Short-term effects of preoperative beta-blocker use for isolated coronary artery bypass grafting: A systematic review and meta-analysis

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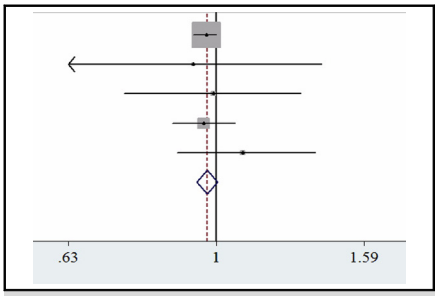
ABSTRACT

Objective: The use of preoperative beta-blockers has been used as a quality standard for patients undergoing coronary artery bypass grafting (CABG). However, the benefits of beta-blockers use before CABG remain controversial. We performed a systematic review and meta-analysis to investigate the short-term effects of preoperative beta-blocker use for patients undergoing isolated CABG.

Methods: We searched PubMed, Embase, and the Cochrane Library for English articles published from inception to August 16, 2016. Observational studies comparing preoperative beta-blockers therapy or non-beta-blockers therapy were considered eligible for the current study.

Results: Six observational studies with 1,231,850 patients were included. The pooled analyses of unadjusted outcome (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.71-0.95; $P = .007$) or risk-adjusted outcome (OR, 0.95; 95% CI, 0.92-0.97; $P = .000$) showed slight reduction in operative mortality, whereas an insignificant difference in mortality rate was observed in pooling postoperative data from propensity score analysis (OR, 0.97; 95% CI, 0.94-1.00; $P = .088$). Removing one study that used propensity-score covariate adjustment, subgroup analysis of propensity-matched patients (313,417 in each group) still generated a statistically nonsignificant benefit for preoperative beta-blocker use (OR, 0.97; 95% CI, 0.94-1.00; $P = .093$). Furthermore, the preoperative use of beta-blockers did not reduce the incidence of major postoperative complications, such as postoperative myocardial infarction, stroke, atrial fibrillation, reoperation, renal failure, prolonged ventilation, and sternal wound infection.

Conclusions: Our study suggests that the use of preoperative beta-blockers did not reduce either operative mortality or the incidence of postoperative complications in patients undergoing CABG. (J Thorac Cardiovasc Surg 2018;155:620-9)



Forest plot of operative mortality outcome from propensity score analysis.

Central Message

The use of preoperative beta-blockers did not reduce either operative mortality or the incidence of postoperative complications in patients undergoing coronary artery bypass grafting.

Perspective

The use of preoperative beta-blockers has been used as a quality standard for patients undergoing coronary artery bypass grafting (CABG). However, the benefits of beta-blockers use before CABG remain controversial. This study suggests that the use of preoperative beta-blockers does not have short-term benefits for patients undergoing CABG.

See Editorial Commentary page 630.

Currently, coronary heart disease remains the leading cause of death worldwide.[1] Coronary artery bypass grafting (CABG) remains the standard of care for patients with complex, multivessel coronary artery disease.[2-5] In patients with angina, myocardial ischemia commonly results from a prolonged mismatch between oxygen demand and supply.[6-8] As one of the most commonly used drugs for the treatment of coronary artery disease, beta-blockers can attenuate cardiac ischemia by correcting the imbalance between oxygen demand and supply.[7,9,10] However, beta-blockers may cause hemodynamic

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Abbreviations and Acronyms

AF = atrial fibrillation
CABG = coronary artery bypass grafting
CI = confidence interval
MI = myocardial infarction
OR = odds ratio
PSA = propensity score analysis
RA = risk-adjusted
RCTs = randomized controlled trials

instability, bronchospasm, and postoperative congestive heart failure, and, consequently, lead to poor prognosis.[11,12]

At present, the effectiveness and safety of preoperative beta-blocker use in patients undergoing isolated CABG remain controversial. In the late 1990s, preoperative beta-blocker use was demonstrated to be associated with a lower operative mortality.[13] Since 2007, the use of preoperative beta-blockers has been used as a quality standard for patients undergoing CABG.[14] However, there are limited studies investigating the effects of preoperative beta-blocker use for patients undergoing isolated CABG. Indeed, very few randomized controlled trials (RCTs) have examined the benefits of preoperative beta-blocker use in CABG. In contrast, some retrospective cohort studies showed that the use of preoperative beta-blockers did not affect either short-term mortality or morbidity in patients undergoing CABG.[15,16]

To date, no meta-analysis has investigated the clinical outcomes of preoperative beta-blocker use in CABG. Moreover, the majority of clinical trials have targeted beta-blocker use after CABG rather than their preoperative use.[17,18] Although recent guidelines have downgraded the recommendations for initiation of beta-blockers in high-risk patients with coronary disease, the supporting evidence is inadequate. Given the debatable efficacy of preoperative blockers, we conducted a systematic review and meta-analysis of all published studies comparing a preoperative beta-blocker group with a non–beta-blocker group, aiming to investigate the short-term effects of preoperative beta-blocker use for patients undergoing isolated CABG.

