ORIGINAL RESEARCH

Impact of Beta-Blocker Initiation Timing on Mortality Risk in Patients With Diabetes Mellitus Undergoing Noncardiac Surgery: A Nationwide Population-Based Cohort Study

Ray-Jade Chen, MD;* Hsi Chu, MD;* Lung-Wen Tsai, PhD

***Background*—**Relevant clinical studies have been small and have not convincingly demonstrated whether the perioperative initiation of beta-blockers should be considered in patients with diabetes mellitus undergoing noncardiac surgery.

***Methods and Results*—**In this nationwide propensity score–matched study, we included patients with diabetes mellitus undergoing noncardiac surgery between 2000 and 2011 from Taiwan's National Health Insurance Research Database. Patients were classified as beta-blocker and non–beta-blocker cohorts. We further stratified beta-blocker users into cardioprotective beta-blocker (atenolol, bisoprolol, metoprolol, or carvedilol) and other beta-blocker users. To investigate time of initiation of beta-blocker use, initiation time was stratified into 2 periods (>30 and ≤30 days preoperatively). The outcomes of interest were in-hospital and 30-day mortality. After propensity score matching, we identified 50 952 beta-blocker users and 50 952 matched controls. Compared with non–beta-blocker users, cardioprotective beta-blocker users were associated with lower risks of in-hospital (odds ratio 0.75, 95% CI 0.68–0.82) and 30-day (odds ratio 0.75, 95% CI 0.70–0.81) mortality. Among initiation times, only the use of cardioprotective beta-blockers for >30 days was associated with decreased risk of in-hospital (odds ratio 0.72, 95% CI 0.65–0.78) and 30-day (odds ratio 0.72, 95% CI 0.66–0.78) mortality. Of note, use of other beta-blockers for ≤30 days before surgery was associated with increased risk of both in-hospital and 30-day mortality.

***Conclusions*—**The use of cardioprotective beta-blockers for >30 days before surgery was associated with reduced mortality risk, whereas short-term use of beta-blockers was not associated with differences in mortality in patients with diabetes mellitus. **(*J Am Heart Assoc*. 2017;6:e004392. DOI: 10.1161/JAHA.116.004392.)**

Key Words: diabetes mellitus • epidemiology • mortality • surgery • beta-blocker

The 2014 American College of Cardiology/American Heart Association guidelines recommend consideration of beta-blocker initiation for patients with inducible ischemia on stress testing or with a Revised Cardiac Risk Index of ≥3.[1] In addition, the European Society of Cardiology guidelines suggest that preoperative initiation of beta-blockers may be considered for patients scheduled for high-risk surgery and who have 2 clinical risk factors or American Society of Anesthesiology Physical Status Classification status of 3.[2] Patients with diabetes mellitus (DM) have an increased risk of substantial mortality, similar to those with coronary heart disease (CHD) without DM.[3–6] DM is thus regarded as a CHD risk equivalent and should be treated as aggressively as CHD.[7] Current guidelines, however, do not provide strong recommendations for perioperative beta-blocker therapy for patients with DM because of limited evidence.

The results of a multicenter study suggested that this therapy conferred a significant survival benefit for patients with CHD and DM, but the study did not focus specifically on patients with DM.[8] In contrast, the Diabetes Postoperative Mortality and Morbidity (DIPOM) trial,[9] which involved 921 patients with DM, showed that perioperative metoprolol administration did not significantly affect mortality. These controversial findings have raised concern about the

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Accompanying Tables S1 through S4 and Figure S1 are available at http://jaha.ahajournals.org/content/6/1/e004392/DC1/embed/inline-supplementary-material-1.pdf

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beneficial effects of perioperative beta-blocker therapy in patients with DM undergoing noncardiac surgery. Furthermore, the timing of beta-blocker initiation before such surgery may influence the survival benefit, but this factor has not been addressed. Compared with longer durations of preoperative beta-blocker therapy, previous studies have shown that shorter durations tend to be associated with worse outcomes.[10–12]

In light of these controversial findings and the knowledge gap regarding the timing of beta-blocker initiation in patients with DM, we conducted a nationwide population-based study of the Taiwanese population with DM covering the period 2000 to 2011 (the largest scale study to date), with the primary objective of exploring the effects of the time of initiation of beta-blockers and subsequent mortality among patients with DM undergoing noncardiac surgery in real-world scenarios.

Methods

Data Source

Taiwan's National Health Insurance (NHI) program, launched in 1995, provides comprehensive medical coverage (including outpatient care, emergency room and hospital care, dental services, laboratory and medical examinations, drug prescriptions, and surgical and interventional procedures) and is universally available to all citizens. As part of the national health care reimbursement scheme, NHI enrollment is mandatory and required by law. In 2007, ≈98.4% of Taiwan's 22.96 million citizens were registered and enrolled. The Taiwanese government releases linked health care registry data for research purposes. In the current study, we used the Longitudinal Cohort of Diabetes Patients data set, which consists of deidentified secondary data from a random sample of 120 000 patients with the diagnosis of DM in each year since 1999 and has been validated previously.[13] For privacy purposes, all personal identifiers were encrypted before release of the data set to researchers, with unique numbers used for linking of individuals' data. Medical diagnoses were classified using International Classification of Diseases, Ninth Revision, Clinical Modification codes, and surgical procedures were coded according to the NHI classification system. The institutional review board of Taipei City Hospital exempted this study from full review (TCHIRB-10404107-W) because the sample comprised deidentified secondary data.

