



The Use of Beta-Blockers Before Major Trauma and Posttrauma Outcome: A Nationwide Population-based Study

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Background: Beta-blockers are widely used for the treatment of arrhythmia, hypertension, and congestive heart failure. Major trauma causes significant blood loss and subsequent tachycardia and hypotension. Although beta-blockers may induce negative compensatory sympathetic responses to hemorrhagic shock, the effects of beta-blocker use before major trauma on posttrauma outcomes are controversial. **Aim:** We examined the association between the use of beta-blockers before major trauma and posttrauma outcomes using a nationwide population-based database. **Methods:** The data for this nationwide population-based retrospective cohort study were obtained from the National Health Insurance Research Database in Taiwan. A total of 2245 beta-blocker users were assigned to the study cohort, and another 8980 patients matched for age, sex, comorbidity, and medication use by inverse probability of treatment weighting formed the comparison cohort. The major outcome assessed was all-cause mortality during a 30-day follow-up period in major trauma patients with or without pretrauma beta-blocker use. **Results:** Our study included 2245 patients who used beta-blockers before major trauma. Individuals who used beta-blockers did not have a significantly higher cumulative risk of mortality than individuals who did not use beta-blockers (beta-blockers users: 17.19%, nonbeta-blockers users: 16.70%, $P = 0.662$). **Conclusion:** Pretrauma beta-blocker users did not have a higher mortality rate after a major trauma even after adjusting for several comorbidities and medications in a nationwide population database.

Key words: Beta-blocker, trauma, National Health Insurance Research Database

Strengths and limitations of this study

- The strength of our study is its population-based cohort design. We excluded confounding factors, including comorbidities, from our study
- We controlled for potential disease-associated confounders to the utmost extent possible, but unmeasured or unknown confounders may exist in our findings

- The NHIRD did not provide detailed information on laboratory results or lifestyle factors of the patients
- Our results are limited to human data. Mechanistic and animal studies are required for further clarification.

INTRODUCTION

Beta-blockers are competitive antagonists that block the receptor sites for the endogenous catecholamines epinephrine

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and norepinephrine on adrenergic beta receptors of the sympathetic nervous system. Beta-blockers are generally used to treat arrhythmia. Although these agents are not used as first-line therapy, they are used to treat hypertension.¹⁻³

Uncontrolled hemorrhage is a leading cause of death in multiple trauma patients.⁴ The training program of the Advanced Trauma Life Support, the American College of Surgeons defined four classes of hypovolemic shock by the estimated blood loss using variations in heart rate, systolic blood pressure, and mental status.⁵ Therefore, the initial assessment of heart rate and blood pressure is an important step in evaluating the severity of the trauma, and it is one tool to help clinical physicians make rapid therapeutic decisions. Blockade of compensatory sympathetic activation to hypotension may have detrimental effects on hemodynamics.

The effects of beta-blocker use on injury victims are controversial. A few studies showed that pretrauma beta-blocker administration did not produce a hemodynamic response.^{6,7} However, some studies indicated that beta-blocker exposure improved clinical outcomes.^{8,9}

To determine whether associations exist between pretrauma beta-blocker use and the clinical outcome of major trauma victims, we performed this exploratory study using the National Health Insurance Research Database (NHIRD) to evaluate the effects of beta-blocker use before major trauma on posttrauma outcomes.

MATERIALS AND METHODS

Data source

The National Health Insurance (NHI) Program was launched in Taiwan in 1995. The NHI includes more than 99% of the entire Taiwanese population (more than 23 million beneficiaries). The NHIRD contains data on birthdate, sex, dates of admission and discharge, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes (up to five each), and outcomes. All information to identify patients is encrypted. The NHI Administration randomly reviews the medical records periodically to verify the accuracy of the diagnoses, and the accuracy of the diagnoses of major diseases in the NHIRD, such as acute coronary syndrome and stroke, was validated in previous studies.¹⁰ The data we used were from a subset of the NHIRD called the Longitudinal Health Insurance Database 2005 (LHID 2005). The LHID 2005 contains information on the medical service utilization of approximately two million randomly selected beneficiaries, which represents approximately 8% of the population in Taiwan in 2005. Data from 2000 to 2015 were extracted from the NHIRD. Injury events were identified from the

