Observational Study

Medicine

OPEN

Association between selective serotonin reuptake inhibitor and risk of peripheral artery disease in diabetes mellitus

Propensity score matching and landmark analysis

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Abstract

An increasing number of studies have demonstrated the bidirectional hemostatic effect of selective serotonin reuptake inhibitors (SSRIs) on the risk of cerebrovascular and cardiovascular diseases. However, no previous study has focused on the relationship between SSRI and the risk of peripheral artery disease (PAD) in diabetes mellitus (DM). We sought to evaluate the association between SSRIs and the PAD risk in individuals with DM.

We conducted a retrospective, population-based cohort study using data from the Longitudinal Health Insurance Database from 1999 to 2010 in Taiwan. A total of 5049 DM patients were included and divided into 2 groups: DM with SSRI users and DM with SSRI non-users. Propensity score matching and 1-year landmark analysis were used for our study design. Stratified Cox proportional hazard regressions were used to analyze the hazard ratio of the PAD risk in certain subgroups.

DM with SSRI users did not affect the PAD risk compared to DM with SSRI non-users. These findings were consistent with all sensitivity analyses (i.e., age, sex, SSRI doses, antithrombotic medication use, and medical and psychiatric comorbidities).

In this study, we found that there was no significant difference of PAD risk between DM with SSRI users and DM with SSRI non-users. DM with SSRI user did not affect PAD risk across any SSRI dose, age, sex, antithrombotic medications, and multiple comorbidities in the subgroup analysis.

Abbreviations: aHR = adjusted hazard ratio, AMI = acute myocardial infarction, ATC = anatomical therapeutic chemical, CCI = Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2005 = Longitudinal Health Insurance Database 2005, OR = odds ratio, PAD = peripheral artery disease, SSRI = selective serotonin reuptake inhibitor.

Keywords: antidepressant, diabetes mellitus, peripheral artery disease, SSRI

1. Introduction

Approximately 13% to 24% of patients with diabetes mellitus (DM) coexist with depression[1] and selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed antidepressants.[2] An increasing number of studies have documented the hemostatic effects of SSRIs.[3] Bleeding tendency and vasocon-

Editor: Mihnea-Alexandru Găman.

This study was supported by the Chang Gung Memorial Hospital Research Project Grant, Taiwan (No. CFRPG6J0111).

This study was approved by Institutional Review Board of Chang Gung Memorial Hospital (No. 201901529B1).

Patient consent for publication is not required.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Chen KH, Wang TY, Lee CP, Yang YH, McIntyre RS, Subramaniapillai Mh, Lee Y, Chen VC. Association between selective serotonin reuptake inhibitor and risk of peripheral artery disease in diabetes mellitus: propensity score matching and landmark analysis. Medicine 2022;101:18(e29202).

Received: 25 May 2021 / Received in final form: 11 March 2022 / Accepted: 11 March 2022

http://dx.doi.org/10.1097/MD.0000000000029202

strictive stroke have been reported with SSRI use in high-risk populations.[4] In contrast, SSRIs have been reported to have an antiplatelet effect,[5] inhibit thrombus formation in the coronary artery,[6,7] and dilatate cerebral arteries[4,8] among healthy individuals. This antiplatelet effect has been found in some special populations, such as patients with depression,[9] acute coronary disease,[10] acute myocardial infarction (AMI),[11] and congestive heart failure.[12] It seems that there were bidirectional effects of SSRI on cardiovascular and cerebrovascular complications.[4–12] However, the hemostatic effect of SSRI on peripheral arterial complications remains unknown.