Study Design

This population-based observational cohort study aimed to investigate the associations of different beta-blocker initiation times with subsequent mortality in patients with DM undergoing noncardiac surgery. We included all patients aged ≥20 years with the diagnosis of DM and hospitalization for noncardiac surgery between January 2000 and December 2011. Noncardiac surgery was classified according to surgical specialty and extent as *vascular, orthopedic, abdominal, thoracic*, or *other* surgery. Patients undergoing >1 type of surgery and those with previous history of cardiac surgery were excluded from our analysis. The exposures of interest were beta-blockers (including acebutolol, alprenolol, atenolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, and timolol). Based on the beta-blocker type used before noncardiac surgery, we stratified patients into the beta-blocker and non–beta-blocker cohorts. We assigned patients receiving atenolol, bisoprolol, metoprolol, or carvedilol to *cardioprotective* beta-blocker users because these beta-blockers have been proven to be beneficial in patients with ischemic heart disease or congestive heart failure and may be associated with improved outcomes in patients undergoing noncardiac surgery.[14–18] Patients using all other beta-blockers were assigned to *other* beta-blocker users. We extracted data on beta-blocker prescriptions before hospital admission and dichotomized beta-blocker initiation timing into 2 periods (>30 and ≤30 days).

To examine the clinical characteristics of the study population, we extracted demographic variables, diagnostic and surgical procedure codes, socioeconomic information (including monthly income and urbanization level [4 levels, 1=urban and 4=rural]), number of outpatient visits in the past year, Charlson Comorbidity Index,[19] revised cardiac risk index (including 6 variables: high-risk surgery, cerebrovascular disease, ischemic heart disease, congestive heart failure, DM, and renal insufficiency),[20,21] and adapted Diabetes Complications Severity Index for the severity of DM.[22–24] We also identified other comorbidities related to general health and treatment with concomitant medications, including antidiabetic drugs, alpha-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics, other antihypertensive drugs, aspirin, clopidogrel, ticlopidine, warfarin, dipyridamole, nitrates, and statins.

Propensity Score Matching

Because indication bias may have been introduced based on the use of beta-blockers, we performed a propensity score analysis to adjust for baseline imbalances among cohorts, including baseline comorbidities and concomitant medications that may confound the association between treatment and outcomes of interest. We used the propensity score analysis to match each participant in the beta-blocker cohort to 1 patient in the non–beta-blocker cohort respectively according to the closest propensity score for any beta-blocker use, using nearest neighbor matching without replacement and calipers of width equal to 0.1 SD of the logit of the propensity score. The

details of the propensity score model (Table S1) and the distribution of the propensity scores before and after propensity score matching (Figure S1) are provided.[25] The 30-day mortality started at the time of discharge from the hospital. In-hospital mortality was also the outcome of interest.

Statistical Analysis

We used descriptive statistics (means, SDs, and frequencies) for basic characterization of the study population. Standardized mean differences were used to compare baseline characteristics among groups. We performed conditional logistic regression analysis to calculate odds ratios (ORs) for comparison of outcomes among groups. The likelihood ratio test was used to detect interaction with covariates (including age, sex, hypertension, dyslipidemia, cerebrovascular disease, myocardial infarction, heart failure, chronic kidney disease, revised cardiac risk index, and vascular surgery), and subgroup analyses were performed accordingly.

We used Microsoft SQL Server 2012 (Microsoft Corp) for data linkage, processing, and sampling. The algorithm of propensity score matching was applied using SAS software (version 9.3; SAS Institute Inc). All other statistical analyses were performed using Stata statistical software (version 13.0; StataCorp). All 2-tailed P values <0.05 were considered to be statistically significant.

Results

Characteristics of the Study Population

For the study period of January 2000 to December 2011, a total of 452 220 patients with DM undergoing noncardiac surgery were enrolled. After propensity score matching, we identified 50 952 beta-blocker users and 50 952 matched controls. Mean age in the beta-blocker and matched cohorts was 64.4 years (SD 12.2 years). Women were slightly predominant (53.1%). Among all participants, 27.1% of patients underwent high-risk surgery. Detailed characteristics of the cohorts before (Table S2) and after (Table 1) propensity score matching are presented.

Associations Between Perioperative Beta-Blocker Use and In-Hospital and 30-Day Mortality Risks

Compared with the matched controls, the beta-blocker cohort was associated with lower risks of in-hospital mortality (OR 0.83, 95% CI 0.78–0.90) and 30-day mortality (OR 0.83, 95% CI 0.79–0.89) (Table 2). In addition, we assessed the effects of beta-blockers on cardiovascular risks and found a trend, albeit not significant, toward reduced risk of myocardial infarction (OR 0.76, 95% CI 0.42–1.38) but increased risk of stroke (OR 1.33, 95% CI 0.94–1.88) in beta-blocker users compared with matched controls.

In further analyses, use of cardioprotective beta-blockers was associated with lower risks of in-hospital mortality (OR 0.75, 95% CI 0.68–0.82) and 30-day mortality (OR 0.75, 95% CI 0.70–0.81). However, use of other beta-blockers was not associated with the decreased risk of in-hospital mortality (OR 1.00, 95% CI 0.90–1.12) or 30-day mortality (OR 0.99, 95% CI 0.90–1.09). Similar results were found before propensity score matching (Table S3).

Associations Between Perioperative Beta-Blocker Initiation Time and In-Hospital and 30-Day Mortality Risks

In analyses stratified according to perioperative initiation time of cardioprotective beta-blockers, only the use of the beta-blockers for >30 days before surgery was associated with lower risks of in-hospital mortality (OR 0.72, 95% CI 0.65–0.78, $P_{interaction}$=0.002) and 30-day mortality (OR 0.72, 95% CI 0.66–0.78, $P_{interaction}$<0.001) (Table 3). When we stratified the risk of mortality associated with different subtypes of cardioprotective beta-blockers, we found that only atenolol and bisoprolol were associated with lower risks of in-hospital mortality (Table 4). For the longer period of outcomes, atenolol, bisoprolol, and metoprolol were associated with lower risks of 30-day mortality, whereas carvedilol was not associated with such reduced risk.