Registry of Catastrophic Illness Patient Database, a subset of the NHIRD. Patients who were newly diagnosed with major trauma (injury severe score ≥ 16) can apply for a catastrophic illness certificate issued by the government, which allowed tracing. A panel of specialists and experts on the specific disease reviewed the medical records and imaging results before issuing a catastrophic illness certificate. This study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board of Tri-Service General Hospital at the National Defense Medical Center in Taipei, Taiwan approved this study (TSGHIRB No. 1-105-05-142), which waived the need to obtain individual consent because all of the identifying data were encrypted.

Sampled patients

This study involved study and comparison cohorts. We selected adult patients aged ≥ 20 years who were newly diagnosed with traumatic injury (ICD-9-CM N800-999) and were followed up between 2000 and 2015. Inclusion criteria included patients who¹ had an ISS higher than 16 and² received a beta-blocker prescription at least twice in the 3 months before the trauma. We excluded patients who were diagnosed with major trauma before the index date. Patients who were lost to follow-up or whose sex was not known were also excluded from the study. The date of the major trauma diagnosis was used as the index date. Control candidate sampling comparisons were selected from individuals in the LHID 2005 who did not use beta-blockers during the 3 months before the index date. The patients and control cohorts were selected using 1:4 inverse probability of treatment weighting matching according to the following baseline variables: age; sex; comorbidities, including hypertension (ICD-9-CM 401-405), DM (ICD-9-CM 250), cardiac dysrhythmias (ICD-9-CM 427), ischemic heart disease (ICD-9-CM 410-414), heart failure (ICD-9-CM 428), asthma (ICD-9-CM 493), COPD (ICD-9-CM 490-496), obesity (ICD-9-CM 278), and chronic kidney disease (ICD-9-CM 582-589); and medication history, including digoxin, warfarin, and platelet aggregation inhibitors.

Statistical analysis

All statistical analyses were performed using SPSS software, version 22 (SPSS Inc., Chicago, IL, USA). The clinical characteristics of the patients enrolled in the study are expressed as numbers. Categorical variables are presented as percentages and were compared using Fisher's exact and Chi-squared tests. Continuous variables are presented as the means and standard deviations and were compared using *t*-tests. The primary goal of the study was to determine whether the use of beta-blockers was associated with all-cause

mortality, intensive care unit (ICU) length of stay, and the need for blood transfusion within a 30-day follow-up period after major trauma. Associations between time-to-event outcomes (prognoses) and clinical characteristics were examined using the Kaplan-Meier method and multivariate Cox regression analysis with stepwise selection. The results are presented as adjusted hazard ratios (HRs) with the corresponding 95% confidence intervals. The Omnibus value of Cox regression of this study was <0.001 . Statistical significance was indicated by $P < 0.05$.

Patients and public involvement

Patients and the public were not involved in the design or planning of the study.

RESULTS

Among the 1,936,512 patients in the LHID 2005 from the NHIRD, 4241 beta-blocker users were diagnosed with major trauma. A total of 2245 patients were assigned to the study cohort, and another 2245 age-, sex-, comorbidity- and medication-matched patients formed the comparison cohort [Figure 1]. There were no significant differences in sex, age, comorbidities, or the number of medical follow-up visits between the groups that did and did not use beta-blockers after matching [Table 1].