MATERIALS AND METHODS

Searching Platforms and Methods

This systematic review and meta-analysis was reported according to the guidelines of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group[19] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[20] We searched PubMed, Embase, and the Cochrane Library for English articles published from inception to August 16, 2016, using the following search terms: "beta-blocker" or "β-blocker" and "coronary artery bypass grafting." We also searched for ongoing or completed studies on the same topic on ClinicalTrials.gov and reviewed references of the identified studies to identify further relevant studies.

Literature Selection Criteria

The population, intervention, comparator, outcome, and study design approach was used to establish the selection criteria for our meta-analysis. Studies meeting the following criteria were included:

1. Population: The population of interest was patients undergoing isolated CABG. Studies targeting patients undergoing CABG with other cardiac operations or other cardiac procedures (heart valve repair or replacement, aneurysm repair, or percutaneous coronary intervention) were excluded. When the same population was reported in the several articles, only the largest study was considered for inclusion.
2. Intervention: Preoperative beta-blocker use. Studies that focused on the combination therapy of beta-blockers and other drugs were not included in the meta-analysis.
3. Comparator: The beta-blocker group versus the non-beta-blocker group.
4. Outcome: Operative mortality, myocardial infarction (MI), stroke, atrial fibrillation (AF), prolonged ventilation, renal failure, reoperation, and sternal wound infection.
5. Study Design: Observational epidemiological studies (cohort study).

Data Collection and Quality Assessment

Two authors (L.W. and H.W.) independently assessed the selected literature and singled out all observational studies meeting the inclusion criteria. For cases with missing information or when clarification was needed, we contacted the original authors to obtain additional information. Disagreements within the team were resolved through discussion. The 2 authors independently reviewed all eligible studies and extracted the following information: first author and year of publication, setting, design, study size, inclusion and exclusion criteria, basic patient characteristics, intervention, and outcomes (as mentioned previously). The Newcastle Ottawa Scale was used to assess the methodologic quality of observational studies.[21] A greater overall score indicated a lower risk of bias; a score of 5 or less (of 9) suggested a high risk of bias. Risk of bias also was evaluated independently by 2 authors.

Outcomes and Definitions

The primary outcome was operative mortality, defined as death within 30 days of surgery. The secondary outcomes were the following major postoperative, in-hospital complications: MI, stroke, AF, prolonged ventilation, renal failure, reoperation, and sternal wound infection. Prolonged ventilation included any pulmonary ventilator use for more than 24 hours. Postoperative renal failure was defined as creatinine level increases to more than twice the preoperative value, an absolute value >2.0 mg/dL, or new requirement for dialysis. Any reoperation included reoperation for bleeding, graft occlusion, valvular dysfunction, or other cardiac reasons.

Statistical Analyses

This study used Stata/SE12.0 (StataCorp, College Station, Tex) for data analysis. The results were expressed as odds ratios (OR) with a 95% confidence interval (95% CI). Statistical heterogeneity was evaluated with the Q statistic ($P < .1$ was considered indicative of statistically significant heterogeneity) and I^2 test ($I^2 > 50\%$ denoted a high degree of statistically significant heterogeneity).[22] The random-effects model was used for all comparisons due to the wide range of clinical and methodological variability across the studies. The pooled OR estimates were calculated with the Mantel-Haenszel method. Pooled analyses of unadjusted data, risk-adjusted (RA) data, and data from propensity score analysis (PSA) were all performed to identify the effect of preoperative risks on outcomes. Pooled analysis of PSA data was the primary analysis. Subgroup analysis of propensity-matched data were performed to control bias and to test the sensitivity of the primary result. Publication biases were evaluated with the Begg and Egger tests.[23,24] Furthermore, one-way