In contrast, the analyses stratified according to perioperative initiation time of other beta-blockers showed use of other beta-blockers within 30 days before surgery was associated with increased risks of in-hospital mortality (OR 1.56, 95% CI 1.21–2.02, $P_{interaction}$<0.001) and 30-day mortality (OR 1.39, 95% CI 1.12–1.72, $P_{interaction}$<0.001) (Table 5).

Associations Between Perioperative Initiation Time of Any Beta-Blocker and In-Hospital and 30-Day Mortality Risks

In the subgroup analysis, vascular surgery showed significant interaction ($P_{interaction}$=0.044) (Figure; Table S4). Perioperative beta-blockers in patients with DM undergoing vascular surgery had greater 30-day mortality risk reduction (OR 0.74, 95% CI 0.68–0.82) than those undergoing nonvascular surgery (OR 0.85, 95% CI 0.78–0.92).

Discussion

To our knowledge, this population-based study is the largest to explore associations between perioperative beta-blocker

Table 1. Baseline Characteristics of Diabetes Mellitus Patients After Propensity Score Matching

Characteristics	Beta-Blockade Cohort	Control Cohort	StD*
Patient, n	50 952	50 952	
Mean age (SD), y	64.4 (12.2)	64.4 (12.2)	0.000
Male	23 857 (46.8)	23 857 (46.8)	0.000
Monthly income, NT$			
Dependent	17 403 (34.2)	17 451 (34.2)	−0.002
<19 100	10 612 (20.8)	10 589 (20.8)	0.001
19 100 to 41 999	20 456 (40.1)	20 422 (40.1)	0.001
≥42 000	2481 (4.9)	2490 (4.9)	−0.001
Urbanization†			
Level 1	17 611 (34.6)	17 594 (34.5)	0.001
Level 2	30 486 (59.8)	30 505 (59.9)	−0.001
Level 3	2414 (4.7)	2405 (4.7)	0.001
Level 4 (rural area)	441 (0.9)	448 (0.9)	−0.001
Outpatient visits, in the past 1 year			
0–5 visits	456 (0.9)	461 (0.9)	−0.001
6–10 visits	1915 (3.8)	1915 (3.8)	0.000
11–15 visits	3994 (7.8)	3982 (7.8)	0.001
>15 visits	44 587 (87.5)	44 594 (87.5)	0.000
Charlson Comorbidity Index‡ (SD)	7.5 (3.1)	7.5 (3.2)	0.000
Adapted Diabetes Complications Severity Index§ (SD)	2.9 (2.4)	2.9 (2.5)	0.001
Duration of diabetes mellitus, months (SD)	47.5 (38.4)	47.6 (38.4)	−0.001
Revised cardiac risk index			
High-risk surgery	13 807 (27.1)	13 798 (27.1)	0.000
Ischemia heart disease	29 093 (57.1)	29 020 (57.0)	0.003
Cerebrovascular disease	480 (0.9)	478 (0.9)	0.000
Heart failure	10 288 (20.2)	10 279 (20.2)	0.000
Renal insufficiency	786 (1.5)	781 (1.5)	0.001
Type of procedure			
Vascular	4716 (9.3)	4673 (9.2)	0.003
Orthopedic	13 616 (26.7)	13 645 (26.8)	−0.001
Abdominal	8385 (16.5)	8370 (16.4)	0.001
Thoracic	1046 (2.1)	1045 (2.1)	0.000
Other	23 189 (45.5)	23 219 (45.6)	−0.001
Concomitant medications			
Antidiabetic drugs			
Acarbose inhibits enzymes	2263 (4.4)	2276 (4.5)	−0.001
Sulfonylurea	12 406 (24.3)	12 406 (24.3)	−0.002
Insulin	1770 (3.5)	1787 (3.5)	−0.002
Metformin	14 047 (27.6)	14 127 (27.7)	−0.004
Thiazolidinediones	2071 (4.1)	2086 (4.1)	−0.001
Glinide	1906 (3.7)	1929 (3.8)	−0.002
Dipeptidyl peptidase 4 inhibitor	765 (1.5)	765 (1.5)	0.000

Continued

Table 1. Continued

Characteristics	Beta-Blockade Cohort	Control Cohort	StD*
Antihypertensive drug			
Alpha-blocker	3320 (6.5)	3290 (6.5)	0.002
ACEI or ARB	20 645 (40.5)	20 703 (40.6)	−0.002
Calcium channel blocker	25 905 (50.8)	25 959 (50.9)	−0.002
Diuretics	14 284 (28.0)	14 269 (28.0)	0.001
Other antihypertensive drug	1670 (3.3)	1665 (3.3)	0.001
Aspirin	14 685 (28.8)	14 646 (28.7)	0.002
Clopidogrel	1527 (3.0)	1499 (2.9)	0.003
Ticlopidine	777 (1.5)	773 (1.5)	0.001
Warfarin	621 (1.2)	624 (1.2)	−0.001
Dipyridamole	4822 (9.5)	4803 (9.4)	0.001
Nitrate	5646 (11.1)	5549 (10.9)	0.006
Statin	10 722 (21.0)	10 742 (21.1)	−0.001
Comorbidities			
Hypertension	46 624 (91.5)	46 673 (91.6)	−0.003
Peripheral vascular disease	3560 (7.0)	3569 (7.0)	−0.001
Atrial fibrillation	2678 (5.3)	2652 (5.2)	0.002
Dyslipidemia	32 953 (64.7)	32 962 (64.7)	0.000
Valvular heart disease	7597 (14.9)	7527 (14.8)	0.004
Cancer	8007 (15.7)	8019 (15.7)	−0.001
Autoimmune disease	2607 (5.1)	2610 (5.1)	0.000
Physical limitation	5311 (10.4)	5357 (10.5)	−0.003
Propensity score (SD)	0.30 (0.16)	0.30 (0.16)	0.002

All data were described as number (%), except mean age and propensity score. ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; StD, standardized difference.