Compared with patients who did not use beta-blockers, patients who used beta-blockers did not have a significantly higher cumulative risk of all-cause mortality after the index date [log-rank test $P = 0.724$, Figure 2]. At the end of the 30-day follow-up period, no significant differences in all-cause mortality (17.19% vs. 16.70%, $P = 0.662$), ICU admission (79.11% vs. 78.26%, $P = 0.489$), ICU days (7.33 ± 3.55 vs. 7.31 ± 3.53 , $P = 0.850$), hospitalization duration (7.89 ± 3.69 vs. 7.84 ± 3.65 , $P = 0.648$) or the need for blood transfusion (42.05% vs. 41.69%, $P = 0.809$) were observed in patients who did or did not use beta-blockers [Table 2]. The data were stratified by age and the presence of a head injury. Among head injury patients, beta-blocker users had a higher incidence of admission to the ICU than non-users (38.91 vs. 38.73 per 100,000 person-days, adjusted HR = 1.124, $P = 0.009$). Among patients older than 65 years with head injuries, beta-blocker users had a higher rate of blood transfusion than nonusers [Table 3]. The data were also stratified by the medication possession ratio (MPR). Among the patients who have an MPR greater than 80%, 40%–80%, and below 40%, there was no significant difference in the major outcome [Supplementary Table 1]. The sensitivity test revealed that there is no significant difference in major

outcomes between matching ratios [Supplemental Table 2]. Beta-blockers were divided into nonselective and selective for subgroup analysis. No significant difference was found between subgroups [Supplemental Table 3].

DISCUSSION

This population-based study with a nationwide dataset revealed that the prior use of beta-blockers did not result in a significantly higher 30-day mortality rate in patients who sustained major trauma, even after adjusting for age, sex, comorbidities, and medications.

The inflammatory response begins a few minutes or hours after a major trauma event. Systemic inflammatory response syndrome, adult respiratory distress syndrome, and multiple organ failure following a trauma event affect trauma-related mortality.¹¹ Beta-blocker administration decreases the concentrations of proinflammatory cytokines, such as interleukin-6.¹² Stress-related activation of the sympathetic nervous system results in the increased secretion and circulation of catecholamines.¹³ Sustained and excessive adrenergic activity is associated with increased mortality.¹⁴ The use of beta-blockers blunts the hyperadrenergic state and decreases mortality. Major trauma causes massive blood loss and hypovolemia. Multisystem injuries result in critical cardiac stress. Acute myocardial infarction occurs due to increased myocardial oxygen demand or reduced supply in the absence of acute atherothrombotic plaque disruption. For example, hypovolemic shock is called type 2 myocardial infarction. Some studies observed that beta-blockers reduced the odds of death at 2 years in patients with type 2 myocardial infarction who used beta-blockers compared to the odds in those who did not use these agents.¹⁵ Trauma-related wound infection, surgical wound infection, or hospital-acquired infection affect mortality. A previous prescription of beta-blockers is associated with reduced mortality in patients who were hospitalized in the ICU for sepsis.¹⁶

Beta-blockers lower the systemic blood pressure and cerebral perfusion pressure, and there is concern about their use in patients with hypovolemic shock or head injury. Some studies described that preinjury beta-blocker use was associated with a higher mortality rate. Beta-blockers may blunt the response to shock and decrease the ability to compensate for cardiac output after major trauma-related shock.^{17,18} Another study showed that the pretrauma use of cardiac-specific agents led to a higher mortality rate. However, the use of a combination of beta-blockers and other cardiac-specific agents, such as calcium channel blockers and angiotensin-converting enzyme inhibitors/