The lifetime prevalence of DM in Taiwan is approximately 6%.[13] DM is commonly associated with macrovascular and microvascular complications, such as ischemic stroke, AMI, and peripheral vascular atherosclerosis.[14] However, platelets are important in hemostasis and recent studies have shown that a higher mean platelet volume level (as an indicator of platelet activation) in DM patients was associated with higher cardiovascular, cerebrovascular, or peripheral vascular risk.[15,16] Thus, medications that interfere with platelet function and hemodynamic status may also change the outcomes of vascular complications in DM. For example, aspirin can reduce serious vascular events in patients with DM (odds ratio [OR], 0.88; $P < .01$).[17] However, aspirin also increased the rate of major bleeding events (OR,1.29; $P < .01$).[17] The balance between the benefits and side effects of antiplatelet medication should be considered. Although a few articles have documented the hemostatic effect of SSRI on cardiovascular and cerebrovascular risk of DM,[18,19] there are still no previous studies that have evaluated its effect on peripheral vascular complications of DM. We investigated the effects of SSRIs on peripheral artery disease (PAD) in DM patients.

1.1. Goal of our study

We conducted a 1-year landmark analysis in a large, population-based cohort sample to investigate whether SSRI use affects PAD risk in adults with DM.

2. Materials and methods

2.1. General design

We included adults (age, >18 years) with an incident diagnosis of DM in the present retrospective, population-based cohort study. Longitudinal data were derived from the Taiwanese Longitudinal Health Insurance Database (1999–2013). Patients who met the exclusion criteria were excluded from the study. We evaluated the effects of SSRI use on PAD with 1:10 propensity score matching and a landmark time of 1 year. The PAD risk factors were included as covariates. This study was approved by our hospital's Institutional Review Board (No. 201901529B1).

2.2. Introduction of Longitudinal Health Insurance Database 2005

The National Health Insurance program of Taiwan started in 1995 and covers 99% of the Taiwanese population. In this study, ambulatory care claims, inpatient claims, and registry data were retrieved from the Longitudinal Health Insurance Database 2005 (LHID2005) from 1997 to 2013. Information recorded in the LHID2005 includes patient demographic, diagnostic, catastrophic illness (e.g., malignant neoplasm, rare disease, etc), medical expenditure, and prescription claims data. All beneficiary data are encrypted and de-identified and do not contain identifiable information (e.g., address, contact information, medical record number, name).

2.3. Participants

Adult patients (age, >18 years) with an incident diagnosis of DM during the study period (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 250 and A181) who had pharmacological management (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/G687, which illustrates the anatomical therapeutic chemical [ATC] code of antidiabetic drug) of DM between 1999 and 2010 from the LHID2005 in Taiwan were included. We collected the following demographic variables: age, sex, economic level, urbanization level, geographic region, diagnosis, comorbidities, complications, examinations, laboratory data, and medication history. To avoid selective bias, patients who had used any type of antidepressants within 2 years (see Table S2, Supplemental Digital Content, http://links.lww.com/MD/G688, which illustrates the ATC code of antidepressants), those who had previous PAD, or venous thromboembolism (ICD-9-CM codes 415.1 and 453), or malignant neoplasm (see Table S3, Supplemental Digital Content, http://links.lww.com/MD/G689, which illustrates the ICD-9-CM of malignant neoplasm) before the index date were excluded. After exclusion, the remaining patients with DM were divided into 2 groups depending on their use of SSRIs. The study group was defined as DM with SSRI users, whereas the control group was defined as DM with SSRI non-users.

2.4. Covariates

The following covariates moderating PAD risk were included: age, comorbidities, Charlson comorbidity index (CCI) score, and prescription of antithrombotic medications. Patients were grouped as young-aged adults (18–44 years), middle-aged adults (45–64 years), and elderly adults (≥65 years). Comorbidities included history of alcoholism, atrial fibrillation, bipolar disorder, chronic obstructive pulmonary disease (COPD), depression, hyperlipidemia, hypertension, and schizophrenia (see Table S4, Supplemental Digital Content, http://links.lww.com/MD/G690, which illustrates ICD-9-CM code of the comorbidities). Participants were categorized as having 1 or more of the aforementioned comorbidities if they had 2 or more clinic visits within a 1-year period or 1 or more hospital admissions with the relevant ICD-9-CM code. The CCI score was calculated for a 1-year period preceding the diagnosis of DM.[20,21] Higher scores represented more comorbidities. The antithrombotic medications listed as covariates are vitamin K antagonists (warfarin), platelet aggregation inhibitors (acetylsalicylic acid, cilostazol, clopidogrel, prasugrel, ticagrelor, and ticlopidine), direct thrombin inhibitors (dabigatran etexilate), and direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) (see Table S5, Supplemental Digital Content, http://links.lww.com/MD/G691, which illustrates the ATC code of antithrombotic medications).