*Imbalance defined as absolute value >0.015.

†Urbanization levels in Taiwan are divided into 4 strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.

‡Charlson Comorbidity Index is used to determine overall systemic health. With each increased level of the index, there are stepwise increases in the cumulative mortality.

§The adapted Diabetes Complications Severity Index is a 13-point scale with 7 complication categories (retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic, sum of 7 diabetes complications without severity grading; range 0-7). Each complication produced a numeric score ranging from 0 to 2 (0=no abnormality, 1=some abnormality, 2=severe abnormality).

initiation time and mortality in patients with DM undergoing noncardiac surgery in a real-world setting. We found that the use of cardioprotective beta-blockers for >30 days before noncardiac surgery was associated with lower risks of in-hospital and 30-day mortality in patients with DM. However, the use of these beta-blockers within 30 days before surgery was not associated with lower risks of mortality. Moreover, the use of other beta-blockers before noncardiac surgery was not associated with improved outcomes; it was even associated with increased mortality significantly in those receiving treatment within 30 days before surgery. The interaction results showed a lower mortality risk in patients treated with perioperative beta-blockers in patients undergoing vascular surgery than in those undergoing nonvascular surgery.

A multicenter study of 200 patients with CHD who received atenolol before and during hospitalization showed that this treatment improved survival in patients with CHD and DM by ≈75% (hazard ratio 0.25).[8] That study, however, was limited by the small sample of patients with DM (only one-third of the study population), and the attribution of such a large benefit to a single drug is somewhat implausible. Conversely, the DIPOM trial found that perioperative metoprolol use from the day before surgery (maximum 8 perioperative days) did not significantly affect mortality.[9] Notably, the DIPOM trial is limited by a small

Table 2. Odds Ratios of Effect of Perioperative Beta-Blockade on Mortality Among Patients With Diabetes Mellitus Undergoing Noncardiac Surgery After Propensity Score Matching

	Beta-Blocker Cohort	Matched Control Cohort	Propensity Score Matching		
	No. of Events	No. of Events	Odds Ratio (95% CI)	*P* Value	$P_{interaction}$
In hospital mortality					
All beta-blockade	1512	1795	0.83 (0.78–0.90)	<0.001	<0.001
Atenolol, bisoprolol, carvedilol, and metoprolol (n=31 957)	872	1156	0.75 (0.68–0.82)	<0.001	
Other beta-blockade (n=18 995)	640	639	1.00 (0.90–1.12)	0.977	
30-day mortality					
All beta-blockade	2099	2494	0.83 (0.79–0.89)	<0.001	<0.001
Atenolol, bisoprolol, carvedilol, and metoprolol (n=31 957)	1234	1621	0.75 (0.70–0.81)	<0.001	
Other beta-blockade (n=18 995)	865	873	0.99 (0.90–1.09)	0.844	

number of events, and that is what led to the wide CIs and may have affected the precision of results. These findings are similar to those of the present study, suggesting that short-term perioperative use of beta-blockers confers no survival benefit in patients with DM.

Meta-analysis of randomized controlled trials showed that perioperative beta-blocker initiation increased mortality by 27%.[26] However, most randomized controlled trials enrolled in that analysis included patients using beta-blockers ≤1 day before noncardiac surgery.[1] Thus, until the results of further large randomized controlled trials focusing specifically on patients with DM become available, our findings regarding the survival benefits conferred by perioperative beta-blocker use according to initiation time in a nationwide population are of importance in this field. Our findings help address the current knowledge gap by showing that short-term (≤30 days) preoperative cardioprotective beta-blocker use had no apparent survival benefit in patients with DM, whereas long-term (>30 days) use was associated with a decreased risk of mortality. In addition, the use of other beta-blockers within 30 days before surgery may be harmful.

Controversy exists regarding the efficacy of the use of specific beta-blockers before noncardiac surgery in terms of all-cause mortality. The POISE-1 (Perioperative Ischemic Evaluation 1) trial, which included 8351 participants, showed that perioperative use of extended-release metoprolol succinate increased the risk of mortality in patients undergoing noncardiac surgery.[27] This finding is in contrast to results from the Perioperative Beta-Blockade,[28] DIPOM,[9] and Metoprolol after Vascular Surgery[29] trials. The different results obtained in the POISE-1 trial may be attributable to the use of high-dose, long-acting metoprolol shortly prior to surgery, although that seldom occurs in real-world practice. In our study, we noted that significant interaction between perioperative beta-blocker use and vascular surgery affected the risk of all-cause mortality; the survival benefit of beta-blocker therapy was more prominent in patients with DM undergoing vascular surgery.

Table 3. Effect of Different Duration of Perioperative Atenolol, Bisoprolol, Carvedilol, and Metoprolol Use on Mortality Among Patients With Diabetes Mellitus Undergoing Noncardiac Surgery

	Beta-Blocker Cohort	Matched Control Cohort	Propensity Score Matching		
	No. of Events/No. of Patients	No. of Events/No. of Patients	Odds Ratio (95% CI)	*P* Value	$P_{interaction}$
In-hospital mortality					
All	872/31 957	1156/31 957	0.75 (0.68–0.82)	<0.001	0.002
Use for ≤30 days	99/2468	85/2468	1.17 (0.87–1.57)	0.293	
Use for >30 days	773/29 489	1071/29 489	0.72 (0.65–0.78)	<0.001	
30-day mortality					
All	1234/31 957	1621/31 957	0.75 (0.70–0.81)	<0.001	<0.001
Use for ≤30 days	142/2468	122/2468	1.17 (0.92–1.51)	0.206	
Use for >30 days	1092/29 489	1499/29 489	0.72 (0.66–0.78)	<0.001	

