Beta-blocker Therapy and Future Risk of Lower Limb Amputation in Patients with Diabetes and Peripheral Artery Disease

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Abstract

Background: Theoretically, beta-adrenoceptor blocking agents (beta-blockers) may reduce peripheral perfusion via α-receptor-mediated peripheral vasoconstriction. The use of beta-blockers in patients with peripheral artery disease (PAD) is therefore controversial. According to the European Society of Cardiology guideline for PAD in 2019, beta-blockers are not contraindicated. However, there is little evidence regarding the limb outcomes of beta-blocker use in diabetes mellitus (DM) patients with PAD.

Methods: Patients with type 2 DM and PAD were identified and retrospectively enrolled from Taiwan's National Health Insurance Research Database. To analyze the impact of beta-blocker use on limb outcomes, patients using BB were compared with propensity score-matched BB non-users in a 1:1 ratio. A total of 40,250 propensity score-matched pairs of beta-blocker users (20,125 patients) and non-users (20,125 patients) with type 2 DM and established diagnosis of PAD were examined over the period 2000 to 2011.

Results: A total of 86,859 patients were enrolled. The mean age of beta-blocker users

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was 64.4 ± 11.7 years, and of non-users 64.5 ± 11.6 years. During the mean follow-up of 15 months, a total of 365 beta-blocker users and 434 non-users underwent amputations. Compared with non-users, beta-blocker users were associated with a lower risk of amputation due to PAD (hazard ratio (HR): 0.83; 95% confidence interval (CI): 0.72-0.96). Additionally, beta-blocker users had a lower risk of all-cause mortality than non-users (HR: 0.94; 95% CI: 0.91-0.98). By comparison, the risks of in-hospital cardiovascular death, myocardial infarction and ischemic stroke did not differ significantly between users and non-users.

Conclusions: This nationwide population-based diabetes cohort study demonstrated that treatment with beta-blockers is associated with lower risk of all-cause mortality and amputation in type 2 DM patients with PAD.

Key words: beta-blockers, lower-extremity amputation, type 2 diabetes mellitus, peripheral artery disease

INTRODUCTION

Peripheral arterial disease (PAD) is the process of arteriosclerosis of the arteries of the lower extremities, and is a major risk factor for lower-extremity amputation. Diabetes mellitus (DM) leads to a significant, four-fold increase in the relative risk of PAD,[1] as well as increased incidence of intermittent claudication,[2,3] limb amputation,[4,5] and contralateral leg disease.[6] Moreover, diabetes serves as an indicator to determine the severity,[7] early postoperative complications,[4] and poorer outcome after revascularization[5,8] of PAD.

According to the European Society of Cardiology (ESC) 2019 guidelines on diabetes, beta-blockers (BB) may be considered in patients with DM and coronary artery disease (CAD) (Class IIb, level of evidence (LOE) B).[9] They are also recommended in addition to an angiotensin-converting enzyme (ACE) inhibitor in symptomatic patients with heart failure with reduced ejection fraction and DM to reduce mortality and hospitalization (Class I, LOE A). Theoretically, beta-adrenoceptor blocking agents may reduce peripheral perfusion via α-receptor-mediated peripheral vasoconstriction.[10-12] Moreover, some studies show that BBs may have side effects such as cyanosis, coldness or even Raynaud's phenomenon due to vasoconstriction.[11,13,14] Previous research has indicated that BBs do not worsen critical limb ischemia in patients receiving endovascular therapy.[15] The use of BBs in patients with PAD is therefore controversial. According to the ESC 2019 guideline, BBs are not contraindicated for PAD.[16]

Nevertheless, evidence regarding the safety of BB use in DM patients with PAD is limited. Diabetic foot ulcers are related to higher mortality and morbidity such as amputations.[17] Also, a recent study disclosed that minor amputation was associated with high mortality.[18] Therefore, death is a potential competing risk to amputation, because many diabetic patients with PAD may die before the initial amputation. Thus, taking into account the competing risk of death, we used nationwide diabetic cohort data in the current study. The goal of our study was to determine whether the use of BBs was associated with the lower-extremity amputation rate in Taiwan's DM population.