2.5. Main outcome

We evaluated the risk of PAD in both groups. PAD was operationalized using the ICD-9-CM codes 440.0x, 440.2x, 440.3x, 440.8x, 440.9, 443, 444.0, 444.22, 444.8, 447.8, and 447.9.

2.6. Statistical analysis

Baseline demographics were compared between these 2 groups using Student t tests for continuous variables and χ^2 tests for categorical variables. Propensity scores were estimated using a logistic regression model. Using propensity score matching 1:10 ratio, DM with SSRI users and DM with SSRI non-users had similar distributions of baseline covariates, comorbidities, and antithrombotic medications. A power analysis indicated a power of 0.77 for detecting hazard ratios < 0.67 of SSRI users for developing PAD, at 5% confidence level with a sample size of 5049 for a 14-year follow-up.[22] A 1-year landmark analysis was used to avoid immortal time bias.[23] Participants were followed up during the 1-year landmark time until they were diagnosed with PAD or were decreased. To analyze the PAD risk between groups, stratified Cox proportional hazard regressions with different factors were performed. These factors included SSRI dose, personal factors (age, sex), comorbidities, CCI score, and antithrombotic medications. An SAS macro (SAS for Windows, version 9.4; SAS Institute, Cary, NC) was used for the analysis.[24]

3. Results

3.1. Results of patient selection and demographic data

We identified 57,298 adults with DM in our database, 15,504 of whom were excluded for the following reasons: prescription of any antidepressants before the index date (6003 patients), previous diagnosis of PAD or venous thromboembolism (4010 patients), malignancy (7280 patients), or follow-up periods of less than 1 year (841 patients) (Fig. 1). The remaining 41,794 patients were enrolled in the 1-year landmark analysis and then divided into 2 groups: DM with SSRI users (464 patients) and DM with SSRI non-users (41,330 patients). After using a propensity score matching 1:10 ratio, 459 DM with SSRI users were matched with 4590 DM with SSRI non-users (Table 1). In the DM with SSRI users, there were approximately 72.98% (335 of 459) of patients in the low-dose SSRI group (Table 2).

3.2. PAD in DM with SSRI users compared with DM with SSRI non-users

The occurrence of PAD was 6.75% (31/459) of DM with SSRI users and 5.82% (267/4590) of DM with SSRI non-users (Table 3). There was no significant difference between the 2 groups ($P = .417$, Table 3).

In the subgroup analysis by stratified Cox proportional hazard regression model (Table 4), DM with SSRI user did not affect PAD risk across any SSRI dose (adjusted hazard ratio [aHR], 1.04–1.17; $P > .05$), age (aHR, 0.93–1.41; $P > .05$), sex (aHR, 1.02–1.37; $P > .05$), CCI score (aHR, 0.99–1.55; $P > .05$), and antithrombotic medications (aHR, 1.37; $P > .05$). The presence of hypertension, hyperlipidemia, COPD, or depression also did not affect PAD risk in DM with SSRI users (aHR, 1.24–1.83; $P > .05$).