Table 4. Effect of Different Types of Perioperative Atenolol, Bisoprolol, Carvedilol, and Metoprolol Use on Mortality Among Patients With Diabetes Mellitus Undergoing Noncardiac Surgery

	Beta-Blocker Cohort	Matched Control Cohort	Propensity Score Matching		
	No. of Events/No. of Patients	No. of Events/No. of Patients	Odds Ratio (95% CI)	*P* Value	$P_{interaction}$
In-hospital mortality					
All	872/31 957	1156/31 957	0.75 (0.68–0.82)	<0.001	<0.001
Atenolol	290/13 556	459/13 556	0.62 (0.54–0.72)	<0.001	
Bisoprolol	289/11 100	399/11 100	0.72 (0.61–0.84)	<0.001	
Carvedilol	252/6039	254/6039	0.99 (0.83–1.19)	0.928	
Metoprolol	41/1262	44/1262	0.93 (0.60–1.43)	0.741	
30-day mortality					
All	1234/31 957	1621/31 957	0.75 (0.70–0.81)	<0.001	<0.001
Atenolol	429/13 556	634/13 556	0.67 (0.59–0.75)	<0.001	
Bisoprolol	403/11 100	562/11 100	0.71 (0.62–0.81)	<0.001	
Carvedilol	350/6039	348/6039	1.01 (0.86–1.17)	0.938	
Metoprolol	52/1262	77/1262	0.66 (0.46–0.95)	0.025	

The main strength of this study is the examination of data from a large sample drawn from the population of all patients with DM undergoing all types of noncardiac surgery between 2000 and 2011 in Taiwan. Current guidelines recommend perioperative beta-blocker initiation before noncardiac surgery in patients with ischemic heart disease and those undergoing high-risk surgery.[1,2] Some limitations of this study should be addressed. First, the database lacked some relevant information about heart rate, the occurrence of atrioventricular block, and severe hypotension, as well as the diagnosis and severity of DM, such as hemoglobin A1c and glucose measurements; however, the accuracy of DM diagnoses in Taiwan's NHI research database has been validated.[13] In addition, the duration and severity of DM according to the adapted Diabetes Complications Severity Index have been found to be comparable between patients receiving and not receiving beta-blockers.[23] Second, although we used propensity score–matched analysis to provide a balance between patients with DM who did and did not receive beta-blockers, given the retrospective nature of the study, selection bias and unmeasured confounding could not be completely eliminated. Consequently, further prospective randomized clinical trials are warranted to validate our findings. Third, because we focused only on the DM population, the observed effects of beta-blocker initiation time may not be generally applicable to populations without DM.

In conclusion, the short-term (≤30 days preoperatively) use of cardioprotective beta-blockers was not associated with a decreased risk of mortality in patients with DM undergoing

Table 5. Effect of Different Duration of Perioperative Other Beta-Blocker Use on Mortality Among Patients With Diabetes Mellitus Undergoing Noncardiac Surgery

	Beta-Blocker Cohort	Matched Control Cohort	Propensity Score Matching		
	No. of Events/No. of Patients	No. of Events/No. of Patients	Odds Ratio (95% CI)	*P* Value	$P_{interaction}$
In-hospital mortality					
All	640/18 995	639/18 995	1.00 (0.90–1.12)	0.977	<0.001
Use for ≤30 days	155/3222	101/3222	1.56 (1.21–2.02)	0.001	
Use for >30 days	485/15 773	538/15 773	0.90 (0.79–1.02)	0.092	
30-day mortality					
All	865/18 995	873/18 995	0.99 (0.90–1.09)	0.844	<0.001
Use for ≤30 days	206/3222	151/3222	1.39 (1.12–1.72)	0.003	
Use for >30 days	659/15 773	722/15 773	0.91 (0.82–1.01)	0.083	