METHODS

Data source

Taiwan initiated the National Health Insurance (NHI) program, a social insurance program organized by the government, in 1995. This extensive program provides comprehensive medical care including outpatient care, emergency department care, hospital care, dental services,

medical examinations, laboratory tests, drug prescriptions and interventional procedures. Data for this study were obtained from the National Health Insurance Research Database (NHIRD), a nationally representative database maintained for research and policy development by Taiwan's National Health Research Institutes (NHRI). For the current study, we used the Longitudinal Cohort of Diabetes Patients dataset, which has been validated by the NHRI for research purposes after encryption and de-identification. This database, which represents the majority of the population of Taiwan, consists of de-identified secondary data from a random sample of 120,000 patients diagnosed with DM each year since 1999. Diseases are classified using diagnosis codes from the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). The institutional review board of Taipei City Hospital approved this study after full review (TCHIRB-10404107-W) because the data were secondary and de-identified.

Study cohort

In this population-based observational cohort study, we aimed to explore the association between BB use and limb outcomes in diabetic patients with PAD. The study included all diabetic patients aged ≥ 20 years with PAD between 1st January 2000 and 31st December 2011. We assigned the patients to a BB-user group and a BB-non-user group. We defined BB-users as those who received treatment with BBs within 90 days after PAD diagnosis. Other patients not using BBs were allocated to the non-user group. To avoid immortal time bias, we set the index date at 91 days after PAD diagnosis.

For each subject in the study groups, we extracted data on demographic variables, diagnosis and procedure codes, and drug prescriptions for the period between January 1995 and December 2011, and ensured that all individuals had data covering at least 5 years before study inclusion. For the present study, we analyzed sociodemographic data (including age, sex and monthly income), index year, urbanization level (comprising four levels, with level one referring to most urbanized, and level four referring to least urbanized), Charlson Comorbidity Index (CCI) score, adapted Diabetes Complications Severity Index (aDCSI) scores and other comorbidities known to be associated with vascular disease. We also took into consideration the concomitant use of other medications that could be a confounding factor (including alpha blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics, other anti-hypertensive drugs, antiplatelet agents, steroids, nitrates, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, selective serotonin re-uptake inhibitors and anti-diabetic drugs).

Due to the baseline differences, we conducted propensity-score matched analyses, which predicted the probability of receiving BB conditional on the observed baseline covariates, using multivariable logistic regression. Each patient in the BB-non-user group was matched to a patient in the BB-user group with a similar propensity score, based on nearest neighbor matching without replacement, using a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score. Subjects without matched pairs were excluded from the propensity score-matched analyses.

Beta-blockers exposure

From the Longitudinal Cohort of Diabetes Patients dataset, we extracted information on all BB prescriptions, including drug name, quantity, dose and starting and discontinuation dates for the study period. We collected information on prescribed drug types, based on the Anatomic Therapeutic Chemical classification coding system for BBs, including acebutolol, alprenolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, pindolol, propranolol and timolol.

Outcomes

The primary end point was new lower-

extremity amputation. Secondary outcomes of interest were in-hospital cardiovascular death and all-cause mortality. All subjects were followed until death or December 31st, 2012.

Statistical analysis

Descriptive statistics were used to characterize baseline demographic and clinical variables of the study cohort. Standardized differences were used to check for balance between groups after matching. Poisson distribution was used to calculate the incidence rates for the two groups. Cox regression models with a conditional approach and stratification were used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the risk outcomes of each group. Our results are also presented prior to matching using Cox regression model, adjusted for baseline covariates. After propensity score matching, we used the crude results from the propensity score matched cohort without further adjustments. Due to the high mortality rate in diabetic patients with PAD, we also performed a competing-risk regression using Fine and Gray's model. Finally, the likelihood ratio test was used to examine the interaction between the occurrence of lower-extremity amputation and the following variables: age, sex, CCI score, hypertension, chronic kidney disease (CKD), heart failure, coronary artery disease (CAD), use of an antiplatelet agent and the potency of statins. Subgroup analyses were performed accordingly. SQL Server 2012 (Microsoft Corporation, Redmond, WA, USA) was used for data linkage, processing and sampling. Propensity scores were calculated using SAS version 9.3 (SAS Institute, Cary, NC, USA). All other statistical analyses were conducted using STATA statistical software (version 12.0; StataCorp, College Station, TX, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