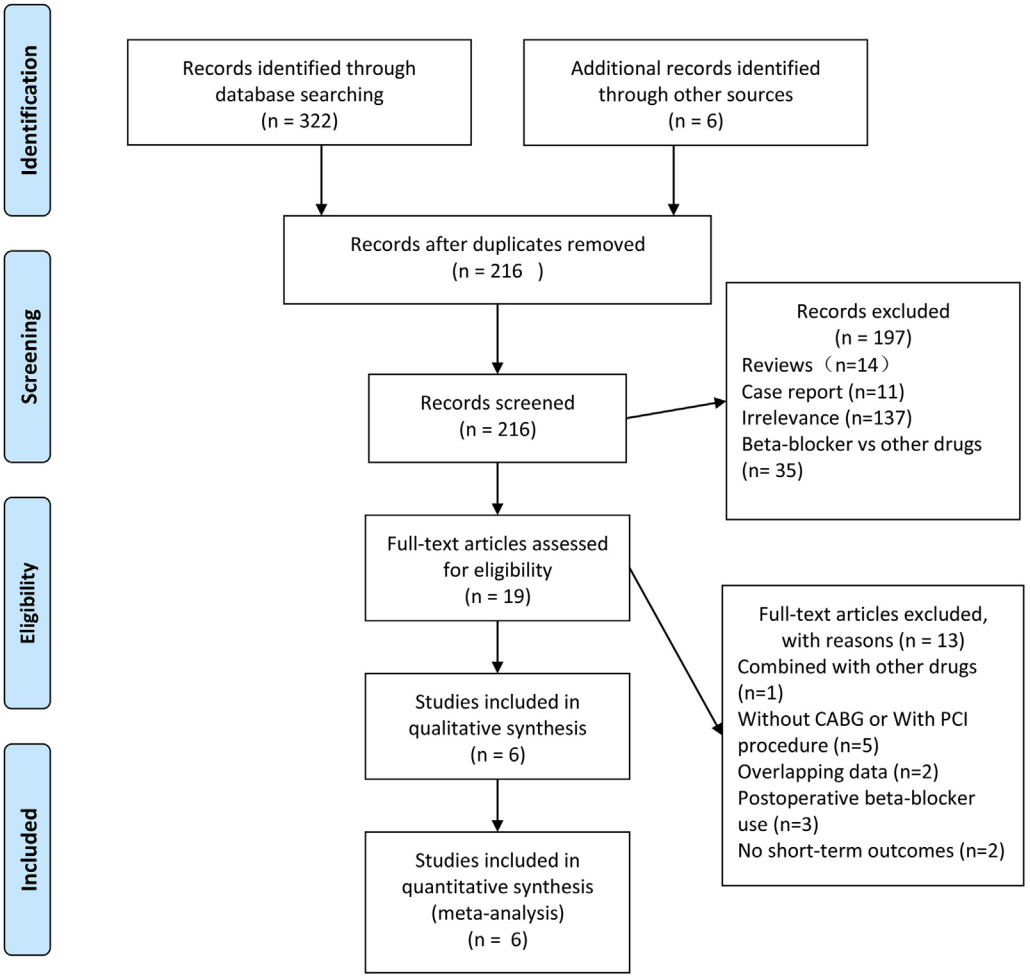

FIGURE 1. Flow diagram for selection of studies. *CABG*, Coronary artery bypass grafting; *PCI*, percutaneous coronary intervention.

sensitivity analysis was performed to examine the influence of individual studies on the summary effect estimate, in which the meta-analysis estimates are computed omitting one study at a time. *P* values less than .05 were considered to be statistically significant.

RESULTS

Search Results and Study Characteristics

Three hundred and twenty-eight records were identified through a computerized literature search, among which 112 were duplicates and 197 were excluded after an initial review of titles and abstracts. The remaining 19 publications were reviewed in full-text and assessed against inclusion criteria. Finally, 6 studies were included in our study.[15,16,25-28] The search and selection process is depicted in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 1). Descriptions of included studies are presented in Table 1. This study included 1,231,850 patients (836,687 in the beta-blocker group and 395,163 in the non-beta-blocker group). All of the included studies were observational studies. Five of the six included studies were multicenter studies. All of the studies investigated operative mortality, incidence of prolonged ventilation, renal failure, and stroke; 3 reported incidence of MI, 4 reported incidence of AF[15,16,26,27]; 5 reported incidence of reoperation[15,16,25-27]; and 5 reported incidence of sternal wound infection.[15,16,25-27] In addition, 5 of the 6 included studies presented major RA outcomes[15,16,25,27,28]; and 5 reported postoperative PSA data.[15,25-28] Of this last group, 4 performed propensity score matching,[15,25,27,28] and the other used propensity score covariate adjustment.[26] All of the variables used for the PSA are presented in Table E1, which were similar among the studies. Inclusion and exclusion criteria were similar among the included studies. In addition, almost 90% of patients were derived from 2 studies.[25,27]

The baseline characteristics of the included observational studies are summarized in Table 2. Patient characteristics were similar between the beta-blocker group and the non–beta-blocker group. The mean age was 65 years for the included studies. Seventy-three percent were male. Most of the patients suffered from hypertension, previous MI, and 3-vessel disease.

TABLE 1. Description of included studies

Author, year	Setting	Design	Patient beta-blocker/ control, patients, n	Time of perioperative beta-blocker use	Inclusion	Exclusion
Ferguson and colleagues,[25] 2002	Multicenter (USA and Canada)	OS with a PSA (PS matching)	343,912/285,965	Preoperatively	Patients in the NCD who underwent CABG between 1996 and 1999	Patients underwent concomitant valve surgery or other cardiac procedures, or whose information on beta-blocker use was not available.
Srinivasan and colleagues,[26] 2003	Single center (UK)	OS with a PSA (PS covariate adjustment)	2836/1545	Preoperatively	Patients undergoing CABG performed on cardiopulmonary bypass	Patients undergoing CABG that was incidental to heart valve repair or replacement, resection of a ventricular aneurysm or other surgical procedure, or who received off-pump CABG.
Brinkman and colleagues,[15] 2011	Multicenter (USA)	OS with a PSA (PS matching)	7967/4888	Preoperatively	STS-certified database undergoing isolated CABG from 2000 to 2008.	None
LaPar and colleagues,[16] 2013	Multicenter (USA)	OS (hierarchal logistic regression)	35,100/8647	Preoperatively	Patients undergoing primary, isolated CABG operations.	None
Brinkman and colleagues,[27] 2014	Multicenter (USA and Canada)	OS with a PSA (PS matching)	436,476/69,634	Within 24 h preceding surgery	Patients 18 y and older who underwent nonemergency isolated CABG surgery at STS-NCD–participating hospitals from January 1, 2008, through December 31, 2012.	Patients with previous MI within 21 d, with a documented contraindication to beta-blocker therapy, or with high-risk presenting symptoms (shock, previous PCI within 6 h, or preoperative IABP or inotropes).
Kohsaka and colleagues,[28] 2016	Multicenter (Japan)	OS with a PSA (PS matching)	10,496/24,484	During the 24-h period before cardiac surgery.	Patients underwent isolated CABG.	Patients underwent concomitant valve surgery or other cardiac procedures.