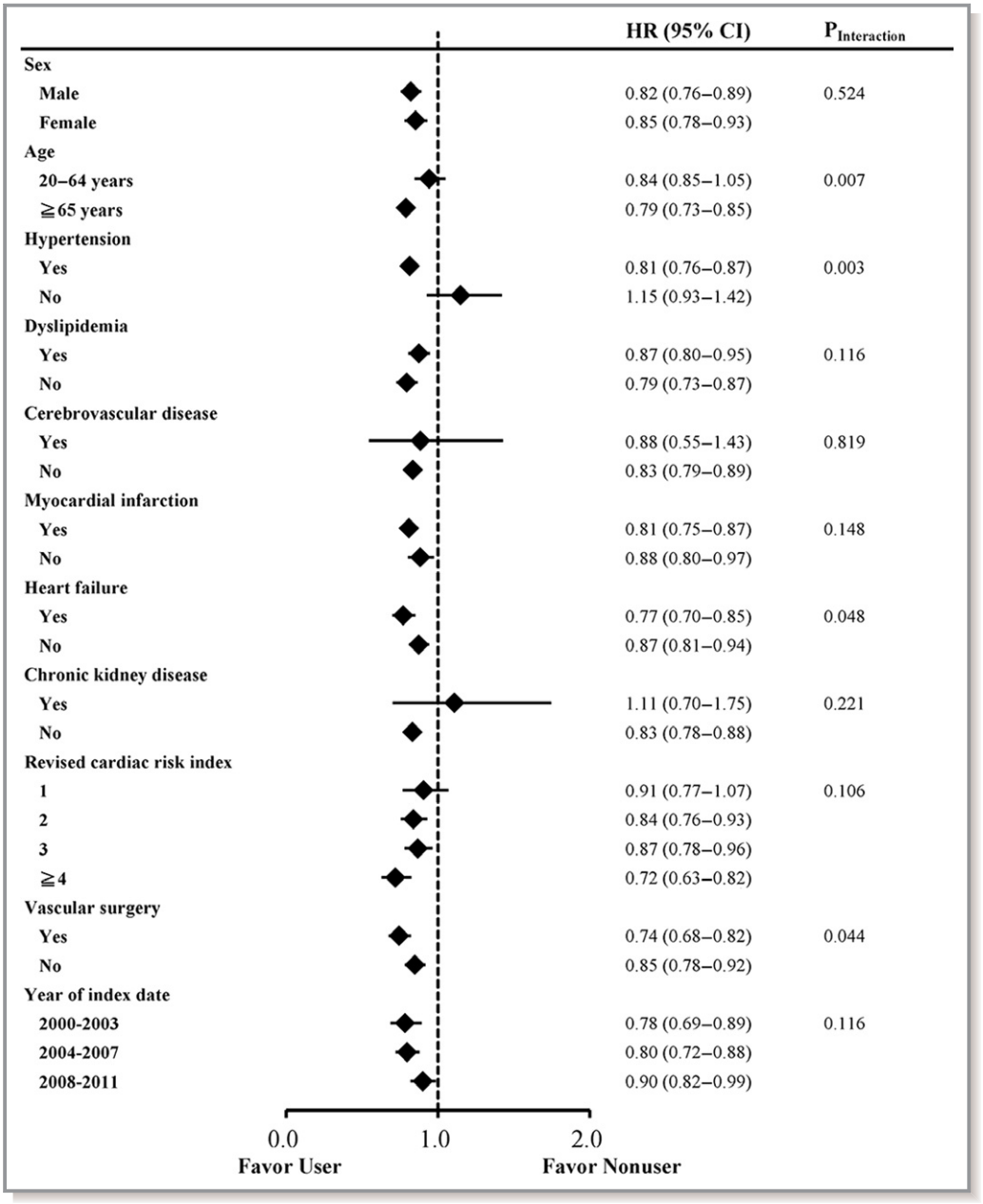

Figure. Subgroup analysis of risk of using any beta-blockers for 30-day mortality among patients with diabetes mellitus undergoing noncardiac surgery. HR indicates hazard ratio.

noncardiac surgery; however, long-term (>30 days preoperatively) use of cardioprotective beta-blockers was associated with a decreased risk of mortality.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Propensity Score Model Results of Probability of Using Any β-blockers

			95% CI		
Parameter	**Estimate**	**Odds Ratios**	**Lower**	**Upper**	**P value**
Age, per year	-0.013	0.987	0.986	0.988	<.0001
Male	-0.2135	0.808	0.79	0.826	<.0001
Year of Index Date					
2000		1			
2001	-0.121	0.886	0.823	0.954	0.0014
2002	-0.1048	0.901	0.838	0.967	0.0041
2003	-0.1156	0.891	0.831	0.955	0.0012
2004	-0.0917	0.912	0.852	0.977	0.0083
2005	-0.0486	0.953	0.89	1.019	0.1585
2006	-0.0903	0.914	0.854	0.978	0.0093
2007	-0.0777	0.925	0.865	0.99	0.0247
2008	-0.115	0.891	0.833	0.954	0.0009
2009	-0.1223	0.885	0.826	0.947	0.0004
2010	-0.1219	0.885	0.827	0.948	0.0005
2011	-0.103	0.902	0.842	0.967	0.0035
Month of Index Date					
January		1			
February	-0.0006	0.999	0.946	1.056	0.984
March	0.0324	1.033	0.981	1.088	0.2202
April	0.0461	1.047	0.994	1.103	0.0837
May	-0.014	0.986	0.936	1.039	0.5997
June	-0.0283	0.972	0.922	1.025	0.2948
July	-0.0316	0.969	0.92	1.02	0.231
August	-0.0498	0.951	0.902	1.003	0.0659
September	-0.0584	0.943	0.895	0.994	0.0304
October	0.0209	1.021	0.97	1.075	0.4257
November	-0.033	0.968	0.919	1.019	0.2124
December	0.0015	1.002	0.951	1.055	0.9537
Monthly income, NT$					
Dependent		1			
<19,100	-0.0387	0.962	0.934	0.991	0.0108
19,100–41,999	-0.1063	0.899	0.877	0.922	<.0001
≥42,000	-0.0763	0.927	0.88	0.975	0.0037
Urbanization[a]					
Level 1		1			

Level 2	-0.0154	0.985	0.963	1.007	0.1768
Level 3	-0.0794	0.924	0.878	0.972	0.0021
Level 4 (rural area)	-0.127	0.881	0.788	0.984	0.025
Outpatient Visits, in the past one year					
0–5 visits		1			
6–10 visits	0.8204	2.271	2.042	2.527	<.0001
11–15 visits	1.1103	3.035	2.743	3.359	<.0001
>15 visits	1.414	4.113	3.735	4.529	<.0001
Charlson Comorbidity Index Score[b]	-0.0317	0.969	0.963	0.975	<.0001
Adapted Diabetes Complications Severity Index score[C]	-0.0015	0.998	0.991	1.006	0.6717
Duration of diabetes, months	-0.001	0.999	0.999	0.999	<.0001
Revised Cardiac Risk Index					
High-risk surgery	-0.0453	0.956	0.925	0.987	0.0066
Ischemia heart disease	0.3219	1.38	1.346	1.414	<.0001
Cerebrovascular disease	-0.0375	0.963	0.863	1.075	0.5025
Heart failure	-0.0256	0.975	0.943	1.007	0.129
Renal insufficiency	-0.0034	0.997	0.915	1.086	0.9383
Type of procedure					
Vascular	0.1437	1.155	1.097	1.215	<.0001
Orthopedic	-0.1806	0.835	0.813	0.857	<.0001
Abdominal	-0.0135	0.987	0.955	1.019	0.4088
Thoracic	-0.1346	0.874	0.808	0.945	0.0007
Other		1			
Anti-diabetic drugs					
Acarbose inhibits enzymes	0.0496	1.051	0.996	1.109	0.0711
Sulfonylurea	-0.0006	0.999	0.972	1.028	0.9688
Insulin	-0.0189	0.981	0.924	1.042	0.5343
Metformin	0.0193	1.019	0.992	1.047	0.1636
Thiazolidinediones	-0.0149	0.985	0.932	1.042	0.5994
Glinide	0.1165	1.124	1.059	1.192	0.0001
Dipeptidyl peptidase-4 inhibitor	0.192	1.212	1.105	1.329	<.0001
Anti-hypertensive drug					
Alpha-blocker	0.199	1.22	1.165	1.278	<.0001
Calcium channel blocker	0.6757	1.965	1.921	2.01	<.0001
Diuretics	0.5486	1.731	1.686	1.777	<.0001
ACEI/ARB	0.2849	1.33	1.298	1.362	<.0001