We identified a total of 86,859 DM patients with newly diagnosed PAD who met the inclusion criteria between January 2000 and December 2011. Among them, 20,708 patients were BB-users, and 66,151 patients were BB-non-users. Overall, the mean age of the study subjects was 64.3 ± 11.8 years for BB-users and 61.8 ± 13.0 years for non-users. Sex was almost equally distributed (male 50.3%). Hypertension, present in 72.8% of PAD patients, was the most common comorbidity in the study cohort. The prevalence of other comorbid conditions was as follows: coronary artery disease (CAD): 44.1%; cerebrovascular disease: 29.3%; myocardial infarction (MI): 4.4%; heart failure: 13.6%; liver disease: 42.1%; chronic kidney disease: 19.6%; atrial fibrillation: 3.2%; dyslipidemia: 62.6%; valvular heart disease: 9.5%, and cancer: 10.7%. The BB-user group exhibited more comorbidities such as CAD, cerebrovascular disease, myocardial infarction, hypertension, heart failure and valvular heart disease. More patients on BB therapy were also taking ACE inhibitors or angiotensin receptor blockers, calcium channel blockers, diuretics and antiplatelet agents, as compared to patients in the non-user group (Table 1).

After propensity score matching, 20125 BB-users were matched to 20125 non-users. As shown in Table 1, after 1:1 matching the baseline characteristics of both cohorts (including socioeconomic status, relevant comorbidities and medication) did not differ significantly between the two groups.

Long-term risks of lower-extremity amputation, in-hospital cardiovascular death, and all-cause mortality

In the propensity score-matched analysis cohort, a total of 365 BB-users and 434 non-users underwent amputation during the mean follow-up of 15 months. Compared to non-users, BB-users were associated with a lower risk of amputation due to PAD (HR: 0.83; 95% CI: 0.72-0.96). Additionally, BB-users had a lower risk of all-cause mortality than non-users (HR: 0.94; 95% CI: 0.91-0.98). By comparison, risks of in-hospital

Table 1. Baseline characteristics of patients with type 2 diabetes mellitus and peripheral arterial disease

Characteristics	Before Propensity Score Matching			After Propensity Score-Matching		
	Beta blocker user	Beta blocker non-user	*Standardized difference*	Beta blocker user	Beta blocker non-user	*Standardized difference*
Patients (no.)	20708	66151		20125	20125	
Mean age (SD), years	64.3 (11.8)	61.8 (13.0)	0.197	64.4 (11.7)	64.5 (11.6)	-0.004
Gender (male)	9301 (44.9)	34363 (51.9)	-0.141	9037 (44.9)	8956 (44.5)	0.008
Monthly income, NT$						
Dependent	6985 (33.7)	19639 (29.7)	0.087	6784 (33.7)	6827 (33.9)	-0.005
< 19,100	4105 (19.8)	13099 (19.8)	0.001	3982 (19.8)	3892 (19.3)	0.011
19,100-41,999	8726 (42.1)	29815 (45.1)	-0.059	8499 (42.2)	8577 (42.6)	-0.008
≥ 42,000	892 (4.3)	3598 (5.4)	-0.053	860 (4.3)	829 (4.1)	0.008
Urbanization level*						
1 (urban area)	7150 (34.5)	22726 (34.4)	0.004	6929 (34.4)	6913 (34.4)	0.002
2	12293 (59.4)	39369 (59.5)	-0.003	11958 (59.4)	11950 (59.4)	0.001
3	1096 (5.3)	3524 (5.3)	-0.002	1074 (5.3)	1106 (5.5)	-0.007
4 (rural area)	169 (0.8)	532 (0.8)	0.001	164 (0.8)	156 (0.8)	0.004
Outpatient visits to metabolism & endocrinology professionals in the one year prior.						
0-5	18017 (87.0)	57197 (86.5)	0.016	17524 (87.1)	17509 (87.0)	0.002
6-10	1704 (8.2)	5904 (8.9)	-0.025	1652 (8.2)	1651 (8.2)	0.000
11-15	604 (2.9)	2053 (3.1)	-0.011	584 (2.9)	600 (3.0)	-0.005
> 15	383 (1.8)	997 (1.5)	0.027	365 (1.8)	365 (1.8)	0.000
Charlson Comorbidity Index score, median (IQR)	7 (6-8)	6 (5-8)	0.221	7 (6-8)	7 (6-8)	-0.005
Adapted Diabetes Complications Severity Index score, median (IQR) †	3 (2-4)	2 (1-4)	0.347	3 (2-4)	3 (2-4)	0.008
Median (IQR) duration of diabetes mellitus, months	46 (17-82)	40 (14-76)	0.110	46 (17-82)	46 (18-81)	0.006
Anti-hypertensive drug use						
Alpha blocker	772 (3.7)	1328 (2.0)	0.103	713 (3.5)	678 (3.4)	0.010
ACE inhibitor or ARB	5883 (28.4)	10677 (16.1)	0.298	5552 (27.6)	5524 (27.4)	0.003
Calcium channel blocker	6622 (32.0)	10325 (15.6)	0.392	6239 (31.0)	6208 (30.8)	0.003
Diuretics	3401 (16.4)	4997 (7.6)	0.276	3110 (15.5)	3110 (15.5)	0.000
Anti-diabetic drugs						
Acarbose inhibits enzymes	795 (3.8)	2208 (3.3)	0.027	771 (3.8)	771 (3.8)	0.000
Sulfonylurea	5934 (28.7)	19251 (29.1)	-0.010	5774 (28.7)	5841 (29.0)	-0.007
Insulin	435 (2.1)	1330 (2.0)	0.006	411 (2.0)	411 (2.0)	0.000
Metformin	5006 (24.2)	15800 (23.9)	0.007	4874 (24.2)	4939 (24.5)	-0.008
Thiazolidinediones	760 (3.7)	2583 (3.9)	-0.012	748 (3.7)	750 (3.7)	-0.001
DPP-4i	245 (1.2)	537 (0.8)	0.037	232 (1.2)	208 (1.0)	0.011
Other concomitant medications						
Antiplatelet agent	6657 (32.1)	11755 (17.8)	0.337	6229 (31.0)	6159 (30.6)	0.008