4. Discussion

4.1. Summary of key results

Considering that up to 13% to 24% of DM patients have depression,[1] the DM population experiences many types of vascular complications,[14] and severe peripheral vascular diseases can also lead to life-threatening complications, we designed this study to investigate whether SSRIs can decrease the PAD risk in DM. To our knowledge, this is the first population-based cohort study to investigate the association between SSRIs and PAD risk in adult DM. In our study, we observed that SSRI prescriptions did not affect the PAD risk in adult DM. This result was consistent in all subgroup analyses, including dose, age, sex, multiple medical and psychiatric comorbidities, and antithrombotic medication use. Our findings are consistent with those of Meier et al's study,[25] who found that SSRIs did not decrease the PAD risk. In contrast to studies that have evaluated SSRI use in populations with depression,[10,12,26] we did not find that SSRI use increases or decreases the PAD risk in adult DM with depression. In addition, we did not find an effect of SSRI use on PAD risk in DM with other comorbid hypertension, hyperlipidemia, or COPD.

4.2. Vascular effect of SSRI

Although there are no previous studies focusing on the vascular effect of SSRI on the PAD risk in DM, there were several studies that have reported on the effect of SSRI on AMI in different populations. In the studies regarding SSRI in AMI patients, variable results have been reported.[10–12,25–27] In England, 1 previous study showed that SSRIs did not decrease the incidence of new onset AMI among patients younger than 75 years of age without any risk factors of ischemic heart disease (OR, 0.9; 95% confidence interval, 0.5–1.8).[25] A separate study of individuals younger than 90 years old in England reported that the risk of AMI was lower in SSRI users than in other antidepressant users or non-users.[11] However, in geriatric patients taking SSRIs with multiple risk factors for ischemic heart disease, SSRI users increased the risk of AMI (OR, 1.85; 95% confidence interval, 1.13–3.04).[27] In depression patients with coronary heart disease, who took aspirin or clopidogrel, previous studies showed that SSRI can reduce the platelet activation and may lead to a further protective effect of vascular complications.[10,12,26]

4.3. Possible mechanisms of SSRI on hemostasis in the literature

There are several possible mechanisms of SSRI on hemostasis documented in the literature, including platelet function, vessels, and blood clot or thrombosis formation.[5,9,12,26,28] The mechanism of SSRI on platelet function was demonstrated in Hergovich et al's study.[5] As serotonin is a platelet agonist, they found that the SSRI paroxetine decreased intraplatelet serotonin concentrations by up to 83% and led to the inhibition of platelet plug formation.[5] In addition, they also found that paroxetine can reduce the platelet activation by lowering its response to thrombin receptor activating peptide.[5] In the study by Serebruany et al,[12] SSRI decreased the platelet activity by reducing in ADP- and collagen-induced aggregation and the surface expression of platelet receptors. The formation of platelet-leukocyte microparticles was reduced by SSRIs.[12]

SSRI also affects endothelial cell function.[9,28] In Lopez-Vilchez et al's[9,28] study, they revealed endothelial dysfunction in major depression patients. As SSRI can downregulate most of the biomarkers and change the viscoelasticity during blood clot formation, the endothelial dysfunction in patients with major