OS, Observational study; *PSA*, propensity score analysis; *PS*, propensity score; *NCD*, National Adult Cardiac database; *CABG*, coronary artery bypass grafting; *STS*, Society of Thoracic Surgeons; *MI*, myocardial infraction; *PCI*, percutaneous coronary intervention; *IABP*, intra-aortic balloon pump.

Quality Assessment

The quality assessment of 6 observational studies is shown in Table 3. According to the Newcastle-Ottawa Scale to assess the risk of bias in the observational studies, 6 observational studies scored between 6 and 8, indicating high methodologic quality.

Primary Outcome: Operative Mortality

All studies reported on operative mortality. The pooled results from the random effect models for operative mortality are shown in Table 4. A total of 1,231,850 patients were included in the analysis. Of the 27,444 deaths among 1,231,850 patients undergoing CABG, 15,882 deaths occurred in 836,687 patients (1.9%) of the beta-blocker group, whereas 11,562 deaths occurred in 395,163 patients (2.9%) of the control group. Overall analysis of the 6 observational studies showed that the preoperative use of beta-blockers significantly reduced operative mortality in patients undergoing isolated CABG compared with the non–beta-blocker group (OR 0.82; 95% CI 0.71-0.95; $P = .007$), with significant heterogeneity among studies ($I^2 = 90.4\%$, $P = .000$). Pooling the RA OR from 5 studies consistently showed a significant reduction in operative mortality in patients receiving beta-blockers before CABG compared with the control group (OR, 0.95; 95% CI, 0.92-0.97; $P = .000$), without heterogeneity ($I^2 = 0.0\%$, $P = .763$).

However, a pooled analysis of postoperative PSA data generated a statistically nonsignificant result favoring preoperative beta-blocker use (OR, 0.97; 95% CI, 0.94-1.00; $P = .088$; Figure 2), and no significant heterogeneity

TABLE 2. Baseline characteristics of included studies

Variable	Ferguson and colleagues,[25] 2002	Srinivasan and colleagues,[26] 2003	Brinkman and colleagues,[15] 2011	LaPar and colleagues,[16] 2013	Brinkman and colleagues,[27] 2014	Kohsaka and colleagues[28] 2016
No. of propensity-matched patients						
Preop.b-b	230,053		4474		69,271	9619
No preop.b-b	230,053		4474		69,271	9619
Mean age, y						
Preop.b-b	64	63.7	63.2	63.8	64.9	68.0
No preop.b-b	65	65.3	64.6	64.7	65.7	68.7
Males, %						
Preop.b-b	70.9	81.0	73.8	73.3	73.7	77.8
No preop.b-b	71.0	80.5	75.1	74.9	75.7	78
Diabetes mellitus, %						
Preop.b-b	30.2	13.9	33.7	38.8	42.6	52.7
No preop.b-b	32.7	19.9	35.9	37.5	39.5	49.8
Hypertension, %						
Preop.b-b		51.6	79.3	81.2	88.7	82.4
No preop.b-b		48.5	72.9	73.4	81.9	73.9
Previous MI, %						
Preop.b-b	53.0	46.1	45.3	16.7	27.4	39.1
No preop.b-b	44.9	47.8	33.4	4.5	18.6	35
Ejection fraction, %						
Preop.b-b	51.0		50.3	0.55	53.3	
No preop.b-b	49.9		50.5	0.55	54.9	
Three-vessel disease						
Preop.b-b	70.6	83.5	79.3	78.3	73.5	71.8
No preop.b-b	69.8	84.9	78.5	76.5	71.2	68.6

The Srinivasan study used PS covariate adjustment rather than PS matching, and the LaPar study was adjusted using hierarchal logistic regression. *Preop.b-b*, Preoperative beta-blocker group; *no Preop.b-b*, preoperative non–beta-blocker group; *MI*, myocardial infarction.

was observed ($I^2 = 0.0\%$, $P = .888$). When we removed one study that used propensity score covariate adjustment, subgroup analysis of propensity-matched patients (313,417 in each group) still generated a statistically nonsignificant benefit for preoperative beta-blocker use (OR, 0.97; 95% CI, 0.94-1.00; $P = .093$; Figure 2).