(Continued)

Table 1. *Continued*

Warfarin	288 (1.4)	442 (0.7)	0.072	257 (1.3)	250 (1.2)	0.003
Steroid	1475 (7.1)	4062 (6.1)	0.039	1430 (7.1)	1445 (7.2)	-0.003
NSAID	6941 (33.5)	18237 (27.6)	0.128	6696 (33.3)	6777 (33.7)	-0.009
PPI	338 (1.6)	808 (1.2)	0.035	323 (1.6)	330 (1.6)	-0.003
Statin	2509 (12.1)	5293 (8.0)	0.137	2347 (11.7)	2367 (11.8)	-0.003
Antidepressant	1466 (7.1)	2656 (4.0)	0.134	1324 (6.6)	1368 (6.8)	-0.009
Comorbidities						
Coronary artery disease	13041 (63.0)	25221 (38.1)	0.513	12483 (62.0)	12624 (62.7)	-0.014
Cerebrovascular disease	7876 (38.0)	17545 (26.5)	0.248	7584 (37.7)	7471 (37.1)	0.012
Myocardial infarction	1678 (8.1)	2117 (3.2)	0.214	1400 (7.0)	1400 (7.0)	0.000
Hypertension	19326 (93.3)	43882 (66.3)	0.714	18780 (93.3)	18780 (93.3)	0.000
Heart failure	4215 (20.4)	7580 (11.5)	0.245	3973 (19.7)	3859 (19.2)	0.014
Liver disease	9167 (44.3)	27365 (41.4)	0.059	8900 (44.2)	8989 (44.7)	-0.009
Chronic kidney disease	4855 (23.4)	12127 (18.3)	0.126	4695 (23.3)	4617 (22.9)	0.009
Atrial fibrillation	999 (4.8)	1771 (2.7)	0.113	949 (4.7)	908 (4.5)	0.010
Dyslipidemia	14304 (69.1)	40059 (60.6)	0.179	13833 (68.7)	13865 (68.9)	-0.003
Valvular heart disease	3142 (15.2)	5135 (7.8)	0.234	2926 (14.5)	2841 (14.1)	0.012
Cancer	2411 (11.6)	6841 (10.3)	0.042	2347 (11.7)	2376 (11.8)	-0.004
Autoimmune disease	1148 (5.5)	2809 (4.2)	0.060	1097 (5.5)	1116 (5.5)	-0.004
Physical limit	2663 (12.9)	7223 (10.9)	0.060	2592 (12.9)	2645 (13.1)	-0.008
Propensity score, mean (SD)	0.33 (0.14)	0.21 (0.14)	0.871	0.32 (0.13)	0.32 (0.13)	0.000

All data are presented as n (%), except where otherwise indicated.