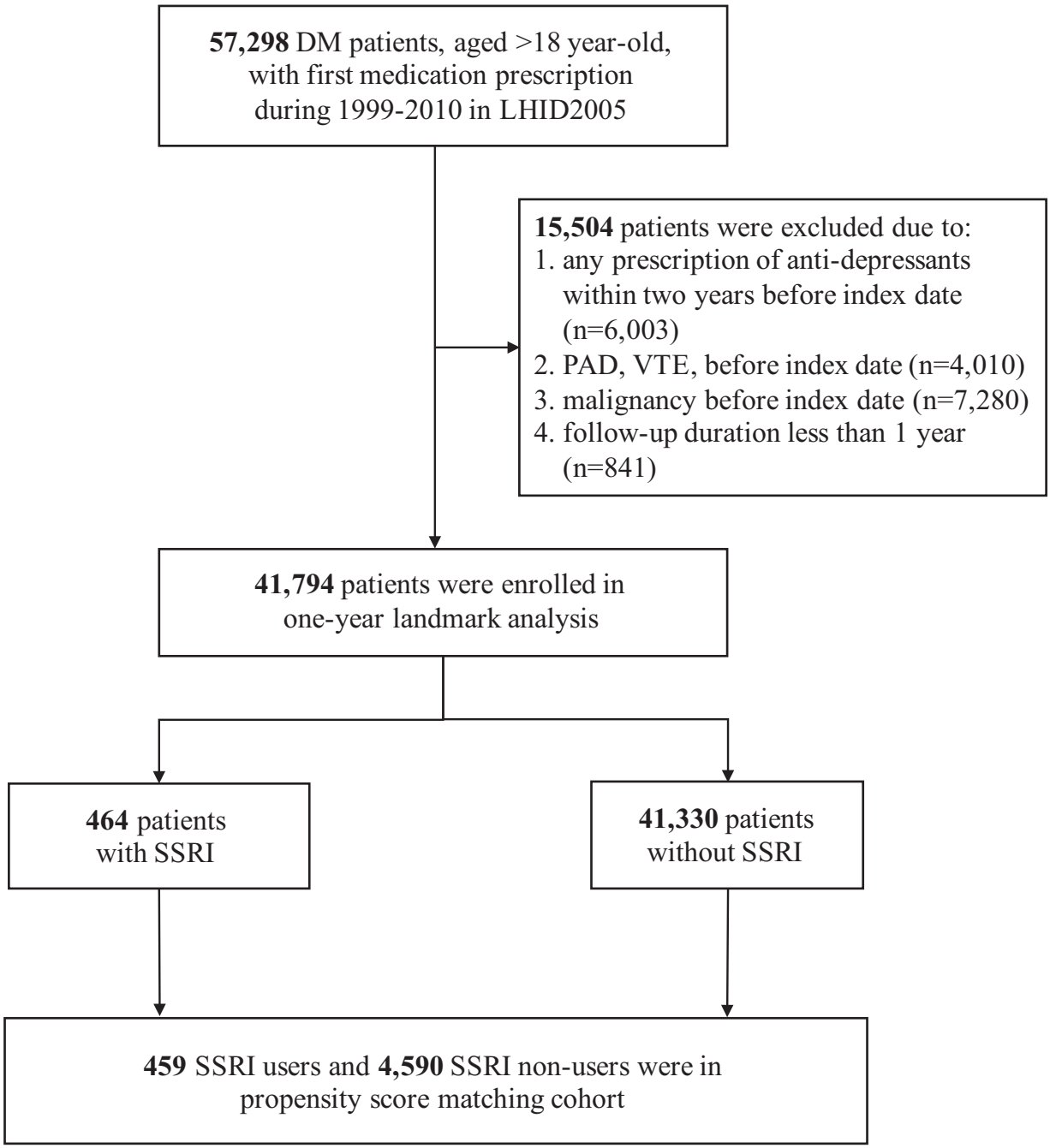

Figure 1. Flowchart of this study. DM = diabetes mellitus, LHID2005 = Longitudinal Health Insurance Database 2005, PAD = peripheral artery disease, SSRI = selective serotonin reuptake inhibitor, VTE = venous thromboembolism.

depression was normalized after 24 weeks of SSRI treatment.[9,28]

4.4. Study strengths and limitations

The strength of our study was that the recall bias (information bias) and reverse causality were reduced by landmark analysis. Propensity score matching also minimizes the confounding effects of baseline differences between patients (i.e., selection bias), allowing us to evaluate the effects of SSRI use on clinical outcomes in our large, observational, population-based dataset. However, there are some limitations in this study. Individuals who ceased to be covered by Taiwan's national insurance program (e.g., by immigration or unemployment) would have been excluded from our analyses, which may have resulted in follow-up bias. Some risk factors for vascular diseases, such as smoking, obesity, and family history, were not registered in the ICD-9-CM and could not be listed as covariates. Therefore, we used COPD, a smoking-related disease, as a proxy for heavy smoking and listed it as a covariate. In this retrospective, population-based study, we could not collect blood samples or the results of previous laboratory data. This limited our

Table 1

Demographic data between 2 groups.