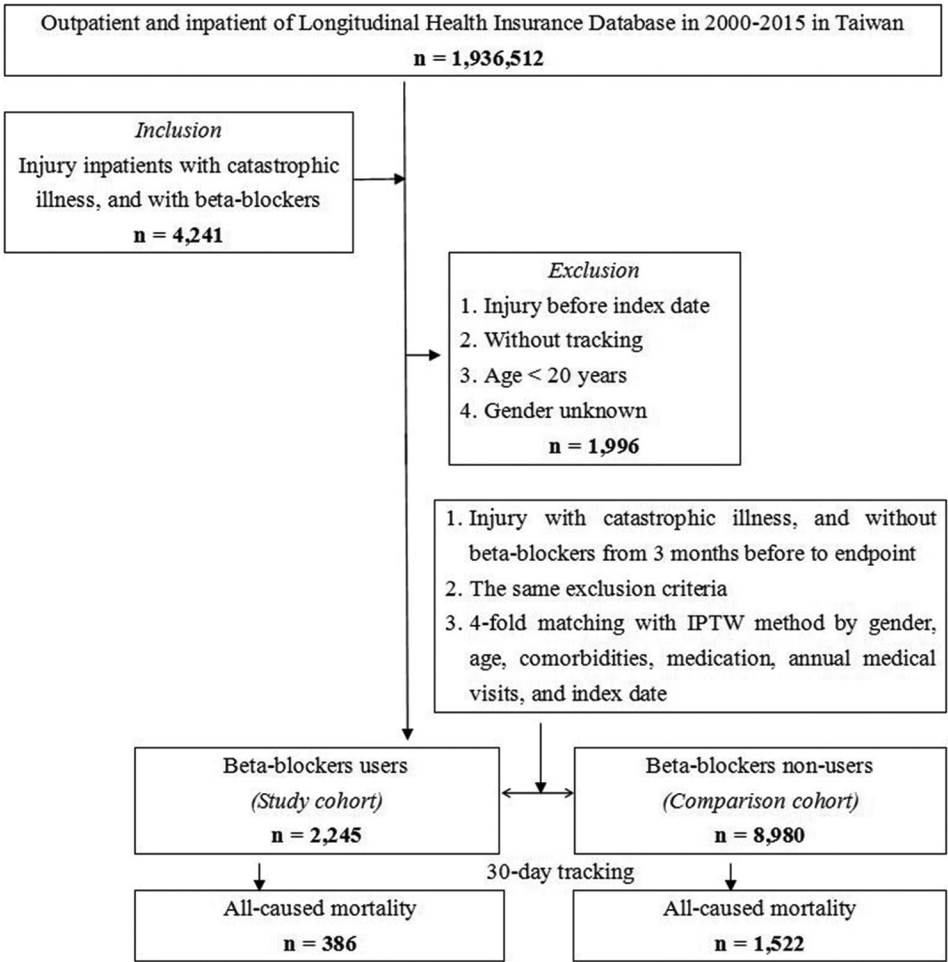


Figure 1: Patient selection flowchart

angiotensin receptor blockers, before trauma does not inhibit the hemodynamic response in trauma cases.⁶

Abnormal heart rate and blood pressure are signs of hypovolemia, and blood transfusion is generally needed when fluid resuscitation does not reverse it. Previous studies of the hemodynamic effect of the preinjury use of beta-blockers produced controversial results. Our study found no difference between beta-blocker users and nonusers in the need for blood transfusion after major trauma.

This study is the first study to investigate the association between the preinjury use of beta-blockers and outcomes after major trauma in an Asian population. The strength of this study is that it was a population-based study. Complete medical and medication use records of patients were registered in the NHIRD. Comorbidities and medications were matched between the beta-blocker users and nonusers in this study. Compared to previous studies on the effect of beta-blockers

on brain trauma patients, our study included trauma patients who have an ISS = 16 or higher. Patients in our study were diverse since major trauma patients usually do not have only single organ injury. The disadvantage of this study compared to the previous studies described above is that the NHIRD did not provide detailed information on vital signs, such as heart rate and blood pressure, of trauma victims of this study. Vital signs would provide some important information, such as hemodynamic status. Cushing triads, a clinical sign of increased intracranial pressure, are also represented by vital signs.

This study was a retrospective cohort study. Although we extensively adjusted our results using multivariate logistic regression models, residual limitations may exist. The NHIRD registry does not provide detailed information on the severity of the injury, exact ISS scores, precise injury site of specific organs, health-related lifestyle factors, heart rate, blood pressure, imaging results or laboratory results, and

