Effects of Preoperative β-Blocker Use on Clinical Outcomes after Coronary Artery Bypass Grafting

A Report from the Japanese Cardiovascular Surgery Database

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ABSTRACT

Background: The authors evaluated the effect of preoperative β-blocker use on early outcomes in patients undergoing coronary artery bypass grafting (CABG) in Japan.

Methods: The authors analyzed 34,980 cases of isolated CABGs, performed between 2008 and 2011, at the 333 sites recorded in the Japanese Cardiovascular Surgical Database. In addition to the use of multivariate models, a one-to-one matched analysis, based on estimated propensity scores for patients with or without preoperative β-blocker use, was performed.

Results: The study population (mean age, 68 yr) comprised 20% women, and β-blockers were used in 10,496 patients (30%), who were more likely to have risk factors and comorbidities than patients in whom β-blockers were not used. In the β-blocker and non-β-blocker groups, the crude in-hospital mortality rate was 1.7 *versus* 2.5%, whereas the composite complication rate was 9.7 *versus* 11.6%, respectively. However, after adjustment, preoperative β-blocker use was not a predictor of in-hospital mortality (odds ratio, 1.00; 95% CI, 0.82 to 1.21) or complications (odds ratio, 0.99; 95% CI, 0.91 to 1.08). When the outcomes of the two propensity-matched patient groups were compared, differences were not seen in the 30-day operative mortality (1.6 *vs.* 1.5%, respectively; $P = 0.49$) or postoperative complication (9.8 *vs.* 9.7%; $P = 1.00$) rates. The main findings were broadly consistent in a subgroup analysis of low-risk and high-risk groups.

Conclusion: In this nationwide registry, the use of preoperative β-blockers did not affect short-term mortality or morbidity in patients undergoing CABG. **(Anesthesiology 2016; 124:45-55)**

THERE are ample data in the literature regarding the perioperative risk reduction associated with β-blocker use in noncardiac surgery. However, data are limited for patients undergoing coronary artery bypass grafting (CABG), who may comprise the group with the highest risk of perioperative events.[1] Small, randomized trials did not find any clinical benefits when β-blocker usage was compared with placebo in patients undergoing CABG,[2] but studies were clearly underpowered, and the 95% CIs showed a wide variation in possible events. Sentinel investigation by Ferguson *et al.*[3] reported results from more than 600,000 patients from the Society of Thoracic Surgeons (STS) database. However, controversies still exist in the literature regarding the effectiveness of preoperative β-blocker use in providing survival and safety advantages. The most recent meta-analysis on the use of β-blocker in noncardiac surgery indicated that β-blocker use was associated with a reduction in nonfatal myocardial infarction (MI) and an increase in nonfatal stroke, hypotension, and bradycardia.[4] There also was a trend toward an increase in the rate of cardiovascular mortality. Accordingly, the use of β-blockers as a quality indicator has been questioned.[5]

What We Already Know about This Topic

- It remains unclear whether preoperative β-blocker use is protective in patients undergoing coronary artery bypass grafting

What This Article Tells Us That Is New

- Using a Japanese national cardiovascular surgical registry, the authors compared patients undergoing bypass grafting who were and who were not taking β-blockers preoperatively
- Unadjusted results favored preoperative β-blocker use
- But after adjustment (the presumably more reliable results), β-blocker use did not alter complications, in-hospital mortality, or 30-day mortality

Hence, the efficacy and safety of β-blocker use during the perioperative period of vascular surgery have not been adequately evaluated. Conducting sufficiently powered, prospective randomized clinical trials to investigate the effect

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of perioperative β-blocker use on cardiovascular patients is difficult. Also, there are ethical concerns regarding the design of such trials because a significant proportion of patients are already likely to be taking β-blockers and the withdrawal of this medication, before surgery, would entail an unacceptable risk.[6] There is some evidence that indicates that acute withdrawal of a β-blocker can lead to substantial morbidity and even mortality.[7–9]

To overcome these difficulties, large-scale registries may be used to support clinical decisions. According to a previous retrospective review of approximately 630,000 patients from the STS database who underwent CABG between 1996 and 1999, β-blocker use resulted in a slight reduction in mortality; however, this was of borderline significance after propensity matching.[3] The aim of the current study was to review the Japanese National Cardiovascular Surgical Database (JCVSD) to evaluate the immediate effects of preoperative β-blocker treatment on early clinical outcomes after CABG. We conducted a propensity-matched analysis to model the association of β-blocker use with the 30-day operative mortality and cardiac morbidity, using a robust set of clinical variables.

Materials and Methods

Database

The JCVSD was established in 1998 to assess adult cardiac surgery outcomes. Data for the JCVSD are collected annually from the majority of Japanese hospitals that perform cardiovascular surgeries. Data were collected between January 2008 and December 2011 from 333 centers in the current analysis; this accounts for 73.8% of the sites performing open-heart bypass surgeries in Japan. Data completeness also was high; the overall preoperative risk factors were missing from less than 2% of the entire assembled data set. The accuracy of submitted data was maintained by data auditing conducted by administrative office members making monthly, random hospital visits and checking the data against clinical records. The ratio of JCVSD-registered data to the actual number of cases at the hospital also was confirmed in advance through a comparison with data reported to the Japanese Association for Thoracic Surgery Registry.[10]

Clinical data were entered at the sites using uniform definitions and certified software systems. The JCVSD variables and their definitions[11] are identical, for the most part, to those of the STS National Adult Cardiac Database.[12] For the current analysis, the use of β-blockers was defined as the use of any β-blocker during the 24-h period before cardiac surgery. This definition was set to assess the direct effect of β-blocker use on cardiac surgery. The definition also was consistent with that used in most previous studies that evaluated the preoperative use of β-blockers (*e.g.*, in most studies, β-blocker therapy was started on the day of surgery). Data quality standards have to be met before a local data set can be entered into the aggregate national data set. Data were maintained by the Department of Healthcare Quality Assessment, Tokyo University, Tokyo, Japan, which produces annual site-specific reports to JCVSD participants for outcome analyses and quality improvement. All available information must be registered in this national database. Therefore, all information regarding medications is required, and none of the registered patients had missing β-blocker information.

The study population for the current analysis was derived from patients in the JCVSD who underwent isolated CABG (*i.e.*, did not undergo concomitant valve surgery or other cardiac procedures) between 2008 and 2011 (n = 34,980).

Endpoints

The JCVSD outcome measures included operative mortality, defined as death within 30 days of the date of surgery, which is equivalent to "the 30-day operative mortality" defined in the STS National Adult Cardiac Database. A composite major complication was defined as any of the five postoperative, in-hospital complications: stroke, reoperation for any reason, need for postoperative mechanical ventilation for more than 24 h, renal failure with newly required dialysis, or deep sternal wound infection. In this analysis, we used postoperative stroke and prolonged mechanical ventilation as individual endpoints, in addition to major morbidity and operative mortality. This was done because of the association of postoperative stroke with β-blocker use in the Perioperative Ischemic Evaluation (POISE) study,[13] and the fact that β-blockers are associated with side effects, including bronchospasms and heart failure.[14,15] Other in-hospital outcomes included bleeding complications that warranted surgical intervention within 30 days of the original surgery, postoperative MI, postoperative renal failure (creatinine level increases to more than twice the preoperative value, an absolute value > 2.0 mg/dl, or newly initiated dialysis), cardiac tamponade that required percutaneous or operative drainage, gastrointestinal bleeding that required blood transfusion or surgical intervention, postoperative pneumonia, rehospitalization within 30 days, and an intensive care unit stay of more than 7 days.

Quality Assurance

To perform routine audits, we created the site visit working group (SV-WG). The WG members consisted of one SV-WG chief (selected from the administrative office members) and six data managers from six areas in Japan. Each month, one hospital was randomly chosen, and the SV-WG chief listed all the deceased patients and drew up printed tables showing all the entered variables for the deceased patients. The chief also created another table that included randomly picked cases from among the living patients.

Statistical Analysis

We compared baseline demographics for patients who received β-blockers with those for patients who did not.

Differences between treated and nontreated patients were determined by using a chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. The impact of preoperative β-blocker use was examined using a multiple logistic regression model that set previously identified clinical risk factors as fixed effects. For adjustment of surgical volume, we first determined the average number of procedures that each surgeon performed during the study period. We then created categorical variables for volume by ranking surgeons in order of increasing estimated total volume and selecting cutoff points that most closely sorted patients into four evenly sized groups (low, low medium, high medium, and high volume).

The modeling was also performed for subgroups of patients with relative contraindications for β-blocker use, such as respiratory disability (1-s forced expiratory volume < 75% and/or use of bronchodilators), symptoms of congestive heart failure within 2 weeks of surgery, cardiopulmonary arrest within 24 h of surgery, cardiogenic shock at the time of surgery (n = 7,787), documented left ventricular dysfunction (defined as a preoperative left ventricular ejection fraction [LVEF] < 50% [n = 4,869]), and for those who underwent CABG for urgent indications (n = 6,531).

Because treatment assignment was nonrandom, we performed a one-to-one matched analysis, based on estimated propensity scores for patients with or without preoperative β-blocker use. The log of the estimated probability that a patient received a β-blocker was calculated as the log of the odds p/(1-p), where p was the estimated propensity score (the logit). By using the estimated logits, each patient treated with a β-blocker was matched, without replacement, to the "closest" non-β-blocker patient. "Close" was defined based on the SD of the estimated logits, using calipers of width equal to 0.2 of the SD. We selected 0.2 because this value has been shown to eliminate approximately 90% of the bias due to the observed confounders.[13] If several non-β-blocker users were successfully matched using these criteria, then one of them was chosen randomly as the match. To ensure that the results were not driven by the major difference between the groups, *c*-scores for discrimination were calculated for the present propensity model and for the propensity model that forced entry of all variables in tables 1 and 2, other than intraoperative variables such as total operative time, perfusion time, or cross-clamp time. The *c*-scores from two models were virtually identical (0.722 and 0.721, respectively). Furthermore, we also calculated the standardized differences for each of the covariates to provide insight into how effectively the propensity score controlled for observed confounders. We compared early outcomes, including 30-day operative mortality and details of postoperative complications, between the groups using the Pearson chi-square test, with *P* value less than 0.05 being the criterion of statistical significance.

Table 1. Baseline Characteristics of the Study Population before and after Propensity Score Matching

	All Patients				Propensity-matched Patients			
	β	Non-β			β	Non-β		
No. of Patients	10,496	24,484	*P* Value	Standardized Difference	9,619	9,619	*P* Value	Standardized Difference
Age, yr	68.0 ± 9.6	68.7 ± 9.6	< 0.001	0.070	68.1 ± 9.5	68.2 ± 9.6	0.53	0.010
Male, %	77.8	78	0.73	0.002	77.7	78.1	0.49	0.005
Body mass index	23.8 ± 3.5	23.6 ± 3.4	< 0.001	0.060	23.7 ± 3.5	23.7 ± 3.4	0.13	0.001
Smoker, %	58.0	55.4	< 0.001	0.024	57.7	56.9	0.31	0.007
Diabetes mellitus, %	52.7	49.8	< 0.001	0.027	52.7	52.7	1.00	0.000
Diabetes mellitus, on treatment, %	43.1	40.7	< 0.001	0.023	43.3	43.4	0.83	0.002
Chronic kidney disease, %	14.1	13.1	0.018	0.013	14.0	13.9	0.92	0.001
Hyperlipidemia, %	66.9	56.5	< 0.001	0.097	65.4	64.2	0.066	0.013
Hypertension, %	82.4	73.9	< 0.001	0.092	81.2	81.1	0.85	0.001
Cerebrovascular disease, %	13.1	13.2	0.84	0.001	12.8	13.3	0.27	0.008
Carotid stenosis, %	9.4	7.8	< 0.001	0.026	9.2	8.6	0.20	0.009
Atrial fibrillation, %	4.6	3.5	< 0.001	0.026	4.2	4.0	0.47	0.005
Respiratory disability, %	9.6	9.4	0.45	0.004	9.5	9.3	0.64	0.003
Peripheral arterial disease, %	16.1	16.6	0.30	0.006	16.4	16.7	0.52	0.005
Previous PCI, %	31.1	23.8	< 0.001	0.076	28.8	28.5	0.61	0.004
Previous myocardial infarct, %	39.1	35	< 0.001	0.039	36.8	35.2	0.022	0.017
Unstable angina at the time of surgery, %	26.9	33.8	< 0.001	0.068	27.4	27.1	0.60	0.004
CCS class 3 or 4, %	28.7	34.3	< 0.001	0.054	28.9	27.9	0.12	0.011
LVEF ≤ 50%, %	53.1	49.9	< 0.001	0.029	51.2	50.0	0.081	0.013
Congestive heart failure within 2 weeks of surgery, %	11.4	13.4	< 0.001	0.027	11.2	10.9	0.46	0.005
Cardiogenic shock at the time of surgery, %	1.6	5	< 0.001	0.08	1.7	1.3	0.030	0.015

CCS = Canadian Cardiovascular Society; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table 2. Concomitant Medical Therapy of the Study Population before and after Propensity Score Matching

	All Patients				Propensity-matched Patients			
	β	Non-β	*P* Value	Standardized Difference	β	Non-β	*P* Value	Standardized Difference
No. of Patients	10,496	24,484			9,619	9,619		
Digitalis, %	1.3	0.9	< 0.001	0.018	1.3	1.0	0.107	0.012
Intravenous nitrates, %	12.1	12.4	0.001	0.004	11.7	11.7	0.875	0.001
Aspirin, %	46.3	34.6	0.455	0.11	43.4	44.6	0.089	0.012
Anticoagulants, %	14.3	15.3	< 0.001	0.014	14.1	14.4	0.536	0.005
Statins, %	55.7	29.9	0.001	0.244	52.0	52.3	0.708	0.003
ACE inhibitors, %	17.5	7.2	< 0.001	0.155	13.4	12.0	0.004	0.021
Angiotensin receptor blockers, %	39.6	23.0	< 0.001	0.169	38.5	39.0	0.564	0.004
Calcium channel blockers, %	36.4	25.7	< 0.001	0.105	35.4	37.4	0.005	0.021

ACE = angiotensin-converting enzyme.

We also performed an additional analysis, based on information available at the time of discharge, in our propensity-matched group. For this additional analysis, 365 patients (1.8%) who died during hospitalization and 3 patients who did not have discharge medication information (< 0.1%) were excluded. The remainder of the patients (n = 18,870) were further subcategorized by the presence or absence of discharge β-blocker prescriptions, as presented in figure 1. In this subgroup of patients, we compared the rate of postoperative MI and heart block, 30-day readmission, and prolonged stay in the intensive care unit (> 8 days). Postoperative MI was defined when any two of the following four criteria were met: (1) chest discomfort lasting more than 20 min, not responsive to nitrates and/or rest, (2) increase in levels of cardiac biomarkers, (3) newly developed myocardial wall motion abnormality, or (4) ST-T changes in more than two anatomically contiguous leads.

Finally, given the results of a recent analysis of "non-cardiac" surgeries in the Veterans Health Administration database that showed the benefit of perioperative β-blocker use among patients with intermediate to high risk,[16] we performed an additional matching analysis in the low-risk and high-risk subgroups, based on risk estimations made using the Japan Score system.[17] The current Japan Score

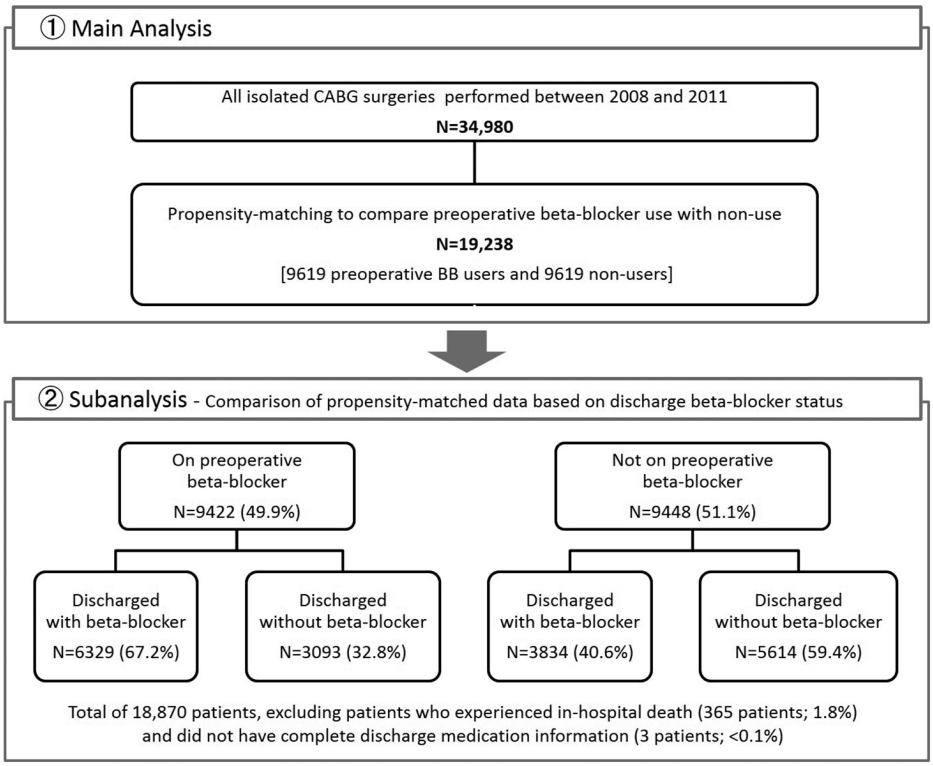

Fig. 1. β-Blocker (BB) use at the time of discharge in the propensity score-matched patients and data comparison and analysis steps. CABG = coronary artery bypass grafting.

was calculated from an 80% development sample derived from 24,704 cases of isolated CABG surgery performed between January 2006 and December 2009 and validated in the remainder of the patient data (20% validation data). Final logistic models and model performance metrics are presented in Supplemental Digital Content 1, http://links.lww.com/ALN/B199, Table S1. All analyses were performed using SPSS Version 20 (SPSS, USA).

Results

According to the preoperative profiles, women accounted for 20% of the patients, and 50% of the overall patient population had diabetes mellitus; the mean patient age was 68 yr. Off-pump CABG was performed 65% of the time, with the mean number of anastomoses being 3.0. Preoperative β-blockers were used in 10,496 patients (30%). Patients receiving β-blockers were younger (68.0 *vs.* 68.7 yr old; $P < 0.001$) than those not receiving β-blockers, but they were more likely to have risk factors or other comorbidities, such as diabetes mellitus, chronic kidney disease, or left ventricular dysfunction (tables 1–3).

The crude 30-day operative mortality rate was 1.7 and 2.7% and the crude, in-hospital major complication rate was 9.7 and 11.6% for patients receiving or not receiving preoperative β-blockers, respectively. However, after adjusting for differences in the patient characteristics (such as younger age), the use of preoperative β-blockers was not associated with 30-day mortality (odds ratio [OR] associated with β-blocker use, 1.00; 95% CI, 0.82 to 1.21) or major in-hospital complications (adjusted OR associated with β-blocker use, 0.99; 95% CI, 0.91 to 1.08).

The adjusted prematch associations of β-blocker use with individual in-hospital outcomes are presented in figure 2. There was no significant association between β-blocker and short-term outcomes, and this was consistent across all subgroups, including the relative contraindications for β-blocker use (*e.g.*, respiratory disability, n = 7,787), patients with left ventricular dysfunction (n = 4,869), and those who underwent CABG for urgent indications (n = 6,531). Of note, use of β-blocker was not associated with either improved or impaired outcome, even after adjustment for surgical case volume (Supplemental Digital Content 1, http://links.lww.com/ALN/B199, Table S2).

After propensity matching, baseline differences were balanced between users and nonusers of preoperative β-blockers; all of our demographic and operative characteristics had postmatching standard reference values less than 0.1; standardized differences of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively. In addition, the overall expected mortality rates (calculated from Japan Score) were 0.0182 ± 0.00042 and 0.0253 ± 0.00038 for β-blocker and non-β-blocker, respectively, before matching ($P < 0.001$); after matching, the rates were 0.0186 ± 0.00045 and 0.0176 ± 0.00038 ($P = 0.10$). Details of the patients' medical and operative backgrounds are given in tables 1 and 2. In terms of immediate outcomes for the matched patients, the 30-day operative mortalities were 1.6 and 1.5% for the

Table 3. Operative Characteristics of the Study Population before and after Propensity Score Matching

	All Patients				Propensity-matched Patients			
	β	Non-β			β	Non-β		
No. of Patients	10,496	24,484	*P* Value	Standardized Difference	9,619	9,619	*P* Value	Standardized Difference
Multivessel disease, %	94.3	93.1	< 0.001	0.023	94.2	93.8	0.30	0.008
Triple-vessel disease, %	71.8	68.6	< 0.001	0.032	71.4	70.5	0.16	0.010
Left main disease, %	37.5	42.1	< 0.001	0.044	38.3	38.6	0.65	0.003
Surgery status, urgent, %	7.4	13	< 0.001	0.082	7.9	7.8	0.77	0.002
Surgery status, emergent, %	3.0	9.2	< 0.001	0.11	3.2	2.7	0.056	0.014
Reoperation, %	2.2	1.6	< 0.001	0.023	2.0	2.1	0.58	0.004
Total operative time, min	328.4 ± 103.3	316.8 ± 101.7	< 0.001	0.11	326.9 ± 103.2	320.4 ± 102.5	< 0.001	0.06
Perfusion time, min	143.0 ± 56.7	137.7 ± 54.6	< 0.001	0.10	142.3 ± 56.6	139.1 ± 54.6	0.027	0.06
Cross-clamp time, min	97.3 ± 40.0	89.9 ± 38.6	< 0.001	0.19	97.0 ± 40.2	93.6 ± 39.4	0.009	0.09
Number of anastomoses, %	3.14 ± 1.17	3.02 ± 1.18	< 0.001	0.10	3.11 ± 1.16	3.10 ± 1.19	0.32	0.01
< 2	28.8	32.7	< 0.001	0.038	29.7	30.0	0.71	0.003
3	35.2	35.8	0.24	0.006	35.3	35.5	0.87	0.001
4–5	33.5	29.6	< 0.001	0.039	32.6	32.4	0.85	0.001
> 6	2.4	1.9	< 0.001	0.018	2.3	2.1	0.24	0.008
Off-pump surgery, %	69.6	62.9	< 0.001	0.065	68.3	69.1	0.26	0.008
Off-pump surgery converted to on-pump, %	2.1	2.2	0.60	0.003	2.0	2.3	0.14	0.011
Left IMA use, %	92.0	90.8	< 0.001	0.019	91.9	91.7	0.53	0.005
Right IMA use, %	36.6	31.2	< 0.001	0.053	35.4	35.9	0.42	0.006
Blood transfusion, %	66.6	66.9	0.54	0.003	66.6	64.4	0.001	0.024

IMA = internal mammary artery.

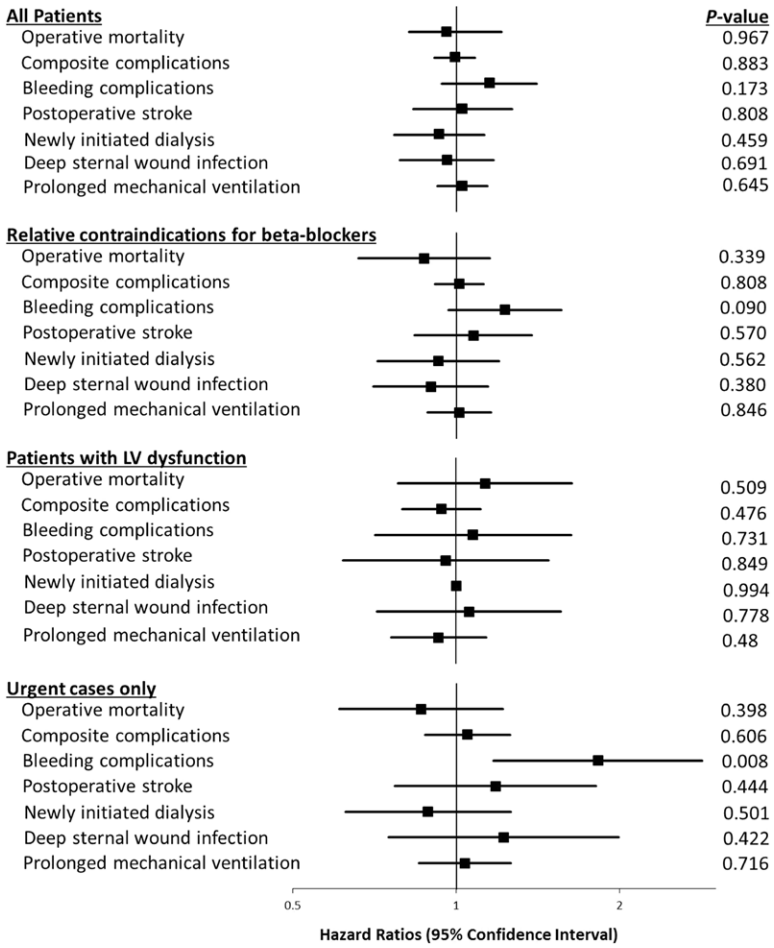

Fig. 2. Adjusted risk of various in-hospital outcomes among all patients and the subgroups of patients with relative contraindications for β-blocker, such as respiratory disability, congestive heart failure within 2 weeks of surgery, cardiopulmonary arrest within 24 h of surgery, cardiogenic shock at the time of surgery (n = 7,787), left ventricular (LV) dysfunction (n = 4,869), and those undergoing coronary artery bypass grafting for urgent indications (n = 6,531).

β-blocker and non-β-blocker groups, respectively (P = 0.49). The overall incidence of postoperative complications, such as stroke (1.3 and 1.4%; P = 0.66), prolonged mechanical ventilation (6.0 and 5.6%; P = 0.43), or perioperative MI (0.8 and 0.7%; P = 0.37), was also similar between patients using and not using β-blockers, respectively (table 4).

Among patients who were using preoperative β-blockers, more patients were discharged without β-blockers when they also had newly initiated dialysis, prolonged mechanical ventilation, or postoperative heart block requiring permanent pacemaker placement. However, in this subgroup analysis, there was no significant difference in the rate of postoperative MI, prolonged intensive care unit stay, or 30-day readmission between those who were discharged with β-blockers and those who were not (table 5). Among those who were not on preoperative β-blockers, more patients were discharged with β-blockers if they experienced postoperative atrial fibrillation (POAF, 50.6% discharged on β-blocker; no POAF, 38.2% discharged on β-blocker; P < 0.001). There were no significant differences in the rate of postoperative MI, prolonged intensive care unit stay, or 30-day readmission between those who were discharged on β-blockers and those who were not.

The immediate outcomes from the use of preoperative β-blocker were compared in two different risk groups (low and high risk). These patients were matched separately, based on a preoperative risk estimation derived from their Japan Scores. The low-risk groups of patients with and without β-blocker included 1,810 and 1,815 patients, and the high-risk groups included 2,439 and 2,418 patients, respectively. The operative mortalities were 0.1 and 0.3% (P = 0.10), respectively, in low-risk patients and 4.7 and 4.5% (P = 0.67) in high-risk patients. β-Blocker use was not associated with a difference in any of the postoperative complication rates, including stroke, prolonged mechanical ventilation, or perioperative MI, in either of these patient subgroups (table 6).

Discussion

The findings from the current study demonstrated that preoperative β-blocker use was not associated with a significant decrease in 30-day operative mortality or in in-hospital

Table 4. Early Postoperative Outcomes of the Study Population before and after Propensity Score Matching

	All Patients				Propensity-matched Patients			
	β	Non-β	Odds Ratio (95% CI)	*P* Value	β	Non-β	Odds Ratio (95% CI)	*P* Value
No. of Patients	10,496	24,484			9,619	9,616		
Operative mortality, %	1.7	2.7	0.607 (0.512–0.719)	< 0.001	1.6	1.5	1.085 (0.885–1.361)	0.49
Composite complications, %	9.7	11.6	0.823 (0.763–0.888)	< 0.001	9.8	9.7	1.001 (0.910–1.101)	1.00
Bleeding complications, %	1.6	1.5	1.046 (0.869–1.074)	0.64	1.6	1.4	1.120 (0.887–1.416)	0.37
Postoperative stroke, %	1.3	1.5	0.873 (0.718–1.061)	0.18	1.3	1.4	0.940 (0.736–1.200)	0.66
Newly initiated dialysis, %	1.7	2.2	0.765 (0.644–0.908)	0.020	1.7	1.7	0.994 (0.799–1.237)	0.96
Deep sternal wound infection, %	1.5	1.6	0.942 (0.782–1.134)	0.54	1.5	1.5	0.952 (0.754–1.202)	0.68
Prolonged mechanical ventilation, %	6.0	7.6	0.771 (0.702–0.846)	< 0.001	6.0	5.8	1.050 (0.931–1.184)	0.43
Postoperative myocardial infarction, %	0.8	0.9	0.946 (0.735–1.216)	0.70	0.8	0.7	1.158 (0.840–1.597)	0.37
Postoperative renal failure, %	4.0	4.5	0.902 (0.805–1.012)	0.81	4.1	3.9	1.033 (0.894–1.194)	0.66
Tamponade, %	0.9	0.9	0.932 (0.731–1.189)	0.62	0.9	0.8	1.087 (0.803–1.472)	0.59
Gastrointestinal bleeding, %	1.2	1.4	0.885 (0.721–1.086)	0.26	1.2	1.3	0.967 (0.750–1.246)	0.80
Postoperative pneumonia, %	1.9	2.5	0.772 (0.657–0.907)	0.020	1.9	1.9	1.006 (0.818–1.236)	1.00
Prolonged stay in intensive care unit (> 8 days), %	5.1	7.6	0.657 (0.595–0.725)	< 0.001	5.2	5.3	0.973 (0.857–1.105)	0.67
Rehospitalization within 30 days, %	2.1	2.1	1.023 (0.871–1.200)	0.78	2.1	2.3	0.930 (0.767–1.128)	0.46

complications, such as stroke, prolonged ventilation, or perioperative MI. These findings were consistent among the various subgroups, such as the group without relative contraindications for β-blocker or the group that included urgent procedures only. In addition, when the outcomes of the two propensity-matched patient groups were compared, differences were not seen in the aforementioned outcomes. The main findings were broadly consistent in the analysis of low-risk and high-risk groups, according to preoperative background information. Although there were some alterations in the use of β-blockers during the perioperative period, they did not seem to alter the main outcomes of the study.

At present, clinical guidelines for CABG surgery recommend preoperative β-blockers for patients without specific contraindications.[18,19] However, the magnitude of the effect

Table 5. Incidence of Perioperative Events, According to β-Blocker Usage at the Time of Discharge

	Patients on Preoperative β-Blockers, n = 9,422 (49.9%)				Patients Not on Preoperative β-Blockers, n = 9,448 (51.1%)			
	Discharged with β-Blockers	Discharged without β-Blockers			Discharged with β-Blockers	Discharged without β-Blockers		
No. of Patients	6,329 (67.2%)	3,093 (32.8%)	Odds Ratio (95% CI)	*P* Value	3,834 (40.6%)	5,614 (59.4%)	Odds Ratio (95% CI)	*P* Value
Bleeding complications, %	1.4	1.4	1.012 (0.699–1.467)	1.000	1.1	1.4	0.766 (0.526–1.116)	0.194
Postoperative stroke, %	1.0	1.4	0.742 (0.502–1.098)	0.145	1.3	1.1	1.207 (0.832–1.753)	0.336
Newly initiated dialysis, %	1.1	1.6	0.648 (0.449–0.934)	0.023	1.4	1.2	1.205 (0.841–1.725)	0.309
Deep sternal wound infection, %	1.2	1.4	0.871 (0.596–1.274)	0.489	1.2	1.4	0.830 (0.576–1.194)	0.363
Prolonged mechanical ventilation, %	4.6	6.8	0.662 (0.551–0.794)	< 0.001	5.2	4.8	1.089 (0.903–1.314)	0.386
Postoperative myocardial infarction, %	0.6	0.7	0.742 (0.438–1.258)	0.265	0.6	0.6	0.894 (0.525–1.522)	0.789
Postoperative heart block, %	0.3	0.6	0.487 (0.262–0.907)	0.027	0.2	0.4	0.487 (0.207–1.147)	0.122
Prolonged stay in intensive care unit (> 8 days), %	4.2	5.0	0.820 (0.669–1.004)	0.056	5.1	4.4	1.153 (0.951–1.398)	0.150
Rehospitalization within 30 days, %	2.2	2.0	1.122 (0.830–1.517)	0.498	2.3	2.3	1.030 (0.784–1.353)	0.834

Table 6. Postoperative Outcomes in Matched Patients, Risk Stratified Based on Baseline Background Characteristics

	Low-risk Patients, Matched				High-risk Patients, Matched			
	β	Non-β			β	Non-β		
No. of Patients	1,810	1,815	Odds Ratio (95% CI)	*P* Value	2,439	2,418	Odds Ratio (95% CI)	*P* Value
Operative mortality, %	0.1	0.3	0.200 (0.023–1.717)	0.103	4.7	4.5	1.058 (0.809–1.385)	0.679
Composite complications, %	4.9	4.4	1.121 (0.823–1.527)	0.469	18.3	19.2	0.941 (0.815–1.087)	0.411
Bleeding complications, %	0.9	0.9	0.943 (0.475–1.872)	0.886	2.4	2.2	1.122 (0.772–1.630)	0.547
Postoperative stroke, %	0.9	0.8	1.147 (0.558–2.356)	0.709	2.5	2.1	1.187 (0.815–1.729)	0.372
Newly initiated dialysis, %	0.3	0.4	0.625 (0.204–1.915)	0.407	4.4	4.5	0.988 (0.753–1.296)	0.928
Deep sternal wound infection, %	1.0	1.2	0.858 (0.455–1.615)	0.634	2.4	2.3	1.062 (0.732–1.539)	0.753
Prolonged mechanical ventilation, %	2.1	1.9	1.119 (0.706–1.775)	0.632	12.9	13.1	0.979 (0.829–1.157)	0.806
Postoperative myocardial infarction, %	0.6	0.7	0.847 (0.379–1.896)	0.686	1.0	0.9	1.178 (0.658–2.110)	0.581
Postoperative renal failure, %	1.5	1.4	1.081 (0.631–1.850)	0.778	8.4	8.4	1.003 (0.819–1.228)	0.977
Tamponade, %	0.4	0.7	0.538 (0.214–1.351)	0.999	1.6	1.0	1.616 (0.963–2.695)	0.318
Gastrointestinal bleeding, %	0.5	0.8	0.714 (0.316–1.612)	0.180	2.2	2.6	0.846 (0.587–1.218)	0.640
Postoperative pneumonia, %	0.5	0.4	1.128 (0.434–2.930)	0.416	4.8	4.4	1.105 (0.845–1.445)	0.368
Rehospitalization within 30 days, %	2.0	1.6	1.249 (0.763–2.046)	0.804	2.2	2.8	0.765 (0.532–1.101)	0.466
Prolonged stay in intensive care unit (> 8 days), %	1.5	1.5	0.966 (0.567–1.645)	0.376	12.3	11.9	1.037 (0.873–1.232)	0.148

varies considerably across studies, with the literature supporting the use of β-blockers being modest, at best; the supportive literature is based on a few small, nonblinded studies with a focused patient population.[13,20] The study by Ferguson *et al.*,[3] upon which preoperative β-blocker use rests, showed only a slight reduction in mortality, which was of borderline significance after propensity matching (OR, 0.97; 95% CI, 0.93 to 1.00). Furthermore, the procedures in the previous study were performed in the 1990s and were predominantly on-pump. Reflecting the current practice of cardiovascular surgery, over half of our patients underwent off-pump surgery. Finally, the study reported a trend toward increased mortality in a subgroup of patients with an LVEF of less than 30%. We also performed a subanalysis in the patients with a mildly reduced ejection fraction (defined as a preoperative LVEF < 50%; N = 6,531) and severely reduced ejection fraction (LVEF < 30%; N = 1,039); this showed no association between the use of β-blocker and outcome. The present data, from the Japanese national registry, reflect the practical use of β-blockers in the "real world" and seem scientifically sound, with the analyses showing consistent results.

The effects of β-blocker use may vary depending on the preoperative risks of the patients.[18,21,22] Therefore, we analyzed the association of β-blocker use with perioperative outcomes in various subgroups, but the results were similar in all cases. The effect of β-blockers was neutral, even when patients with left ventricular dysfunction were analyzed separately, and when low-risk and high-risk patients, based on preoperative variables, were matched separately. Several authors postulated that the preoperative administration of β-blockers in these patients could contribute to a profound lowering of heart rates and blood pressures in the early postoperative phase, resulting in shock and renal dysfunction.

Implementation of patient care under stringent guidelines might have led to the neutral effect of β-blocker use. The beneficial effects of β-blockers seem less pronounced under the modern application of evidence-based medications and appropriate preoperative evaluations.[23] Current recommendations typically include aspirin or lipid-lowering agents, and approximately 50% of these patients used an angiotensin-converting enzyme inhibitor. These medications for secondary prevention further decrease the risk of perioperative events. Reflecting modern, real-world, cardiovascular surgical practice, we observed a relatively low rate of 30-day operative mortality and in-hospital complications.

In addition, international differences in the patterns of practice, as well as the ethnic background of the patients, may also have influenced the observed magnitude of the effects of β-blocker treatment. The rate of β-blocker use varies in international registries compared with the rates reported in clinical studies. In the current analysis, only 30% of patients received preoperative β-blockers. This rate is considerably lower than the β-blocker prescription rate reported from North America (50 to 60%),[3] but it is similar to the rate reported from other studies conducted in Japan.[24] Genetic variants strongly alter the responsiveness to β-blockade, and increased responsiveness to β-blockade, among Asians, has been noted previously.[25] In an early pharmacokinetic/pharmacodynamic study, Chinese subjects had at least a two-fold greater sensitivity to the β-blocking effects of propranolol than did white subjects.[26] Furthermore, concern over the use of β-blockers has emerged in Japan because Japanese patients with coronary artery disease (CAD) have higher incidences of coronary spasms compared with patients in other ethnic groups.[27,28] In the Japanese Beta-Blockers and Calcium Antagonist Myocardial Infarction study, the incidence of coronary spasms was

significantly higher in the β-blocker group than in the calcium antagonist group (1.2 and 0.1%; $P = 0.027$), without any difference in the incidence of cardiovascular death (1.2 and 1.1%; $P = 0.37$).[29] These differences may have contributed to the lower rate of β-blocker use in this population.

Clinical guidelines suggest that the perioperative β-blocker dose should be titrated to achieve adequate heart rate control and increase the likelihood that patients will benefit from the medication. However, the relation between the magnitude of heart rate reduction and the efficacy of β-blockers has not been confirmed. In a recent meta-analysis, no significant relation was observed between β-blocker dose and improvement in all-cause mortality. In addition, the results from the POISE trial indicate that routine administration of high-dose β-blockers, in the absence of dose titration, is not useful and may be harmful.[13] Therefore, the preoperative use of β-blockers may have a limited role in reducing the risk of perioperative events.

The low 30-day operative mortality and in-hospital complication rates are also consistent with other large-scale cardiovascular registry studies conducted in East Asia.[30,31] A previously published study had an unadjusted operative mortality rate of 2.8 to 3.4%,[3] whereas the 30-day operative mortality rate was 1.7 to 2.7%. Therefore, insufficient statistical power may have played a role in the current study. Other potential explanations for the lack of a significant association of β-blocker use with improved outcomes include selection bias and/or the close monitoring associated with prolonged hospital stays under the national insurance coverage system in Japan.

The use of statins and aspirin, which reduce mortality in patients with CAD, was low in our patients; approximately 50% received preprocedural statins (within 24 h of surgery) and aspirin (within 5 days of surgery). This finding suggests that obstacles persist in the identification of ideal patients and in balancing the risks and benefits of treatment. The increasing proportion of patients with comorbidities in the modern era of CABG surgery may render treatment more challenging. Gaps in care might also result from inadequate provider knowledge and structural inadequacies in the systems of care. Our findings underscore the need for national initiatives to understand the reasons for persistent gaps in care and to improve the use of evidence-based care for CABG patients.

Our study has several important limitations. First, selection bias regarding the use of β-blockers is unavoidable in observational studies. Although we used a propensity score to adjust for baseline β-blocker use, we could not exclude the influence of unmeasured confounders on clinical outcomes. However, as listed in our tables (tables 1–3), all of our demographic and operative characteristics had postmatching standard reference values less than 0.1; standardized differences of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively.[32] Second, we did not have clarification of MI history (recent *vs.* nonrecent or description of time since MI). This might have been useful in identifying the role of β-blockers, particularly because the benefit of β-blockers observed in early studies may been driven by those with recent MIs, a cohort known to benefit from aggressive β-blockade. Third, our analyses of β-blocker use were limited to class effects and categorical/qualitative effects because we did not monitor the use of individual drugs or their dosages. Kohro *et al.*[33] have described these data previously in 13,812 Japanese patients with angiographically confirmed CAD (with ≥ 75% stenosis). The study was performed during approximately the same time period as our study, and the most frequently used β-blocker was carvedilol (1,421 of 4,160, 34.1%), followed by metoprolol tartrate (913 of 4,160, 9.3%), atenolol (774 of 4,160, 14.8%), and bisoprolol (547 of 4,160, 8.8%). Finally, the incidence of β-blocker therapy withdrawal in the non-β-blocker group could have affected our result. Because the reason for β-blocker discontinuation was not recorded in JCVSD, it remains unclear whether β-blocker discontinuation influenced the occurrence of POAF or *vice versa* (POAF occurrence might have led to the use of β-blockers postoperatively). In the current study, β-blocker-naive patients who experienced POAF, 50.6% were discharged on β-blockers (*vs.* 38.2% of patients who did not experience POAF); therefore, latter scenario seemed to have occurred rather frequently. Whether the timing of β-blocker initiation or discontinuation or other unrecorded covariates may contribute to this observation warrants further investigation.

In conclusion, in a propensity-matched, balanced cohort of CABG patients, the use of β-blockers was not associated with decreased mortality or in-hospital complications, regardless of the patient's preoperative risk profile. The present findings suggest that preoperative β-blocker use in patients undergoing CABG is not associated with improved short-term outcomes.

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Competing Interests

Dr. Kohsaka received unrestricted research grants for the Department of Cardiology, Keio University School of Medicine, Tokyo, Japan, from Pfizer Japan Inc. (Tokyo, Japan) and Bayer Pharmaceutical Co., Ltd. (Osaka, Japan). The other authors declare no competing interests.

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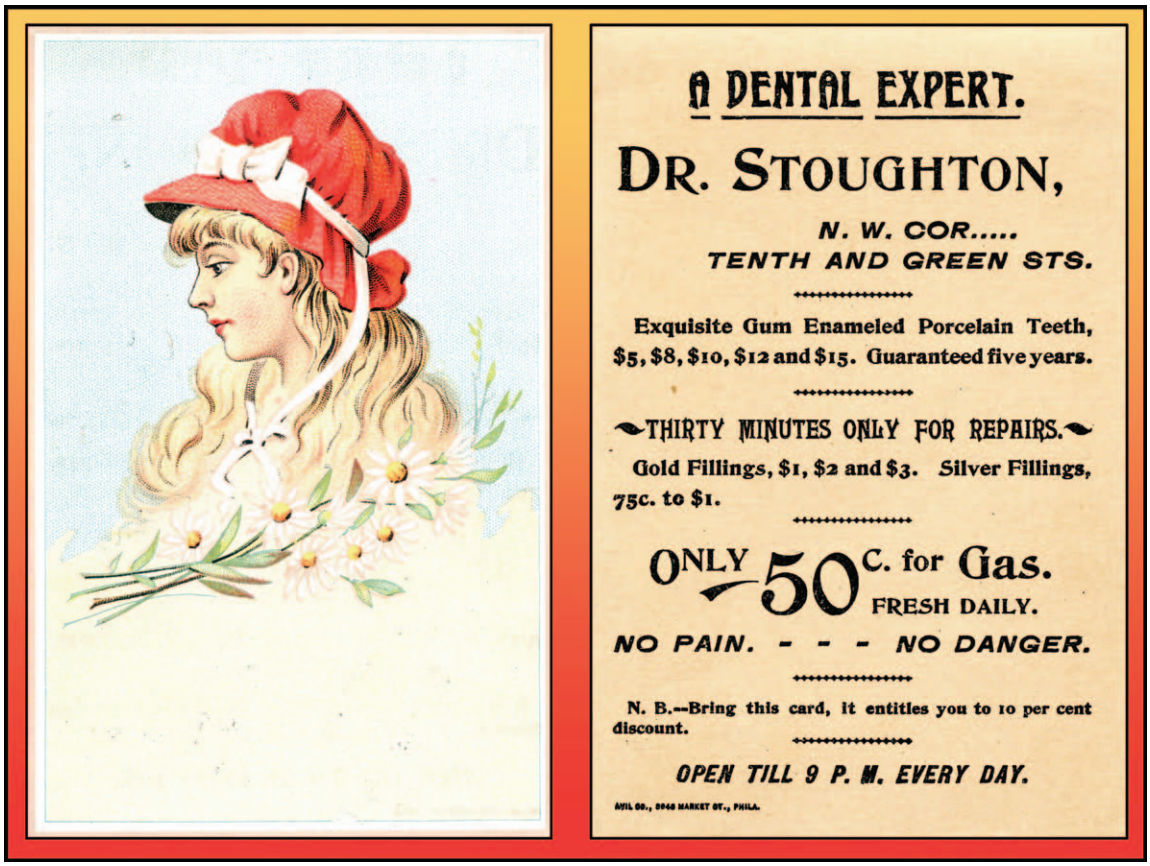
Dr. H. A. Stoughton's Fresh Laughing Gas



At the northwest corner of 10th & Green Streets in Philadelphia, Pennsylvania, Dr. Herbert Arlington Stoughton practiced as "a dental expert." The reverse (back, *right*) of his trade card notes that his laughing gas was made "fresh daily," an important point in the late 1800s when leaky anesthetic equipment and even pockets of moisture could rob gas mixtures of their potency. Before the widespread use of compressed gas cylinders for nitrous oxide, many dentists and surgeons had to "bake up" their own laughing gas for anesthetic purposes. Advertised at "only 50 c." (cents), the nitrous oxide gas cost about $67 in labor value in year 2015 U.S. dollars. On the obverse (front, *left*) of Dr. Stoughton's trade card, he used an eye-catching image of a young woman with long tresses covered partially by a red bonnet. Note, however, that he chose not to stamp any additional business information onto the white blank space provided at the obverse's bottom by the manufacturer of this mass-produced trade card. This item is part of the Wood Library-Museum's Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists, Inc.)

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