* Urbanization levels in Taiwan were divided into four strata based on the Taiwan National Health Research Institute publications. Level 1 designates the most urbanized areas, and level 4 designates the least urbanized areas.

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

Abbreviations: SD: standard deviation; NT$: new Taiwan dollars; IQR: interquartile range; DPP-4i: dipeptidyl peptidase-4 inhibitor; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor.

cardiovascular death, myocardial infarction and ischemic stroke were not significantly different between BB-users and non-users (Table 2).

Subgroup analysis of the risks of lower-extremity amputation

Focusing on lower-extremity amputation as outcome, tests of interactions were not significant for sex (p = 0.946), age≧65 years (p = 0.393), hypertension (p = 0.926), myocardial infarction (p = 0.971), cerebrovascular disease (p = 0.442), heart failure (p = 0.734) or chronic kidney disease (p = 0.978) (Table 3).

DISCUSSION

The main question addressed in this study is whether BBs have adverse effects on the progression of PAD, given type 2 DM, the most importance predictive factor for PAD, and thus increase the rate of amputation.[19] We demonstrated that BB-users had a 17% lower risk of amputation, when compared with non-users, among patients with type 2 DM. This is consistent with results reported in a nationwide propensity score-matched study from Denmark, where BB-users were exposed to a lower hazard ratio

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Table 2. Incidence and risks of mortality, amputation and other complications, comparing between beta-blocker users and non-users among patients with diabetes and PAD after propensity score matching

	Beta blocker user			Beta blocker non-user			Crude	
	No. of Events	Person-Years	Incidence Rate*	No. of Events	Person-Years	Incidence Rate*	Hazard Ratio (95% CI)	*P*
All-cause mortality	4332	124421	34.82	4536	123277	36.80	0.94 (0.91-0.98)	0.006
In-hospital CVD death	1159	124396	9.32	1209	123228	9.81	0.95 (0.87-1.03)	0.178
Myocardial infarction	733	122669	5.98	717	121738	5.89	1.01 (0.91-1.12)	0.797
Ischemic stroke	2070	117879	17.56	2101	116497	18.03	0.97 (0.92-1.04)	0.401
Amputation	365	123501	2.96	434	122174	3.55	0.83 (0.72-0.96)	0.010

*per 103 person-years.
Abbreviations: CI: confidence interval.

Table 3. Subgroup analysis of risk of amputation among beta-blocker users and non-users in diabetic patients with peripheral arterial disease

Characteristic	Hazard Ratio (95% CI)*	*P* Value	Interaction *P* Value
Sex			
Male	0.835 (0.695-1.003)	0.054	0.946
Female	0.827 (0.667-1.024)	0.082	
Age			
20-64 years	0.890 (0.725-1.093)	0.267	0.393
≥ 65 years	0.788 (0.652-0.953)	0.014	
Hypertension			
Yes	0.832 (0.720-0.961)	0.012	0.926
No	0.856 (0.504-1.456)	0.567	
Myocardial infarction			
Yes	0.830 (0.544-1.265)	0.386	0.971
No	0.834 (0.719-0.966)	0.016	
Cerebrovascular disease			
Yes	0.777 (0.620-0.974)	0.029	0.442
No	0.869 (0.728-1.036)	0.118	
Heart failure			
Yes	0.760 (0.577-1.001)	0.051	0.437
No	0.857 (0.730-1.007)	0.061	
Chronic kidney disease			
Yes	0.833 (0.648-1.073)	0.157	0.978
No	0.831 (0.704-0.982)	0.030	

* Adjusted for propensity score
Abbreviations: CI: confidence interval.

when compared with non-users, among patients who had undergone primary vascular surgical or endovascular reconstruction.[20] However, this study did not take into account the DM effect. Noteworthy, in the Danish study, BB-users were associated with increased risks of recurrent myocardial infarction and/or stroke. In our study, we found no trend towards increased in-hospital cardiovascular (CV) death, MI or ischemic stroke. Previous study has shown that BB is associated with a 53% reduction of coronary events in patients with prior MI and PAD. The proportion of prior MI in our study population was only 7%, which may not have sufficed to reveal a significant difference in in-hospital CV death or MI. Nonetheless, the findings of our study were consistent with the Danish study,[20] i.e., similar trends were seen in different ethnic groups.