Table 1: Characteristics of the study participants at baseline

	Beta-blockers				<i>P</i>
	Users, <i>n</i> (%)	Nonusers (matched), <i>n</i> (%)		Nonusers (unmatched), <i>n</i> (%)	
Total	2245	8980		19,487	
Gender					<0.001*
Male	1287 (57.33)	5148 (57.33)	0.999	10,295 (52.83)	
Female	958 (42.67)	3832 (42.67)		9192 (47.17)	
Age (years)	51.52±18.64	51.48±18.58	0.927	49.83±17.22	<0.001*
Age groups (years)					<0.001*
20-44	781 (34.79)	3124 (34.79)	0.999	5052 (25.92)	
45-64	715 (31.85)	2860 (31.85)		7774 (39.89)	
≥65	749 (33.36)	2996 (33.36)		6661 (34.18)	
Hypertension	624 (27.80)	2489 (27.72)	0.941	5011 (25.71)	0.033*
Diabetes mellitus	729 (32.47)	2917 (32.48)	0.992	6785 (34.82)	0.027*
Cardiac dysrhythmias	401 (17.86)	1610 (17.93)	0.941	2244 (11.52)	<0.001*
IHD	135 (6.01)	533 (5.94)	0.889	1318 (6.76)	0.178
Heart failure	112 (4.99)	447 (4.98)	0.561	678 (3.48)	0.001*
COPD	206 (9.18)	829 (9.23)	0.935	1346 (6.91)	<0.001*
Obesity	13 (0.58)	50 (0.56)	0.899	104 (0.53)	0.781
CKD	379 (16.88)	1519 (16.92)	0.970	1998 (10.25)	<0.001*
Digoxin	501 (22.32)	2006 (22.34)	0.982	2245 (11.52)	<0.001*
Warfarin	482 (21.47)	1929 (21.48)	0.991	2763 (14.8)	<0.001*
Annual medical visiting	5.65±6.86	5.59±6.77	0.780	6.84±7.19	<0.001*
Laparotomy	386 (17.19)	1546 (17.22)	0.980	3540 (18.17)	0.257
Thoracotomy	335 (14.92)	1342 (14.94)	0.979	3886 (19.94)	<0.001*
Craniectomy	241 (10.73)	968 (10.78)	0.951	3724 (19.11)	<0.001*

**P* values (categorical variables: Chi-square/Fisher's exact test; continuous variables: *t*-test) <0.05 were considered statistically significant. IHD=Ischemic heart disease, COPD=Chronic obstructive pulmonary disease, CKD=Chronic kidney disease

Table 2: Incidence rates of outcomes and other characteristics in the enrolled study participants at the end of the 30 days follow-up period

	Total, <i>n</i> (%)	Beta-blockers		<i>P</i>
		Users, <i>n</i> (%)	Nonusers (matched), <i>n</i> (%)	
Total	11,225	2245	8980	
All-cause mortality	1908 (17.00)	386 (17.19)	1522 (16.95)	0.782
ICU admission	8801 (78.41)	1776 (79.11)	7025 (78.23)	0.365
ICU days	7.31±3.52	7.33±3.55	7.31±3.51	0.810
Hospital days	7.84±3.63	7.89±3.69	7.83±3.62	0.484
Blood transfusion	4710 (41.96)	944 (42.05)	3,766 (41.94)	0.924
Mean of follow-up (years)	6.83±6.52	6.78±6.49	6.84±6.52	0.696
Median of follow-up (years)	5.55	5.52	5.57	

ICU=Intensive care unit

these conditions may be confounding factors. The NHIRD registry only provides the prescriptions patients obtained, and there is no information on patient compliance with the prescription.

CONCLUSION

We observed that beta-blocker users did not have a higher all-cause mortality rate than non-users, even after adjusting