Secondary Outcome: Incidence of Major Postoperative Complications

Pooled outcomes of the incidence of major postoperative complications are presented in Table 4. Incidence of stroke was available in all studies. Preoperative beta-blocker use was associated with a slightly lower incidence of stroke (OR, 0.89; 95% CI, 0.80-0.99; $P = .039$). The random-effects model was applied because heterogeneity was evident among the studies ($I^2 = 73.5\%$, $P = .002$). However, there was no significant difference between the 2 groups regarding the incidence of stroke when pooling either the RA outcome (OR, 0.97; 95% CI, 0.93-01.01; $P = .094$) or PSA outcome (OR, 0.96; 95% CI, 0.89-1.04; $P = .313$). Only 4 studies investigated the incidence of AF. Overall analysis of studies revealed that the preoperative use of beta-blockers significantly increased the incidence of AF (OR, 1.08; 95% CI, 1.06-1.10; $P = .000$), without substantial heterogeneity ($I^2 = 0\%$, $P = .504$). These findings were consistent with the pooled analysis of either RA outcome or PSA outcome. Reoperation was extracted in 5 studies. The incidence of reoperation in patients receiving preoperative beta-blockers was reduced by 4% compared with patients who did not receive preoperative beta-blockers (OR, 0.96; 95% CI, 0.92-1.00; $P = .036$). Conversely, pooled analyses of RA outcome or PSA outcome demonstrated no statistically significant difference in the incidence of reoperation between the 2 groups.

Moreover, preoperative beta-blocker use did not significantly reduce the incidence of MI (PSA: OR, 1.05; 95% CI, 0.84-1.31, $P = .693$), the incidence of renal failure (OR, 0.92; 95% CI, 0.84-1.01; $P = .086$; PSA: OR, 1.00; 95% CI, 0.95-1.06, $P = .989$), or the incidence of prolonged ventilation (OR, 0.90; 95% CI, 0.80-1.01; $P = .080$; PSA: OR, 1.00; 95% CI, 0.96-1.04; $P = .967$). Similarly, the incidence of sternal wound infection did not markedly decrease after preoperative beta-blocker use (OR, 0.93; 95% CI, 0.86-1.01, $P = .098$; PSA: OR, 0.95; 95% CI, 0.86-1.05, $P = .285$).

TABLE 3. Quality assessment of observational studies

Study	Selection				Comparability	Outcome			
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of Interest		Assessment of outcome	Length of follow-up	Adequacy follow-up	Total score
Ferguson and colleagues,[25] 2002	*	*	*	*	*	*	*	*	8
Srinivasan and colleagues,[26] 2003	*	*	*	*	*	-	*	-	6
Brinkman and colleagues,[15] 2011	*	*	*	*	*	*	*	*	8
LaPar and colleagues,[16] 2013	*	*	*	*	*	*	*	*	8
Brinkman and colleagues,[27] 2014	*	*	*	*	*	*	*	*	8
Kohsaka and colleagues,[28] 2016	*	*	*	*	*	*	*	*	8

Risk of bias was assessed with the Newcastle–Ottawa Scale. A greater overall score indicated a lower risk of bias; a score of 5 or less (of 9) suggested a high risk of bias.

Publication Basis and Sensitivity Analyses

The results of publication bias tests are presented in Table 4. All of the *P* values for the Begg and Egger tests were greater than .05, suggesting a low probability of publication bias. We also performed a one-way sensitivity analysis of PSA outcomes to estimate the effect of each study on operative mortality. In this analysis, omission of each study did not make a significant difference (Figure 3), confirming the stability of our results.

TABLE 4. Meta-analysis for all outcomes and publication bias

Outcomes	OR (95% CI)	z	*P* value	I^2 (%)	Begg's *P*	Egger's *P*
Operative mortality	0.82 (0.71-0.95)	2.70	.007	90.4	1.000	.934
RA	0.95 (0.92-0.97)	3.78	.000	0.0	.806	.239
PSA	0.97 (0.94-1.00)	1.71	.088	0.0	1.000	.542
Stroke	0.89 (0.80-0.99)	2.07	.038	73.4	.707	.360
RA	0.97 (0.93-1.01)	1.68	.094	0.0	.734	.313
PSA	0.96 (0.89-1.04)	1.01	.313	33.2	.221	.225
Atrial arrhythmia	1.08 (1.06-1.10)	7.97	.000	0.0	1.000	.755
RA	1.10 (1.06-1.14)	4.87	.000	32.9	1.000	
PSA	1.12 (1.02-1.22)	2.50	.012	42.9	1.000	
Prolonged ventilation	0.90 (0.80-1.01)	1.75	.08	96.4	1.000	.870
RA	0.97 (0.94-1.01)	1.65	.099	45.8	1.000	.256
PSA	1.00 (0.96-1.04)	0.04	.967	35.7	1.000	.291
Renal failure	0.92 (0.84-1.01)	1.72	.086	85.2	1.000	.671
RA	1.00 (0.91-1.10)	0.02	.988	84.9	.734	.173
PSA	1.00 (0.95-1.06)	0.01	.989	40.0	1.000	.332
Reoperation	0.96 (0.92-1.00)	2.10	.036	35.2	.462	.328
RA	0.99 (0.97-1.00)	1.60	.110	0.0	1.000	.568
PSA	1.00 (0.98-1.03)	0.38	.705	0.0	1.000	.744
Sternal wound infection	0.93 (0.86-1.01)	1.65	.098	22.3	.462	.204
RA	0.86 (0.72-1.03)	1.65	.098	71.2	1.000	.227
PSA	0.95 (0.86-1.05)	1.07	.285	22.2	.806	.589
Myocardial infraction (PSA)	1.05 (0.84-1.31)	0.39	.693	0.0		

OR, Odds ratio; *CI*, confidence interval; *RA*, risk-adjusted; *PSA*, propensity score analysis.