Other anti-hypertensive drug	0.3421	1.408	1.322	1.5	<.0001
Other concomitant medications					
Aspirin	0.5399	1.716	1.671	1.762	<.0001
Clopidogrel	0.552	1.737	1.618	1.864	<.0001
Ticlopidine	0.5634	1.757	1.597	1.932	<.0001
Warfarin	0.2744	1.316	1.184	1.462	<.0001
Dipyridamole	0.2663	1.305	1.255	1.357	<.0001
Nitrate	0.4043	1.498	1.439	1.56	<.0001
Statin	0.1323	1.141	1.109	1.175	<.0001
Comorbidities					
Hypertension	1.1722	3.229	3.114	3.349	<.0001
Peripheral vascular disease	0.0415	1.042	0.998	1.088	0.0588
Atrial fibrillation	-0.0201	0.98	0.93	1.033	0.4554
Dyslipidemia	0.0754	1.078	1.053	1.104	<.0001
Valvular heart disease	0.2002	1.222	1.183	1.262	<.0001
Cancer	0.0634	1.065	1.031	1.101	0.0002
Autoimmune disease	0.1246	1.133	1.079	1.189	<.0001
Physical limitation	-0.1069	0.899	0.867	0.932	<.0001

[a] Urbanization levels in Taiwan are divided into four strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.

[b] Charlson Comorbidity Index score is used to determine overall systemic health. With each increased level of CCI score, there are stepwise increases in the cumulative mortality.

[C] Adapted Diabetes Complications Severity Index is a 13-point scale from 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic, ranging from each complication. Each complication produced a numeric score ranging from 0 to 2 (0 = no abnormality, 1 = some abnormality, 2 = severe abnormality)

Abbreviations: CI, confidence interval;NT dollars, new Taiwan dollars; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker.

Table S2. Baseline Characteristics of Patients with Diabetes Mellitus Before Propensity Score-Matching

Characteristics	β blockade cohort	Control cohort	*StD*[†]
Patient (no.)	51668	230539	
Mean age (SD), year	64.3 (12.20)	61.8 (13.9)	0.186
Male	24,203 (46.8)	122,821 (53.3)	-0.129
Monthly income, NT$			
Dependent	17,643 (34.1)	68,425 (29.7)	0.096
<19,100	10,780 (20.9)	48,473 (21.0)	-0.004
19,100–41,999	20,174 (39.0)	99,618 (43.2)	-0.063
≥42,000	2,531 (4.9)	14,023 (6.1)	-0.052
Urbanization[§]			
Level 1	17,882 (34.6)	79,688 (34.6)	0.001
Level 2	30,893 (59.8)	137,004 (59.4)	0.007
Level 3	2,444 (4.7)	11,637 (5.0)	-0.015
Level 4 (rural area)	449 (0.9)	2,210 (1.0)	-0.009
Outpatient Visits, in the past one year			
0–5 visits	456 (0.9)	17,591 (7.6)	-0.339
6–10 visits	1,918 (3.7)	20,983 (9.1)	-0.221
11–15 visits	4,019 (7.8)	26,609 (11.5)	-0.128
>15 visits	45,275 (87.6)	165,356 (71.7)	0.403
Charlson Comorbidity Index Score[‖] **(SD)**	7.5 (3.1)	6.6 (3.3)	0.286
Adapted Diabetes Complications Severity Index score[¶] **(SD)**	2.9 (2.5)	2.0 (2.1)	0.392
Duration of diabetes mellitus, months (SD)	47.5 (38.5)	43.5 (37.8)	0.106
Revised Cardiac Risk Index			
High-risk surgery	14,200 (27.5)	53,476 (23.2)	0.099
Ischemia heart disease	29,695 (57.5)	82,340 (35.7)	0.447
Cerebrovascular disease	483 (0.9)	1,651 (0.7)	0.024
Heart failure	10,592 (20.5)	27,812 (12.1)	0.230
Renal insufficiency	800 (1.5)	2,833 (1.2)	0.027
Type of procedure			
Vascular	4,998 (9.7)	11,896 (5.2)	0.173
Orthopedic	13,694 (26.5)	71,133 (30.9)	-0.096