Table 3: Factors associated with outcomes according to the Cox regression model

Outcomes	Beta-blockers Stratified	Users			Nonusers (matched)			Users versus nonusers (reference)				Interaction <i>P</i>
		Events	PDs	Rate	Events	PDs	Rate	Adjusted HR	95% CI	95% CI	<i>P</i>	
All-cause mortality	Overall	386	65,124.23	5.93	1552	252,882.85	6.14	1.052	0.591	1.568	0.488	0.682
	Age group (years)											
	20-44	198	29,785.46	6.65	807	115,468.65	6.99	1.044	0.417	1.559	0.535	
	45-64	144	21,070.20	6.83	591	81,691.40	7.23	1.029	0.382	1.506	0.583	0.737
	≥65	44	14,268.57	3.08	154	55,722.79	2.76	1.083	0.635	1.653	0.440	
	Head injury											
	Without	167	30,993.97	5.39	678	120,504.56	5.63	1.026	0.517	1.553	0.505	0.737
	With	219	34,130.26	6.42	874	132,378.29	6.60	1.065	0.613	1.658	0.470	
ICU	Overall	1776	64,298.15	27.62	7025	249,265.14	28.18	1.090	0.832	1.901	0.218	0.077
	Age group (years)											
	20-44	596	29,054.11	20.51	2354	112,650.99	20.90	1.084	0.821	1.874	0.288	
	45-64	522	20,986.70	24.87	2072	81,386.20	25.46	1.072	0.792	1.849	0.314	0.017*
	≥65	658	14,257.34	46.15	2599	55,227.91	47.06	1.095	0.984	2.009	0.058	
	Head injury											
	Without	461	30,499.65	15.11	1792	118,229.72	15.16	1.059	0.776	1.879	0.279	0.017*
	With	1315	33,798.50	38.91	5233	131,035.38	39.94	1.110	1.076	2.087	0.009*	
Transfusion	Overall	944	65,027.50	14.52	3766	252,362.46	14.92	1.151	0.825	1.873	0.164	0.063
	Age group (years)											
	20-44	312	29,731.20	10.49	1248	115,264.48	10.83	1.158	0.893	1.900	0.130	
	45-64	304	21,084.38	14.42	1206	81,780.95	14.75	1.144	0.818	1.802	0.199	0.001*
	≥65	328	14,211.92	23.08	1312	55,317.07	23.72	1.184	0.991	1.978	0.053	
	Head injury											
	Without	559	30,938.26	18.07	2237	120,049.29	18.63	1.118	0.796	1.764	0.181	0.001*
	With	385	34,089.24	11.29	1529	132,313.20	11.56	1.192	1.090	2.206	<0.001*	

* $P < 0.05$ were considered statistically significant. PDs=Person-days, Rate=Per 1000 person-days, ICU=Intensive care unit, HR=Hazard ratio, CI=Confidence interval

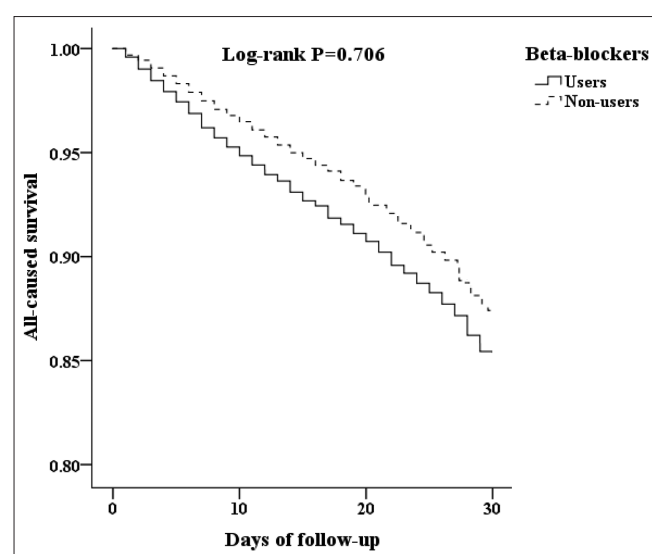


Figure 2: Kaplan-Meier curve of all-cause survival after trauma

for several comorbidities and medications in a nationwide population database.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Factors associated with outcomes among different medication possession ratios according to the Cox regression model

Outcomes	Beta-blockers	Population	Events	PDs	Rate	Adjusted HR	95% CI	95% CI	<i>P</i>
All-cause mortality	Nonusers (matched)	8980	1552	252,882.85	6.14	Reference			
	Users	2245	386	65,124.23	5.93	1.052	0.591	1.568	0.488
	MPR: <40%	594	103	17,231.09	5.98	1.061	0.596	1.581	0.492
	MPR: 40%-80%	1286	221	37,305.02	5.92	1.051	0.591	1.567	0.488
	MPR: >80%	365	62	10,588.13	5.86	1.039	0.584	1.549	0.482
ICU	Nonusers (matched)	8980	7025	249,265.14	28.18	Reference			
	Users	2245	1776	64,298.15	27.62	1.090	0.832	1.901	0.218
	MPR: <40%	594	471	17,012.52	27.69	1.093	0.834	1.905	0.219
	MPR: 40%-80%	1286	1018	36,831.81	27.64	1.091	0.833	1.902	0.218
	MPR: >80%	365	287	10,453.82	27.45	1.083	0.827	1.889	0.217
Transfusion	Overall	8980	3766	252,362.46	14.92	Reference			
	Age group (years)	2245	944	65,027.50	14.52	1.151	0.825	1.873	0.164
	MPR: <40%	594	255	17,205.49	14.82	1.175	0.842	1.912	0.167
	MPR: 40%-80%	1286	541	37,249.61	14.52	1.152	0.825	1.874	0.164
	MPR: >80%	365	148	10,572.40	14.00	1.110	0.796	1.806	0.158