DISCUSSION

This study analyzed 6 observational studies to investigate the short-term effects of preoperative beta-blocker use versus non–beta-blocker use for patients undergoing isolated CABG. The current meta-analysis showed that preoperative beta-blocker use did not significantly reduce operative mortality and the incidence of some postoperative complications, such as postoperative MI, stroke, reoperation, renal failure, prolonged ventilation, and sternal wound infection. However, we found that preoperative beta-blocker use significantly increased the incidence of AF.

Beta-blockers have been used routinely as a main therapy for patients with cardiovascular disease over the past 20 years, based on the evidence that beta-blockers can correct the imbalance between oxygen demand and supply.[29] Recent guidelines suggest that preoperative beta-blockers may be beneficial for patients undergoing CABG without contraindications.[30,31] However, there always has been controversy regarding whether the potential benefits of preoperative beta-blockers use outweigh its risks for patients undergoing CABG.

Previously, many meta-analyses have focused on the comparison of beta-blocker use and non-beta-blocker use. Bangalore and colleagues[32] included 33 RCTs with 12,306 patients undergoing noncardiac surgery and found that beta-blockers did not significantly reduce the risk of all cause-mortality, cardiovascular mortality or heart failure, but it reduced the incidence of non-fatal MI by 35% and increased the incidence of nonfatal stroke by 101%. Wan and colleagues[33] also found no significant difference in the risk of death between patients undergoing CABG who either did or did not receive beta-blockers before surgery. Bangalore and colleagues[34] conducted a meta-analysis of 6 RCTs including 102,003 patients to evaluate beta-blockers in MI, and they demonstrated that beta-blockers had no mortality benefit but reduced recurrent MI and angina (short term) at the expense of increase in heart failure and cardiogenic shock. These findings may challenge the value of beta-blockers in preventing cardiovascular events. Nevertheless, most previous meta-analyses have not centered on patients undergoing CABG.

To the best of our knowledge, this study is the first systematic review and meta-analysis to target patients undergoing isolated CABG for comparing the short-term effects of preoperative beta-blocker use with non–beta-blocker use. In the present study, we included 6 observational studies with a total of 1,231,850 patients and performed pooled analyses of RA and PSA outcomes, which may reduce the risk of patient selection bias. In addition, the results of risk assessment of bias showed that our included studies were at low risk of bias. Hence, the included studies in the present meta-analysis were of satisfactory methodological quality.

It has been demonstrated that beta-blockers are efficient in preventing ventricular arrhythmias and sudden death.[35] Moreover, beta-blockers may be associated with a reduction

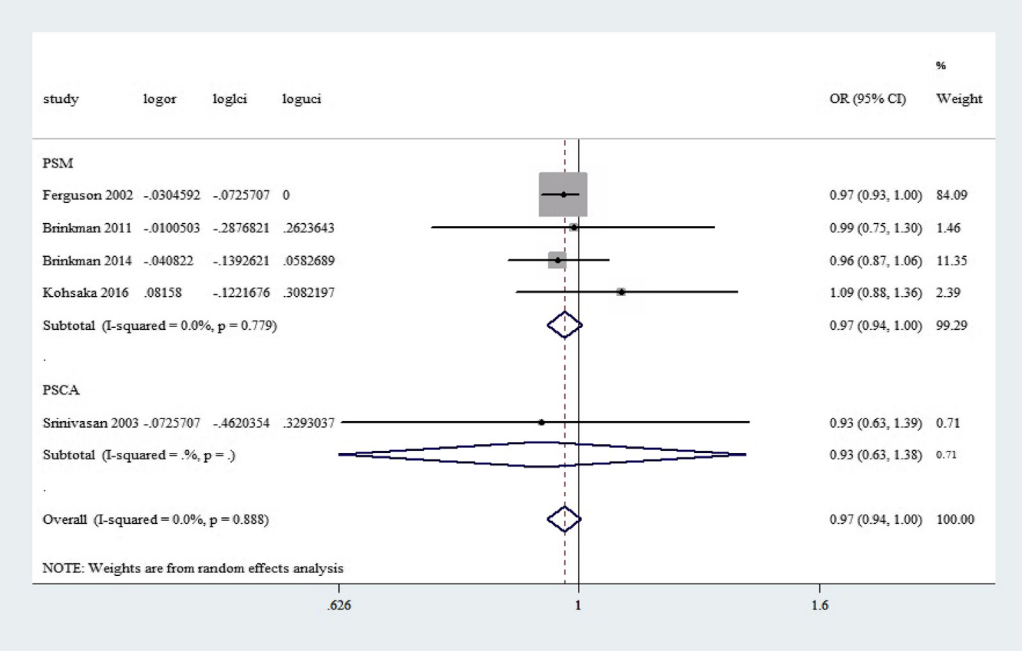

FIGURE 2. Forest plot of operative mortality outcome from propensity score analysis. *PSM*, Propensity score matching; *PSCA*, propensity-score covariate adjustment; *OR*, odds ratio; *CI*, confidence interval.