			DM with SSRI users		DM with SSRI non-users PSM 1:10		
Patients	**5049**	**100.00%**	**459**	**100.00%**	**4590**	**100.00%**	***P* value**
Age on index date, year							.618
18–44	831	16.46%	79	17.21%	752	16.38%	
45–64	2621	51.91%	244	53.16%	2377	51.79%	
≥65	1597	31.63%	136	29.63%	1461	31.83%	
Sex							.773
Female	2914	57.71%	262	57.08%	2652	57.78%	
Male	2135	42.29%	197	42.92%	1938	42.22%	
Economic level (NT$/month)						0.979	
0	1903	37.69%	175	38.13%	1728	37.65%	
1–15,840	1037	20.54%	91	19.83%	946	20.61%	
15,841–25,000	1441	28.54%	133	28.98%	1308	28.50%	
≥25,001	668	13.23%	60	13.07%	608	13.25%	
Urbanization level							.918
Very high	1378	27.29%	126	27.45%	1252	27.28%	
High	2291	45.38%	207	45.10%	2084	45.40%	
Moderate	792	15.69%	76	16.56%	716	15.60%	
Low	588	11.65%	50	10.89%	538	11.72%	
CCI score							.482
1	2106	41.71%	191	41.61%	1915	41.72%	
2	1467	29.06%	143	31.15%	1324	28.85%	
≥3	1476	29.23%	125	27.23%	1351	29.43%	
Comorbidities							
Hypertension	3023	59.87%	264	57.52%	2759	60.11%	.280
AMI	156	3.09%	13	2.83%	143	3.12%	.738
Hyperlipidemia	1554	30.78%	138	30.07%	1416	30.85%	.729
Af	206	4.08%	19	4.14%	187	4.07%	.946
COPD	1178	23.33%	105	22.88%	1073	23.38%	.809
Depression	518	10.26%	50	10.89%	468	10.20%	.639
Bipolar disorder	56	1.11%	8	1.74%	48	1.05%	.174
Schizophrenia	111	2.20%	12	2.61%	99	2.16%	.524
Alcoholism	73	1.45%	7	1.53%	66	1.44%	.882
Antithrombotic medications	1253	24.82%	108	23.53%	1145	24.95%	.503
Warfarin	66	1.31%	10	2.18%	56	1.22%	.085
Clopidogrel	112	2.22%	13	2.83%	99	2.16%	.349
Ticlopidine	120	2.38%	10	2.18%	110	2.40%	.770
Acetylsalicylic acid	1195	23.67%	102	22.22%	1093	23.81%	.445

Af = Atrial fibrillation, AMI = acute myocardial infarction, CCI = Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, PSM = propensity score match, SSRI = selective serotonin reuptake inhibitor.

evaluation of the hemostatic effects of SSRI with relevance to PAD.

5. Conclusions

Our landmark analysis with propensity score matching in a large, validated, and well-characterized national sample found that the occurrence of PAD was 6.75% of DM with SSRI users and 5.82% of DM with SSRI non-users. There was no significant difference between these 2 groups. This finding suggested that SSRI prescriptions did not affect the PAD risk in adult DM. In addition, this result was also consistent in the subgroup analysis. DM with SSRI user did not affect PAD risk across any SSRI dose, age, sex, antithrombotic medications, and multiple comorbidities.

Table 2

Defined daily dose (DDD) of antidepressants in diabetes mellitus during landmark analysis.

	DM with SSRI users		DM with SSRI non-users (PSM 1:10)	
SSRI level	459	100.00%	4590	100.00%
Non-users	0	0.00%	4590	100.00%
cDDD: 1–83	335	72.98%	0	0.00%
cDDD: ≥84	124	27.02%	0	0.00%

cDDD = cumulative defined daily dose, DM = diabetes mellitus, PSM = propensity score match, SSRI = selective serotonin reuptake inhibitor.

Table 3

The occurrence of peripheral artery disease in both groups.