MPR=Medication possession ratio, PDs=Person-days, Rate=Per 1,000 person-days, ICU=Intensive care unit, HR=Hazard ratio, CI=Confidence interval

Supplementary Table 2: Sensitivity analysis

Matching of beta-blockers nonusers	<i>Post hoc</i> power	Outcomes	Beta-blockers users versus nonusers (reference)			
			Adjusted HR	95% CI	95% CI	<i>P</i>
Unmatched	0.733	All-caused mortality	1.179	0.662	1.757	0.547
	0.711	ICU	1.222	0.933	2.131	0.244
	0.723	Transfusion	1.290	0.925	2.099	0.184
1:1	0.799	All-caused mortality	1.050	0.590	1.564	0.487
	0.775	ICU	1.087	0.830	1.896	0.217
	0.788	Transfusion	1.148	0.823	1.869	0.164
1:2	0.809	All-caused mortality	1.051	0.590	1.566	0.487
	0.784	ICU	1.089	0.831	1.899	0.218
	0.797	Transfusion	1.150	0.824	1.871	0.164
1:3	0.853	All-caused mortality	1.050	0.590	1.564	0.487
	0.828	ICU	1.087	0.830	1.897	0.217
	0.841	Transfusion	1.148	0.823	1.869	0.164
1:4	0.864	All-caused mortality	1.052	0.591	1.568	0.488
	0.838	ICU	1.090	0.832	1.901	0.218
	0.852	Transfusion	1.151	0.825	1.873	0.164
1:5	0.865	All-caused mortality	1.053	0.592	1.570	0.489
	0.839	ICU	1.091	0.833	1.903	0.218
	0.853	Transfusion	1.152	0.826	1.875	0.164

ICU=Intensive care unit, CI=Confidence interval

Supplementary Table 3: Factors associated with outcomes among different kinds of beta-blockers according to the Cox regression model

Outcomes	Beta-blockers	Population	Events	PDs	Rate	Adjusted HR	95% CI	95% CI	<i>P</i>
All-cause mortality	Nonusers (matched)	8980	1552	252,882.85	6.14	Reference			
	Users	2245	386	65,124.23	5.93	1.052	0.591	1.568	0.488
	Nonselective beta blockers	1265	220	36,695.84	6.00	1.064	0.598	1.586	0.494
	Selective beta blockers	980	166	28,428.39	5.84	1.036	0.582	1.545	0.481
ICU	Nonusers (matched)	8980	7025	249,265.14	28.18	Reference			
	Users	2245	1776	64,298.15	27.62	1.090	0.832	1.901	0.218
	Nonselective beta blockers	1265	1011	36,230.36	27.90	1.101	0.841	1.921	0.220
	Selective beta blockers	980	765	28,067.79	27.26	1.076	0.821	1.876	0.215
Transfusion	Overall	8980	3766	252,362.46	14.92	Reference			
	Age group (years)	2245	944	65,027.50	14.52	1.151	0.825	1.873	0.164
	Nonselective beta blockers	1265	539	36,641.33	14.71	1.166	0.836	1.898	0.166
	Selective beta blockers	980	405	28,386.17	14.27	1.131	0.811	1.841	0.161

PDs=Person-days, Rate=Per 1,000 person-days, ICU=Intensive care unit, CI=Confidence interval, HR=Hazard ratio