated CABG	Any valve procedure in addition to or separate from CABG
16. Surgery on thoracic aorta	Aortic aneurysm/dissection repair
17. Postinfarct septal rupture	Ventricular septal defect

EuroSCORE, European System for Cardiac Operative Risk Evaluation score; *STS,* Society of Thoracic Surgery; *FEV_1*, forced expiratory volume in 1 second; *RIND,* reversible ischemic neurologic deficit; *TIA,* transient ischemic attack; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *IABP,* intra-aortic balloon pump; *CPR,* cardiopulmonary resuscitation; *OR,* operating room; *CABG,* coronary artery bypass grafting. Data from Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16:9-13.

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TABLE E2. Baseline characteristics after propensity score adjustment (n = 5248)

Characteristic	BBs: No BB group (n = 2246)	BBs: CYP2D6 group (n = 2246)	BBs: Non-CYP2D6 group (n = 756)	*P* value
Demographics				
Age range (y)				.37
<55	20.49	19.92	16.92	
55-64	29.23	29.34	32.21	
65-74	31.17	32.42	33.85	
75-84	17.67	16.6	15.29	
≥ 85	1.44	1.74	1.74	
Race				.37
White	77.97	76.02	77.31	
Black	17.65	19.61	18.3	
Hispanic	0.43	0.63	0.35	
Asian	0.8	1.01	0.88	
Native American	3.05	2.68	3.16	
Other	0.09	0.05	0	
Female gender	30.21	29.51	30.08	.94
Medical history				
EuroSCORE-related variables*				
COPD	15.75	15.43	14.41	.74
PVD	16.85	16.92	17.53	.91
CVA	10.0	10.0	10.44	.93
Previous cardiac surgery	1.03	1.07	1.17	.96
Chronic renal insufficiency	36.56	36.77	35.94	.93
Critical preoperative state	2.63	2.68	2.63	.99
Unstable angina pectoris	12.26	12.84	13.29	.77
Left ventricular function				.27
Normal	49.46	50.98	50.47	
Moderate dysfunction	41.85	39.03	42.13	
Severe dysfunction	8.69	9.99	7.39	
Recent MI	23.35	23.29	25.24	.54
Pulmonary hypertension	0.61	0.94	0.41	.40
Emergency cardiac surgery	5.75	5.73	6.2	.89
Postinfarct septal rupture	0.2	0.04	0.08	.26
Diabetes mellitus	10.65	9.7	9.55	.74
Preoperative medications				
Acetylsalicylic acid	66.26	66.58	66.79	.97
α-Receptor blockers	6.11	6.17	6.15	.99
ACE inhibitors	43.68	43.2	43.69	.97
Angiotensin II receptor antagonist	10.06	9.54	9.45	.88
Calcium channel blockers	20.69	20.58	20.65	.99
Clopidogrel	15.33	14.04	14.8	.75
Diuretics	32.92	31.07	33.33	.54
Nitrates	33.63	31.79	33.12	.68
Statins	52.62	52.36	52.63	.99
Warfarin	4.35	4.07	3.85	.84
Year of surgery				.84
2001	18.28	18.58	17.51	
2002	16.32	17.78	16.87	
2003	12.96	12.81	13.43	
2004	9.28	9.04	11.81	
2005	9.76	9.65	9.29	
2006	9.13	8.6	9.08	
2007	8.95	7.2	8.4	
2008	8.31	8.25	6.7	
2009	7.03	8.1	6.92	

Data presented as percentages. For method of propensity score adjustment, see the "Statistical Analysis" section in the "Methods" section. *BB, β*-Blocker; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation score; *COPD*, chronic obstructive pulmonary disease; *PVD*, peripheral vascular disease; *CVA*, cerebrovascular accident; *MI*, myocardial infarction; *ACE*, angiotensin-converting enzyme. *The definitions of these risk factors were determined from the definitions (Table E1) used by the EuroSCORE scoring system [Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16:9-13.]