	Total		DM with SSRI user		DM with SSRI non-user PSM 1:10		*P* value
Patients	5049	100.00%	459	100.00%	4590	100.00%	
PAD	298	5.90%	31	6.75%	267	5.82%	.417

DM = diabetes mellitus, PAD = peripheral artery disease, PSM = propensity score match, SSRI = selective serotonin reuptake inhibitor.

Table 4

The hazard ratio of peripheral artery disease (PAD) risk in DM with SSRI users, comparing to DM with SSRI non-users.

	PAD			
	HR	95% CI	*P* value	
SSRI effects (ref: non-users)				
Crude	1.16	0.80	1.68	.436
Adjusted*	1.13	0.76	1.69	.553
SSRI cumulative dose effects (ref: non-users)†				
cDDD: 1–83	1.17	0.74	1.83	.507
cDDD: ≥84	1.04	0.50	2.15	.926
SSRI average dose effects (ref: non-users)†				
cDDD: 1–83	1.17	0.74	1.83	.507
cDDD: ≥84	1.04	0.50	2.15	.926
SSRI effects in each subgroup (ref: non-users)†				
Age				
18–44	1.41	0.50	3.98	.512
45–64	0.93	0.52	1.65	.803
≥65	1.33	0.75	2.39	.332
Sex				
Female	1.02	0.59	1.77	.946
Male	1.37	0.82	2.28	.230
CCI score				
1	1.00	0.52	1.92	.991
2	1.55	0.85	2.81	.152
≥3	0.99	0.48	2.05	.969
Hypertension				
Without	0.95	0.51	1.77	.867
With	1.40	0.87	2.23	.164
Hyperlipidemia				
Without	0.99	0.62	1.57	.959
With	1.83	0.95	3.54	.073
COPD				
Without	1.13	0.73	1.76	.585
With	1.24	0.61	2.52	.560
Depression				
Without	1.12	0.75	1.68	.566
With	1.45	0.46	4.58	.523
Antithrombotic medications				
Without	1.10	0.71	1.71	.675
With	1.37	0.67	2.80	.392

CCI = Charlson comorbidity index, CI = confidence interval, cDDD = cumulative defined daily dose, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HR = hazard ratio, PAD = peripheral artery disease, SSRI = selective serotonin reuptake inhibitor.

* HRs were adjusted for age, sex, economic level, urbanization level, CCI score, hypertension, acute myocardial infarction, hyperlipidemia, atrial fibrillation, COPD, depression, bipolar disorder, schizophrenia, alcoholism, antithrombotic medications, tricyclic antidepressant, and other antidepressants use.

† Adjusted HR.

Acknowledgments

The authors are grateful for the comments and assistance in the data analysis of the Health Information and Epidemiology Laboratory (No. CLRPG6G0041) of Chang Gung Memorial Hospital, Chiayi, Taiwan.

Author contributions

The statistical analyses were mainly performed by Chuan-Pin Lee PhD, who is graduated from the statistical field. Other statistical suggestions were also provided by Yao-Hsu Yang MD, MSc and Vincent Chin-Hung Chen MD, PhD, who are experts in the statistical field and study design.

This retrospective population-based cohort study was performed at the Chang Gung Memorial Hospital, Chiayi, Taiwan. All authors agree with the conception and design, acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published. The institutional affiliations of all the authors are listed and were not changed at the time of the study.

KHC and VCHC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization and approval of the submission: all authors. Validation: KHC, YHY, CPL, and VCHC. Formal analysis: YUY and CPL. Investigation: KHC, TYW, CPL, YHY, and VCHC. Data resource and data curation: CPL and YHY. Writing: KHC, TYW, CPL, RSM, MhS, YL, and VCHC. Supervision: VCHC. Funding acquisition: KHC.

Dr. Roger McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC); speaker/consultation fees from Lundbeck, Janssen, Alkermes, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Abbvie, Atai Life Sciences. Dr. Roger McIntyre is a CEO of Braxia Scientific Corp.

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