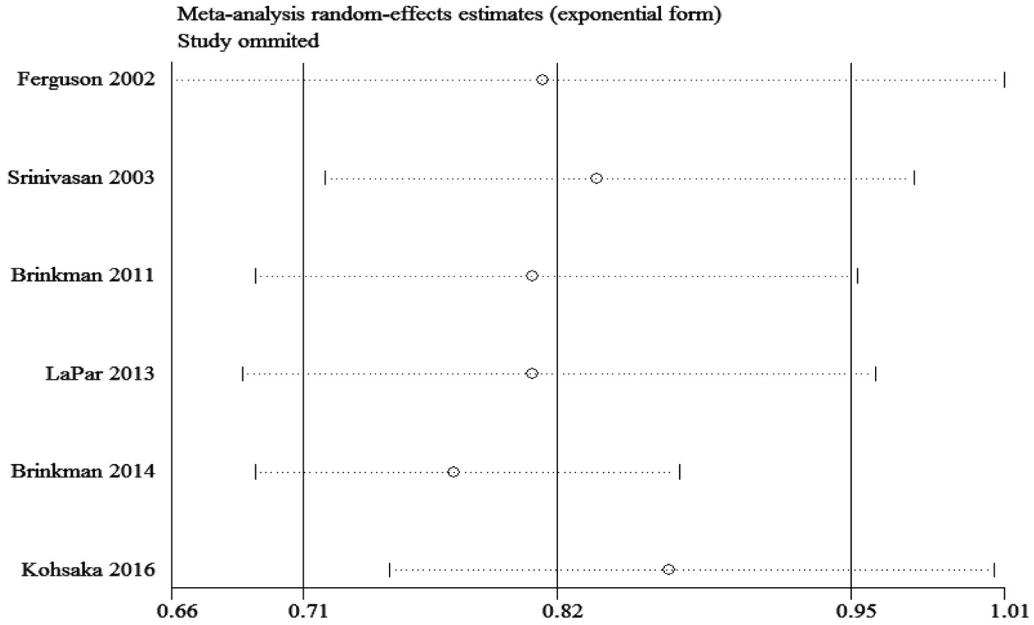

FIGURE 3. One-way sensitivity analysis of operative mortality outcome from propensity score analysis.

in the incidence of MI because their negative inotropic effects may reduce myocardial contractility and consequently result in a decline in oxygen demand.[34] Nonetheless, negative inotropic effects also could lead to heart failure and cardiogenic shock. In this current meta-analysis, we found that preoperative beta-blocker use did not significantly reduce the incidence of MI. Ventricular arrhythmias, sudden death, heart failure, and MI are the major causes of operative mortality. Among the included studies, outcomes of ventricular arrhythmias, sudden death, or cardiogenic shock were not reported. In the present meta-analysis, no significant improvement in short-term survival was observed in the beta-blocker group compared with the control group. The benefits of preoperative beta-blocker use may be counteracted by the risk of heart failure. Furthermore, contemporary medical and device therapies are reducing the impact of beta-blockers, due to their efficacy in reducing the risk of arrhythmic deaths and cardiogenic shock.

Beta-blocker use was found to be associated with the increased risk of nonfatal stroke in the previous meta-analyses and RCTs.[32,36,37] The results from the Perioperative Ischemic Evaluation (POISE) trial suggested that beta-blockers could increase the risk of stroke due to hypotension.[36] Conversely, the overall results showed that beta-blockers had no effect on stroke in the real word. Similarly, these studies showed that beta-blockers also could lead to kidney injury due to hypotension, whereas this phenomenon was not observed in our studies. In the real word, blood pressure monitoring is performed routinely, and appropriate and stable blood pressure should be obtained during the perioperative period, which may account for our findings.

Postoperative AF is a common complication of cardiovascular surgery, and it occurs in more than 20% of patients undergoing CABG.[38] Postoperative AF has a marked association with the prolonged length of hospital stay and increased hospital charges. In addition, the incidence of major adverse cardiovascular events is always greater in patients with postoperative AF.[39] Beta-blockers consistently have been shown to prevent AF after surgery by heart rhythm control. However, this study observed that preoperative beta-blocker therapy significantly increased the incidence of postoperative AF. The pooled odds ratio was 1.12, indicating a small magnitude of difference between 2 groups regarding development of AF. Among the included studies, information of the use of amiodarone was absent. Amiodarone is often the preferred prophylactic antiarrhythmic agent in the real world,[40] and the use of this drug in the non–beta-blocker group might have reduced postoperative AF, which might explain the relatively increased rate of postoperative AF in the beta-blocker group.

According to several reports,[41,42] $beta_2$-blockade agent in noncardioselective beta-blockers may increase airflow obstruction in susceptible patients, possibly through unopposed parasympathetic bronchoconstriction. In the current meta-analysis, we found no difference in prolonged ventilation between the beta-blocker group and the control group. This result suggested that low-dose initiation of beta-blockers also might be recommended to patients with mild and fixed airflow obstruction. However, pulmonary

function should be carefully evaluated before prescribing beta-agonists to patients.