The presence of DM greatly increases the risk of PAD. Thejasvi, et al. conducted a study that dealt with the mechanisms between DM and PAD, which concluded that DM promotes atherosclerosis in cardiovascular and cerebrovascular systems via vascular inflammation, endothelial cell dysfunction, vascular smooth muscle cell derangement, platelet dysfunction, hypercoagulability, rheology and impaired arteriogenesis.[21] Previous clinical studies on BBs and atherosclerosis have disclosed that BBs significantly reduce the intima-media thickness of the carotid bulb and coronary atheroma volume, which indicates that BBs may slow atherosclerosis development.[22,23] However, further research is necessary to better clarify the pathophysiological mechanisms involved.

Hyperglycemia contributes to poor healing and ulcer formation, which ultimately leads to amputation.[24] An animal model showed that local use of the nonselective BB propranolol promotes re-epithelialization in diabetic wounds.[25] Another diabetic animal study demonstrated that oral propranolol improves wound healing by reducing local inflammatory response.[26] In human study, oral propranolol improves wound healing and decreases healing time in burn patients.[27] Moreover, a recent systemic review that identified most studies about BBs and dermatology disclosed that BB administration improves wound healing in either oral or topical form.[28] In our study, BB therapy may have improved the wound healing process of diabetic PAD patients, thereby reducing the risk of amputation of the affected limb.

Our study disclosed that BB-users had a significantly lower risk (by 6%) in all-cause mortality, compared with non-users, among DM patients with PAD. This result is consistent with a retrospective, propensity-scored analysis study in Japan, concluding that the 30-day mortality rate was significantly lower in the BB group than in the non-BB group, among critical limb ischemia patients receiving endovascular therapy.[15] Nevertheless, this study was confined to critical limb ischemia patients who received endovascular therapy. The previous research provides supportive evidence that BB does not worsen PAD, however, clinical studies considering the DM effect still remain limited.[20,29-31] In the 2019 ESC DM guideline, the role of BB for DM patients is undetermined, with a lack of effective empirical evidence. Our study may complement this unmet need for clinical treatment of patients. To the best of our knowledge, our study was the first large-scale, nationwide, population-based analysis to elucidate the relationship between BBs and PAD, taking the DM effect into consideration.

The main strength of our study was that we included one of the largest cohorts of patients with type 2 DM in the world, while minimizing referral bias by using Taiwan's NHIRD database. Moreover, we used propensity scores to reduce confounding effects. However, some limitations remain. First, all type 1 DM patients were excluded from our data, which may have introduced selection bias into the discussion of the mechanism between BBs and PAD in DM patients. Second, we used patients' prescriptions as a proxy for actual drug use, but we had no evidence of patient compliance. Third, some important lifestyle data such as smoking status, alcohol consumption, obesity, dietary habits and

exercise levels were not available through the administrative dataset in the National Health Insurance database. Another limitation was that we lacked data for subgroup analyses based on BB type, dosage, blood pressure, heart rate and glycemic control in individuals. Last, but not least, our data was from the period 2000 to 2011. Therefore, novel drugs such as glucagon-like peptide-1 receptor agonists and sodium glucose cotransporter-2 inhibitors, which may affect outcomes of PAD, were not analyzed in our study.[32-34] Although previous study has indicated that BB type may not affect the outcome, the pharmacokinetic and pharmacodynamic properties introduce heterogeneity into the analysis.[15] Moreover, the BB effects on DM patients with PAD are complex and could not be fully addressed in our study. Hence, further research and experiments on possible mechanisms are necessary to illuminate the BB effect on limb outcomes in DM patients with PAD.

In conclusion, this large-scale nationwide population-based cohort study demonstrated that treatment with BBs is associated with lower risk of amputation and all-cause mortality in type 2 DM patients with PAD. As witnessed by this study, beta-blockers may be administered to patients with PAD and DM, without worsening the clinical outcomes.

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