Abdominal	8,461 (16.4)	41,264 (17.9)	-0.040
Thoracic	1,059 (2.0)	5,572 (2.4)	-0.025
Other	23,456 (45.4)	100,674 (43.7)	0.035
Concomitant medications			
Anti-diabetic drugs			
Acarbose inhibits enzymes	2,324 (4.5)	6,447 (2.8)	0.091
Sulfonylurea	12,631 (24.4)	42,550 (18.5)	0.146
Insulin	1,846 (3.6)	6,337 (2.7)	0.047
Metformin	14,266 (27.6)	48,466 (21.0)	0.154
Thiazolidinediones	2,114 (4.1)	6,680 (2.9)	0.065
Glinide	1,998 (3.9)	4,934 (2.1)	0.101
Dipeptidyl peptidase-4 inhibitor	798 (1.5)	1,904 (0.8)	0.066
Anti-hypertensive drug			
Alpha-blocker	3,443 (6.7)	8,132 (3.5)	0.143
ACEI or ARB	21,214 (41.1)	42,622 (18.5)	
Calcium channel blocker	26,582 (51.4)	47,921 (20.8)	0.674
Diuretics	14,863 (28.8)	26,816 (11.6)	0.437
Other anti-hypertensive drug	1,806 (3.5)	3,277 (1.4)	0.134
Aspirin	15,211 (29.4)	25,584 (11.1)	0.469
Clopidogrel	1,664 (3.2)	2,279 (1.0)	0.156
Ticlopidine	820 (1.6)	1,282 (0.6)	0.100
Warfarin	645 (1.2)	1,230 (0.5)	0.076
Dipyridamole	4,975 (9.6)	10,034 (4.4)	0.208
Nitrate	6,027 (11.7)	76,056 (33.0)	0.322
Statin	11,078 (21.4)	27,948 (12.1)	0.251
Comorbidities			
Hypertension	47,340 (91.6)	146,317 (63.5)	0.717
Peripheral vascular disease	3,613 (7.0)	12,293 (5.3)	0.069
Atrial fibrillation	2,715 (5.3)	6,957 (3.0)	0.113
Dyslipidemia	33,501 (64.8)	122,659 (53.2)	0.238
Valvular heart disease	7,775 (15.0)	19,513 (8.5)	0.205
Cancer	8,088 (15.7)	34,450 (14.9)	0.020
Autoimmune disease	2,648 (5.1)	9,131 (4.0)	0.056
Physical limitation	5,373 (10.4)	19,408 (8.4)	0.068
Propensity score (SD)	0.30 (0.16)	0.16 (0.13)	0.987

* All data were descripted as number (%), except mean age and propensity score.

† Imbalance defined as absolute value greater than 0.015

§Urbanization levels in Taiwan are divided into four strata according to the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.

‖Charlson Comorbidity Index score is used to determine overall systemic health. With each increased level of CCI score, there are stepwise increases in the cumulative mortality.

¶Adapted Diabetes Complications Severity Index is a 13-point scale from 7 complication categories: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic, ranging from each complication. Each complication produced a numeric score ranging from 0 to 2 (0 = no abnormality, 1 = some abnormality, 2 = severe abnormality).

Abbreviations: StD, Standardized difference; SD, standard deviation; NT$, new Taiwan dollars; ACEI, angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers.

Table S3. Odds Ratios of Effect of Perioperative β blockade on Mortality among Patients with Diabetes Mellitus Undergoing Noncardiac surgery Before Propensity Score Matching

	No. of Event/ No. of Patients (%)	Adjusted* Odds Ratio (95% CI)	*P* Value
In hospital Mortality			
β blockade non-user	6925/230539	Reference	
All β blockade	1546/51668	0.89 0.84-0.95	<0.001
Atenolol, bisoprolol, carvedilol, and metoprolol	906/32662	0.80 0.74-0.87	<0.001
Others β blockade	640/19006	1.03 0.95-1.13	0.475
30-day Mortality			
β blockade non-user	9920/230539	Reference	
All β blockade	2145/51668	0.87 0.83-0.92	<0.001
Atenolol, bisoprolol, carvedilol, and metoprolol	1280/32662	0.81 0.76-0.87	<0.001
Others β blockade	865/19006	0.97 0.90-1.05	0.488

* Adjusted all covariates listed in Table 1.

Abbreviations: CI, confidence interval.

Table S4. Subgroup Analysis of Risks of Using Any β-blockers on 30-day Mortality among Patients with Diabetes Mellitus Undergoing Noncardiac Surgery

Characteristic	Odds Ratios (95% CI)	*P* Value	Interaction *P* Value
Sex			
Male	0.820 (0.755-0.889)	<0.001	0.524
Female	0.852 (0.781-0.929)	<0.001	
Age			
20-64 years	0.942 (0.846-1.048)	0.274	0.007
≥65 years	0.788 (0.733-0.847)	<0.001	
Hypertension			
Yes	0.813 (0.764-0.865)	<0.001	0.003
No	1.147 (0.926-1.421)	0.210	
Dyslipidemia			
Yes	0.873 (0.804-0.947)	0.001	0.116
No	0.793 (0.727-0.865)	<0.001	
Cerebrovascular disease			
Yes	0.883 (0.546-1.428)	0.611	0.819
No	0.834 (0.786-0.885)	<0.001	
Myocardial infarction			
Yes	0.807 (0.748-0.870)	<0.001	0.148
No	0.883 (0.801-0.973)	0.012	
Heart failure			
Yes	0.770 (0.698-0.850)	<0.001	0.048
No	0.873 (0.809-0.941)	<0.001	
Chronic kidney disease			
Yes	1.107 (0.701-1.746)	0.663	0.221
No	0.831 (0.782-0.882)	<0.001	
Revised cardiac risk index			
1	0.905 (0.767-1.068)	0.239	0.106
2	0.838 (0.755-0.930)	0.001	
3	0.867 (0.781-0.963)	0.008	
≥4	0.719 (0.628-0.823)	<0.001	
Vascular surgery			
Yes	0.744 (0.675-0.821)	<0.001	0.044
No	0.847 (0.783-0.917)	<0.001	
Year of index date			
2000-2003	0.783 (0.688-0.892)	<0.001	0.116

2004-2007	0.796 (0.722-0.878)	<0.001
2008-2011	0.899 (0.820-0.985)	0.022

Abbreviations: CI, confidence interval.

Figure S1. The Distribution of the Propensity Scores Before and After Propensity Score Matching