Preoperative risks to patients could be an important variable in comparing the morbidity and mortality between 2 groups. In the present study, the pooled analyses of either unadjusted outcomes or RA outcomes showed a slight reduction in operative mortality, whereas an insignificant difference in mortality rates was observed in pooling postoperative PSA data or propensity-matched data. The strength of the evidence from PSA was robust because comparability between the 2 groups was well-established, and selective bias was reduced. Two included studies performed subgroup analyses in patients with left ventricular dysfunction. One found that preoperative beta-blocker therapy was associated with a trend toward a greater mortality rate among patients with a left ventricular ejection fraction of less than 30%, whereas the other showed no association between the beta-blocker use and outcome. Almost 90% of patients were derived from 2 studies, and the results seemed to depend on the data of the 2 studies. However, we also performed a one-way sensitivity analysis of PSA outcomes to estimate the effect of each study on operative mortality. In this analysis, omission of each study did not make a significant difference, confirming the stability of our results.

Limitations

Nevertheless, this study has several limitations. First, only 6 studies were included in this meta-analysis, and all eligible studies were observational studies that lacked random allocation of intervention, which may have resulted in a greater risk of selection bias. Although we also used the data from PSA, the risk of bias could not be excluded completely, because all methods to control for confounding are imperfect. Despite statistical analysis leading to an evident result, this result comes from studies of low scientific weight in terms of level of evidence; thus, the real impact of preoperative beta-blockers on CABG-outcome has not been be defined to date and certainly deserves RCTs. Second, the dose and type of beta-blockers were unknown in all included studies. Discontinuation of preoperative beta-blockade also was unreported. In addition, the timing of taking beta-blockers was different among the studies. These factors might have affected the pooled results. Finally, most studies did not have classification of perioperative risk (low risk and high risk). This classification might have been useful in evaluating the value of beta-blockers due to the controversial outcomes in patients with high-risk. A standardized risk assessment is necessary for future studies.

In conclusion, our study suggests that the use of perioperative beta-blockers did not reduce either operative mortality or the incidence of postoperative complications in patients undergoing CABG. However, the value of beta-blockers could not be determined by current outcomes because short-term CABG mortality rates, which have decreased to approximately 1%, may no longer be a sufficiently sensitive outcome. We should pay more attention to assess the long-term benefit of beta-blockers. Recently, it was reported that the consistent use of beta-blockers was associated with a lower risk of both long-term mortality and adverse cardiovascular events in patients undergoing CABG.[17] Hence, RCTs investigating the long-term effects of beta-blocker therapy are still required to confirm their potential benefits for patients undergoing CABG.

Conflicts of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: coronary artery bypass grafting, operative mortality, perioperative beta-blocker use

TABLE E1. Description of variables used in PSA studies

Author, year	PSA methodology	Selection bias	Variables
Ferguson and colleagues,[25] 2002	1:1 matching method not reported	Lower	Age, body surface area, sex, NYHA class IV, triple-vessel disease, left main coronary disease, LVEF, preoperative IABP, arrhythmia, cerebrovascular disease, heart failure, MI, cardiogenic shock, chronic lung disease, dialysis, reoperation, surgical status.
Srinivasan and colleagues,[26] 2003	Propensity score covariate adjustment	Lower	Age, body mass index, sex, NYHA class IV, unstable angina, previous MI, smoker, diabetes, hypertension, peripheral vascular disease, cerebrovascular disease, renal dysfunction, respiratory disease, heart failure, LVEF < 30%, 3-vessel disease, left main stenosis, emergent procedure.
Brinkman and colleagues,[15] 2011	1:1 matching method not reported	Lower	Sex, angina, arrhythmia, heart failure, left main disease, preoperative IABP, previous PCI, resuscitation, permanent stroke, cerebrovascular disease, diabetes, dyslipidemia, hypertension, peripheral artery disease, renal failure, smoker, cardiogenic shock, urgent operative status, triple-vessel disease, NYHA class IV, chronic lung disease, statins use, age, body surface area, LVEF.
Brinkman and colleagues,[27] 2014	Greedy 1:1 5-to-1 digit matching	Lower	Age, body surface area, sex, Hispanic or nonwhite race, dyslipidemia, previous CABG, previous PCI, 2 or more previous cardiovascular operations, hypertension, immunosuppressive therapy, peripheral vascular disease, unstable angina, left main coronary artery disease, triple-vessel disease, cerebrovascular disease, previous cerebrovascular accident, diabetes, urgent status, congestive heart failure (NYHA class IV or classes III), atrial fibrillation, ejection fraction, chronic lung disease, dialysis, creatinine level, and previous MI.
Kohsaka and colleagues,[28] 2016	1:1 matching nearest-neighbor matching caliber width of 0.2 SD	Lower	Age, sex, body mass index, smoker, diabetes, chronic kidney disease, hyperlipidemia, hypertension, cerebrovascular disease, carotid disease, atrial fibrillation, respiratory disability, peripheral arterial disease, previous PCI, previous MI, unstable angina, LVEF < 50%, heart failure, cardiogenic shock, aspirin, anticoagulants, statins, angiotensin-converting enzyme, triple-vessel disease, left main disease, surgery status, reoperation.

PSA, Propensity score analysis; *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction; *IABP*, intra-aortic balloon pump; *MI*, myocardial infraction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting.