Risk of stroke after unilateral or bilateral TKA in 327,438 matched patients using data from the National Health Insurance Claims for South Korea

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Abstract

Background: This study aims to investigate the incidence rate and risk factors of stroke in patients treated with bilateral TKA compared with patients with unilateral TKA.

Methods: In this retrospective nationwide cohort study, we compared patients undergoing unilateral TKA or bilateral TKA using data from the Korean National Health Insurance claims database between January 1, 2009 and August 31, 2017 and included patients older than 40 years of age who underwent primary TKA by the index date as documented primary diagnosis and first additional diagnosis without a history of stroke during the preceding 1 year. We used matched Cox regression models to compare the incidence rate and risk factors of newly acquired stroke among patients treated with unilateral TKA or bilateral TKA after propensity score (PS) matching.

Results: In the present study, 163,719 patients who received unilateral TKA were matched to 163,719 patients with bilateral TKA based on PS. The risk of stroke during the study period was lower in patients treated with bilateral TKA than in patients with unilateral TKA (adjusted hazard ratio [HR] 0.79). Patients who received bilateral TKA were at decreased risk of stroke when the following variables were present: advanced age (70-79 years, HR 0.76), female sex (HR 0.75), rural area (HR 0.77), small- or medium-sized hospital (HR 0.75), health insurance (HR 0.77), history of hypertension drug use (HR 0.75), congestive heart failure (HR 0.70), connective tissue disease (HR 0.71), diabetes (HR 0.77), and diabetes with complication (HR 0.76).

Conclusions: The risk of stroke was lower in patients treated with bilateral TKA than in patients with unilateral TKA. Patients treated with bilateral TKA were at decreased risk of stroke when the following variables were present: age (70-79 years), female sex, health insurance, history of hypertension drug use, and comorbidities, such as congestive heart failure, connective tissue disease, and diabetes. More importantly, we do state that those with simultaneous bilateral TKA and staged bilateral TKA without discharge could have been healthier. Therefore, those who underwent 2 unilateral TKAs could have been at more risk of stroke, especially in the 2nd unilateral TKA.

Background

Total knee arthroplasty (TKA) is the most efficacious and successful treatment for advanced osteoarthritis (OA) of the knee.[1, 2] However, 23% of patients scheduled for unilateral TKA show severe symptoms in the contralateral knee and 93% of patients required a contralateral TKA within 5 years of index surgery.[3] Moreover, unilateral deformity correction for patients with severe deformities creates asymmetric lower limb alignment that can significantly affect rehabilitation.[4] Thus, simultaneous bilateral TKA (SiBTKA) and staged bilateral TKA (StBTKA) without discharge have increased in popularity due to shorter overall recovery time and decreased total cost compared with unilateral TKA and StBTKA with discharge.[5] However, SiBTKA and StBTKA without discharge are associated with potential issues such as increased perioperative complications, including pulmonary embolism, deep vein thrombosis,

and stroke.[6, 7] Stroke after TKA is a rare but catastrophic complication associated with high rates of morbidity and mortality.[8] Although the risk of stroke after TKA has been investigated in numerous studies, only small sample sizes were used, which can lead to reduced statistical power.[4, 9] In addition, the incidence and risk factors of stroke in patients treated with unilateral TKA compared with subjects with bilateral TKA have been investigated in only a few large-scale studies.

We performed a nationwide, population-based, retrospective cohort study using the National Health Insurance (NHI) claims database, participation in which is compulsory and required by Korean law and covers up to 98% of the approximately 50 million people in South Korea.[10] Korea's national registries have recently been the source of numerous epidemiological studies, demonstrating high completeness and validity, with an overall predictive value of diagnosis of 83.4%.[11] We designed the present study to investigate the incidence rate and risk factors of stroke in patients treated with unilateral TKA compared with subjects with bilateral TKA. It was hypothesized that the risk of stroke would be lower in patients treated with bilateral TKA than in patients with unilateral TKA.

Methods

Study design and data source

This nationwide, population-based, retrospective cohort study used the Korean NHI claims database (diagnoses based on *International Classification of Disease, 10th Revision* [ICD-10] codes and procedure history based on *Electronic Data Interchange* [EDI] codes), which includes all claims data from the Korean NHI program and the Korean Medical Aid program from 2009 until 2016; the data are integrated into the Health Insurance Review and Assessment Service (HIRA) database to include all healthcare utilization data for both inpatients and outpatients. These data contained a de-identification code representing patient age, sex, diagnosis, hospital admissions, dates of visits, and procedure history.[10, 12] Additionally, prescribed drug information containing the generic name, prescription date, and duration of prescription was included. The Institutional Review Board (IRB) of our institution approved the study. Consent was specifically waived by the IRB because all personal identifying information was removed from the database.

Selection of study sample and definitions

The outcomes of interest were incidence rate and risk factors of new-onset postoperative stroke in patients treated with unilateral TKA compared with subjects with bilateral TKA. The study population comprised individuals older than 40 years of age who received TKA (EDI: N2072, N2077) without history of stroke (ICD-10: I60,I61, I62, I63) during the preceding 1 year, as documented by primary diagnosis and first additional diagnosis in the NHI database between January 1, 2009 and December 31, 2016. Patients treated with bilateral TKA were classified into two groups: patients who underwent SiBTKA and had two primary TKA procedure codes entered on the same day and patients who underwent StBTKA and had two primary TKA procedure codes entered without discharge. Similarly, patients treated with unilateral TKA were classified into two groups: patients who underwent only one TKA during the study period and

patients who underwent a second TKA after discharge of index TKA. New-onset postoperative stroke was defined as history of stroke from the date of primary admission or re-admission for stroke in the hospital following TKA. All patients who were deemed to have had a stroke within 12 months after TKA were identified. Patients considered eligible for newly acquired stroke included subjects who received computed tomography (CT) and magnetic resonance imaging (MRI) within one week after admission as well as subjects undergoing relevant surgical procedures, such as burr hole, craniectomy, craniotomy, or thrombectomy. To assess the diagnostic accuracy of the stroke cases registered in the NHI program, we reviewed the image sets and medical records of all registered stroke patients who received TKA at a single medical center. Two neurosurgeons independently investigated whether registered and suspected cases met the diagnostic criteria for strokes released by NHI.

Potential confounders

Patient characteristics, comorbidities, and co-medication were considered as confounders in this study. Characteristics were age, sex, location, hospital size, and insurance type. Comorbidities comprised acquired immune deficiency syndrome (AIDS), congestive heart failure (CHF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), connective tissue disease, transient ischemic attack (TIA), dementia, hemiplegia, myocardial infarction (MI), peptic ulcer disease (PUD), peripheral vascular disease (PVD), liver disease, severe liver disease, malignancy, diabetes, diabetes with complication, atrial fibrillation (AF), valvular heart disease (VHD), carotid artery disease (CAD), and hypothyroidism based on previous diagnoses within one year before the index date. In addition, the Charlson Comorbidities Index was calculated for all patients [13]; those with no comorbidities received a score of 0 points. Information on the use of drugs was based on a three-month period within one year before the index date because, in South Korea, drugs are generally prescribed for three months and are typically used on a continuous basis. Potent anticoagulants, such as aspirin, vitamin K antagonist, factor Xa inhibitor, and direct thrombin inhibitor, also were selected as confounders because they have been used for thrombophylaxis following TKA. In addition, hospitals were classified into two groups based on size (large: tertiary hospital or general hospital; small or medium: hospital or clinic). In the Korean health care system, the parent category of “"hospitals,”" includes subcategories of hospitals, general hospitals, and tertiary hospitals, the requirements for whose qualifications are stated by Korean law. As a subcategory, a hospital signifies a small hospital in Korea (30-100 beds). General hospitals are hospitals equipped with more than 100 beds and several specialty departments as designated by law, and tertiary hospitals are large-sized university hospitals selected by the government.

Statistical analysis

The results of the study should be randomly selected to ensure that there is no difference in characteristics. However, case-control study works on a specific group, so there is no random assignment, and selection bias cannot be avoided. In order to minimize this problem, propensity score (PS) matching is used. PS matching is a method of calculating the PS of cases and controls and matching the most similar PS. In this study, PS was calculated using logistic regression and performed one-to-one nearest

neighbor matching based on the estimated PS. PS-based analyses were used to simultaneously control for a large number of covariates and to mimic some of the particular characteristics of a randomized controlled trial; these analyses provide a more robust, less biased estimate when the number of outcome events is low relative to the number of confounders.[14] We fit a logistic regression model to estimate the probability of treatment with unilateral TKA versus bilateral TKA, adjusted for all covariates including age category, sex, comorbidities, and co-medication. We evaluated the balance of measured confounders before and after weighting using absolute standardized differences and considered balance as an absolute value less than 0.1, which has been used in the literature as the definition of a negligible difference.[15, 16] We calculated the incidence rate per 1,000,000 person-years by dividing the number of stroke events by the total number of person-years at risk and multiplying the result by 1,000,000. The 95% confidence interval (CI) was calculated assuming a Poisson distribution. Subgroup analysis was conducted based on age category, sex, location, hospital size, insurance type, comorbidities and co-medication. Adjusted hazard ratio (HR) and 95% CI were calculated using multivariate logistic regression modelling after adjusting for age, sex, location, hospital size, co-medication, and comorbidities. In addition, a sensitivity analysis was conducted to assess the influence of residual confounding based on insurance type. All analyses were conducted using SAS Enterprise software version 6.1 (SAS Institute, Cary, NC, USA) and R software version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 373,847 patients identified from the Korean NHI claims database who met the inclusion criteria, 210,128 underwent unilateral TKA and 163,719 bilateral TKA. The logistic model by which the PS was estimated showed predictive value (C statistic = 0.843), which is a reasonable level detecting differences between the two groups in the outcome variables. After applying the PS matching, 327,438 patients were included in the comparative analysis of unilateral TKA *versus* bilateral TKA. The details of the cohort selection process are summarized in Figure 1. The association of incidence of stroke and annual procedure volume after unilateral TKA or bilateral TKA in South Korea during the study period is shown in Figure 2, indicating that the incidence of stroke decreased steadily regardless of the type of surgery. The decrease in SiBTKA over time in Korea was unlikely to affect our results because PS matching allowed us to match each patient within the smaller SiBTKA cohort with the patient in the SBTKA with discharge or unilateral TKA cohort who had the most similar patient characteristics. These two subjects were then removed from the group, and the process continued in the same fashion until each patient in the SiBTKA cohort had been matched with a patient in the SBTKA with discharge or unilateral TKA cohort.

Table 1 shows the baseline characteristics of patients treated with unilateral TKA compared with subjects with bilateral TKA in the overall and PS-matched cohorts. After PS matching, the two groups were balanced in terms of baseline covariates (Fig. 3). Among patients who received unilateral TKA, 1,411 (0.86%) developed stroke; 1,168 (82.8%) cases were ischemic and the remaining 243 (17.2%) were hemorrhagic stroke, whereas 1,120 patients (0.68%) who underwent bilateral TKA developed stroke; 905 (80.8%) cases were ischemic and the remaining 215 (19.2%) were hemorrhagic stroke.Of the patients

experiencing new-onset stroke, 301 (21.3%) treated with unilateral TKA and 220 (19.7%) with bilateral TKA experienced a stroke within two weeks.

Table 2 shows the risk of stroke in subgroups based on surgical type, age, sex, location, hospital size, insurance type, comorbidities, and co-medication. The risk of stroke during the entire study period was lower in patients treated with bilateral TKA than in patients with unilateral TKA (HR 0.79, 95% CI: 0.73 to 0.85). Furthermore, patients who received bilateral TKA were at a decreased risk of stroke when the following variables were present: advanced age (70-79 years, HR 0.76, 95% CI: 0.69 to 0.84), female sex (HR 0.75, 95% CI: 0.71 to 0.86), rural area (HR 0.77, 95% CI: 0.70 to 0.86), small- or medium-sized hospital (HR 0.75, 95% CI: 0.68 to 0.83), health insurance (HR 0.77, 95% CI: 0.71 to 0.84), history of hypertension drug use (HR 0.75, 95% CI: 0.54 to 1.04), CHF (HR 0.70, 95% CI: 0.51 to 0.97), connective tissue disease (HR 0.71, 95% CI: 0.54 to 0.92), diabetes (HR 0.77, 95% CI: 0.67 to 0.89), and diabetes with complication (HR 0.76, 95% CI: 0.59 to 0.98).

Table 3 shows the association of unilateral TKA with bilateral TKA after adjusting for variables that were significant on univariate analysis, indicating that the risk of stroke was lower in patients treated with bilateral TKA than in patients with unilateral TKA (adjusted HR 0.79, 95% CI: 0.73 to 0.86). The sensitivity analysis also supported this finding after adjusting for the same variables as in multivariate analysis and insurance type.

Discussion

In this nationwide cohort study, patients treated with bilateral TKA had a significantly lower rate of stroke (adjusted HR 0.79) than patients with unilateral TKA. These findings conflict with results in a previous study that showed no significant difference between unilateral TKA and bilateral TKA with respect to postoperative stroke evaluated in a single institution.[9] Furthermore, subgroup analyses stratified based on the factors that affect outcome showed that patients treated with bilateral TKA had a lower risk of postoperative stroke than patients with unilateral TKA when the following variables were present: age (70-79 years), female sex, health insurance, history of hypertension drug use, and comorbidities such as CHF, connective tissue disease, and diabetes.

Sex differences are specific characteristics of postoperative stroke with respect to clinical manifestations and outcomes. In a general surgical population, the manifestations of postoperative stroke were found more frequently in female patients than in male patients.[17] In contrast, when investigating different patient-related factors and their association with postoperative stroke, the risk of stroke was not significantly different between female and male patients.[9] Notably, in the present study, the risk of stroke was significantly decreased in both male (HR 0.79) and female (HR 0.75) patients treated with bilateral TKA compared with subjects with unilateral TKA, indicating that Korean female patients treated with unilateral TKA have an increased risk of stroke. The mechanism by which the risk of stroke is increased in female patients remains unclear. Proposed explanations for the association between stroke and female sex include a higher rate of embolism in females than males and decreased sensitivity to

anticoagulant agents.[18, 19] Another potential explanation is that a substantial number of female patients treated with unilateral TKA who required prophylactic anticoagulant agents might be at greater risk of stroke due to lack of use of prophylactic anticoagulant agents during the postoperative period compared with patients with bilateral TKA even though prophylaxis with universal anticoagulant agents is not generally recommended to patients undergoing TKA in South Korea because the incidence of postoperative stroke is relatively low.[20]

CHF is a commonly reported cardiac complication after bilateral TKA because of suboptimal cardiopulmonary reserve in patients with preexisting comorbid medical conditions and in elderly patients, resulting in greater need for monitoring cardiopulmonary parameters, subsequently leading to a higher rate of admission to the intensive care unit patients treated with bilateral TKA than patients with unilateral TKA.[21, 22] Conversely, in previous studies with relatively small cohorts, significant differences were not reported in terms of cardiac complications between unilateral TKA and bilateral TKA.[23, 24] The large differences among study findings is likely caused by the small numbers of patients enrolled in individual studies. In the present study, a nationwide population-based cohort analysis of 210,128 patients treated with unilateral TKA and 163,719 patients with bilateral TKA was performed, and CHF was most strongly associated with new-onset stroke in patients treated with unilateral TKA. In the current study, patients who received bilateral TKA were divided into two groups: patients who underwent SiBTKA and had two primary TKA procedure codes entered on the same day and patients who underwent StBTKA and had two primary TKA procedure codes entered without discharge. These situations may better identify healthier patients or medically optimized patients who had received bilateral TKA, and the results adequately represent the real-world incidence and disease association.

Unexpectedly, other factors such as advanced age, connective tissue disease, and diabetes were all high risk factors for developing postoperative stroke in patients treated with unilateral TKA. This could be explained by the fact that patients treated with unilateral TKA may be more likely to experience stress and complications associated with preexisting conditions affecting the heart and kidneys which can lead to an ischemic stroke. This suggests that these patients have less access to be under the care of neurologists and may not receive optimal treatment of preexisting comorbidities.

Patients receiving hypertension drug use (less cardioselective β-blockers), not surprisingly, had a higher incidence of postoperative stroke resulting from inhibition of β2-mediated cerebral vasodilation.[25] We found that hypertension drug use was a high risk factor for developing postoperative stroke in patients treated with unilateral TKA. These results may be attributable to the fact that patients treated with unilateral TKA have more patients receiving less cardioselective β-blocker therapy, leading to a higher incidence of postoperative hypotension and bradycardia, subsequently increasing postoperative stroke.

This study had several limitations. First, the NHI claims database may contain incorrect diagnoses. To minimize this issue, patients with new-onset stroke were defined as subjects whose documented admission yielded principal diagnoses of stroke, patients who were administered relevant CT or MRI within one week after admission, or subjects who were undergoing surgical procedures for new-onset

stroke. Second, lifestyle factors, such as smoking status, alcohol consumption, and dietary data, were not evaluated although they could affect the development of stroke. Moreover, we were unable to capture patients who died from a stroke. These seem important since some patients die before reaching the hospital. Third, not every patient needs a TKA on the opposite knee. Thus, all other kinds of unilateral patients who may have had bilateral osteoarthritis but were only treated with TKA on one side should be excluded from these analyses because it was too risky or too frail to operate the other side later. But, we could not adjust for potential confounders such as the severity levels of comorbidities because the Korean NHI claims database did not provide it and substantial criteria in deciding, which of the two modalities to recommend. Fourth, we do not have any information regarding postoperative outcomes such as infection, blood transfusion, length-of-rehabilitation, range of motion, and functional outcome. Clinical information available in the Korean NHI claims database is insufficiently reported and thus have limited effect in this comparative analysis. Additionally, we could not report the perioperative protocols used for the cases because of the inability to account for the effect of individual surgeons, the absence of measures that could characterize the severity of the joint disease, the dose of perioperative medications, the type of DVT prophylaxis, and mobilization therapy although they could affect the development of stroke. Fifth, we have a likely biased sample in that those who are deemed eligible for bilateral TKA after screening are healthier than those who undergo unilateral TKA even though we have attempted to limit such bias with multivariate logistic regression analysis and propensity score matching. Finally, a one-year period may not be sufficient to exclude all pre-existing strokes. However, the possibility of selection bias in both unilateral and bilateral TKA groups was equal. Despite these limitations, to the best of our knowledge, this is the first nationwide epidemiological study in which the incidence and risk factors for stroke in patients treated with unilateral TKA or bilateral TKA were evaluated using matched control patients.

Conclusions

The risk of stroke was lower in patients treated with bilateral TKA than in patients with unilateral TKA. Patients treated with bilateral TKA were at a decreased risk of stroke when the following variables were present: age (70-79 years), female sex, health insurance, history of hypertension drug use, and comorbidities such as CHF, connective tissue disease, and diabetes. More importantly, we do state that those with SiBTKA and StBTKA without discharge could have been healthier. Therefore, those who underwent 2 unilateral TKAs could have been at more risk of stroke, especially in the 2nd unilateral TKA.

Declarations

Ethics approval and consent to participate

The current study includes the name of the ethics committee and the committee's reference number.

Consent for publication

Consent was specifically waived by the approving IRB because all personal identifying information was removed from the database.

Availability of data and materials

The datasets used and/or analysed during the current study are available within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YSS was responsible for the study concept and design, and supervised the study. SBH, JRY, JYC, and SSL were responsible for analysis and interpretation of data. SBH and JRY wrote the first draft of the manuscript, and YSS critically revised the manuscript. YSS did the statistical analysis. YSS is the study guarantor, had full access to all of the data in the study and takes responsibility for the integrity of the data, and the accuracy of the data analysis, and had the final responsibility to submit for publication.

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Abbreviations

TKA: total knee arthroplasty; PS: propensity score; PSM: propensity score matching; SiBTKA: simultaneous bilateral TKA; StBTKA: staged bilateral TKA; NHI: National Health Insurance

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Tables

Table 1. Baseline characteristics of patients with unilateral total knee arthroplasty, compared to those with bilateral total knee arthroplasty, in overall cohort and PS matched cohort.

Characteristic	Overall cohort		Standardised difference	PS		Standardised difference
	Unilateral TKA, n=210 128	Bilateral TKA, n=163 719		Unilateral TKA, n=163 719	Bilateral TKA, n=163 719	
Demographics						
Stroke type, n (%)			0.029			0.021
ischemic	1641 (83.5)	905 (80.8)		1168 (82.8)	905 (80.8)	
hemorrhagic	324 (16.5)	215 (19.2)		243 (17.2)	215 (19.2)	
Time since TKA, n (%)			0.028			0.220
< 2 weeks	402 (20.5)	220 (19.7)		301 (21.3)	220 (19.7)	
2-6 weeks	130 (6.6)	84 (7.5)		94 (6.7)	84 (7.5)	
6-12 weeks	185 (9.4)	120 (10.7)		126 (8.9)	120 (10.7)	
3-6 months	451 (22.9)	231 (20.6)		313 (22.2)	231 (20.6)	
6-12 months	797 (40.6)	465 (41.5)		577 (40.9)	465 (41.5)	
Mean in-hospital stay ± SD, d (%)	17.9 ± 8.5 (100)	~~SB~~ SiB 18.1 ± 9.3 (23.7)/ StB 28.3 ± 9.9 (76.3)	0.728	17.7 ± 8.3 (100)	~~SB~~ SiB 18.1 ± 9.3 (23.7)/ StB 28.3 ± 9.9 (76.3)	0.746
Mean age ± SD, y	69.8 ±7.3	69.8 ±6.6	0.001	69.8 ± 6.8	69.8 ±6.6	0.001
Age distribution, n (%)			0.123			0.014
40-49	1 217 (0.6)	415 (0.3)		400 (0.2)	415 (0.3)	
50-59	17 566 (8.4)	10 842 (6.6)		11 380 (7.0)	10 842 (6.6)	
60-69	77 086 (36.7)	64 163 (39.2)		63 617 (38.9)	64 163 (39.2)	
70-79	98 182 (46.7)	79 094 (48.3)		78 980 (48.2)	79 094 (48.3)	
≥ 80	16 077 (7.7)	9 205 (5.62)		9 342 (2.7)	9 205 (5.6)	
Sex, n (%)			0.291			0.004
Male	36 710 (17.5)	12 925 (7.9)		13 092 (8.0)	12 925 (7.9)	
Female	173 418 (82.5)	150 794 (92.1)		150 627 (92.0)	150 794 (92.1)	
Location, n (%)			0.182			0.085
Urban	82 445 (39.2)	78 931 (48.2)		71 981 (44.0)	78 931 (48.2)	
Rural	127 683 (60.8)	84 788 (51.8)		91 738 (56.0)	84 788 (51.8)	
Hospital size, n (%)			0.056			0.012
Large	81 706 (38.9)	59 232 (36.2)		60 198 (36.8)	59 232 (36.2)	
Small or medium	128 422 (61.1)	104 487 (63.8)		103 521 (63.2)	104 487 (63.8)	
Insurance type, n (%)			0.023			0.001
Health insurance	192 102 (91.4)	150 727 (92.1)		150 783 (92.1)	150 727 (92.1)	
Medical aid	18 026 (8.6)	12 992 (7.9)		12 936 (7.9)	12 992 (7.9)	
History of drug use and comorbiditiesin previous year						
NSAIDs, n (%)			0.101			0.047
No	54 253 (25.8)	49 710 (30.4)		46 189 (28.2)	49 710 (30.4)	
Yes	155 875 (74.2)	114 009 (69.6)		117 530 (71.8)	114 009 (69.6)	
Statin drugs, n (%)			0.068			0.01
No	203 837 (97.0)	160 543 (98.1)		160 769 (98.2)	160 546 (98.1)	
Yes	6 291 (3.0)	3 173 (1.9)		2 950 (1.8)	3 173 (1.9)	
Antiplatelet drugs, n (%)			0.037			0.006
No	208030 (99.0)	162 635 (99.3)		162 712 (99.4)	162 635 (99.3)	
Yes	2098 (1.0)	1 084 (0.7)		1 007 (0.6)	1 084 (0.7)	
Aspirin, n (%)			0.053			0.006
No	206 077 (98.1)	161 645 (98.7)		161 752 (98.8)	161 645 (98.7)	
Yes	414 (1.9)	2 074 (1.3)		1 967 (1.2)	2 074 (1.3)	
Vitamin K antagonists, n (%)			0.024			0.003
No	209 714 (99.8)	163 549 (100.0)		163 563 (99.9)	163 549 (99.9)	
Yes	414 (0.2)	170 (0.0)		156 (0.1)	170 (0.1)	
Factor Xa inhibitors, n (%)			0.079			0.001
No	209 251 (99.6)	163 651 (100.0)		163 648 (100.0)	163 651 (100.0)	
Yes	877 (0.4)	68 (0.0)		71 (0.0)	68 (0.0)	
Direct thrombin inhibitors, n (%)			0.002			0.001
No	210 113 (100.0)	163 710 (100)		163 709 (100.0)	163 710 (100.0)	
Yes	15 (0.0)	9 (0.0)		10 (0.0)	9 (0.0)	
Hypertension drugs, n (%)			0.077			0.006
No	200 082 (95.2)	158 365 (96.7)		158 549 (96.8)	158 365 (96.7)	

Yes	10 046 (4.8)	5 354 (3.3)		5 170 (3.2)	5 354 (3.3)	
AIDS, n (%)			0.001			0.002
No	210119 (100.0)	163 713 (100.0)		163 711 (100.0)	163 713 (100.0)	
Yes	9 (0.0)	6 (0.0)		8 (0.0)	6 (0.0)	
CHF, n (%)			0.015			0.003
No	201 807 (96.0)	157 694 (96.3)		157 776 (96.4)	157 694 (96.3)	
Yes	8 321 (4.0)	6 025 (3.7)		5 943 (3.6)	6 025 (3.7)	
CKD, n (%)			0.048			0.003
No	206 392 (92.2)	161 763 (98.8)		161 820 (98.8)	161 763 (98.8)	
Yes	3 736 (1.8)	1 956 (1.2)		1 899 (1.2)	1 956 (1.2)	
COPD, n (%)			0.058			0.012
No	124 299 (59.2)	101 467 (62.0)		100 486 (61.4)	101 467 (62.0)	
Yes	85 829 (40.9)	62 252 (38.0)		63 233 (38.6)	62 252 (38.0)	
Connective tissue disease, n (%)			0.009			0.004
No	188 530 (89.7)	147 356 (90.0)		147 158 (89.9)	147 356 (90.0)	
Yes	21 598 (10.3)	16 363 (10.0)		16 561 (10.1)	16 363 (10.0)	
CVA or TIA, n (%)			0.05			0.002
No	187 245 (89.1)	148 357 (90.6)		148 271 (90.6)	148 357 (90.6)	
Yes	22 883 (10.9)	15 362 (9.4)		15 448 (9.4)	15 362 (9.4)	
Dementia, n (%)			0.05			<0.001
No	204 127 (97.1)	160 313 (97.9)		160 310 (97.9)	160 313 (97.9)	
Yes	6 001 (2.9)	3 406 (2.1)		3 409 (2.1)	3 406 (2.1)	
Hemiplegia, n (%)			0.020			0.004
No	209 716 (99.8)	163 529 (99.9)		163 551 (99.9)	163 529 (99.9)	
Yes	412 (0.2)	190 (0.1)		168 (0.1)	190 (0.1)	
Myocardial infarction n (%)			0.028			0.002
No	207 802 (98.9)	162 361 (99.2)		162 390 (99.2)	162 361 (99.2)	
Yes	2 326 (1.1)	1 358 (0.8)		1 329 (0.8)	1 358 (0.8)	
Peptic ulcer disease, n (%)			0.037			0.007
No	133 184 (63.4)	106 698 (65.2)		106 168 (64.8)	106 698 (65.2)	
Yes	76 944 (36.6)	57 021 (34.8)		57 551 (35.2)	57 021 (34.8)	
Peripheral vascular disease, n (%)			0.020			0.006
No	185 614 (88.3)	145 660 (89.0)		145 371 (88.8)	145 660 (89.0)	
Yes	24 514 (11.7)	18 059 (11.0)		18 348 (11.2)	18 059 (11.0)	
Liver disease, n (%)			0.027			0.004
No	204 069 (97.1)	159 719 (97.6)		159 820 (97.6)	159 719 (97.6)	
Yes	6 059 (2.9)	4 000 (2.4)		3 899 (2.4)	4 000 (2.4)	
Severe liver disease, n (%)			0.06			0.001
No	209 610 (99.8)	163 365 (99.8)		163 375 (99.8)	163 365 (99.8)	
Yes	518 (0.2)	354 (0.2)		344 (0.2)	354 (0.2)	
Cancer, n (%)			0.030			0.003
No	199 631 (95.0)	15 670 (95.6)		156 681 (95.7)	15 670 (95.6)	
Yes	10 497 (5.0)	7 149 (4.4)		7 038 (4.3)	7 149 (4.4)	
Metastatic cancer, n (%)			0.009			0.002
No	209 547 (99.7)	163 338 (99.8)		163 353 (99.8)	163 338 (99.8)	
Yes	581 (0.3)	381 (0.2)		366 (0.2)	381 (0.2)	
Diabetes, n (%)			0.024			0.003
No	151 518 (72.1)	119 831 (73.2)		119 604 (73.1)	119 831 (73.2)	
Yes	58 610 (27.9.)	43 888 (26.8)		44 115 (26.9)	43 888 (26.8)	
Diabetes with complication, n (%)			0.029			0.001
No	194 170 (92.4)	152 531 (93.2)		152 470 (93.1)	152 531 (93.2)	
Yes	15 958 (7.6).	11 188 (6.8)		11 249 (6.9)	11 188 (6.8)	
Charlsoncomorbity score, mean ± SD	5.25 ± 1.70	5.12 ± 1.59	0.001	5.13 ± 1.59	5.12 ± 1.59	0.001
Atrial fibrillation, n (%)			0.027			<0.001
No	207 033 (98.5)	161 818 (98.8)		161 822 (98.8)	161 818 (98.8)	
Yes	3 095 (1.5)	1901 (1.2)		1897 (1.2)	1 901 (1.2)	
Valvular heart disease, n (%)			0.002			0.002
No	210 088 (100.0)	163 692 (100.0)		163 687 (100.0)	163 692 (100.0)	

Yes	40 (0.0)	27 (0.0)		32 (0.0)	27 (0.0)	
Carotid artery disease, n (%)			0.013			0.003
No	208 925 (99.4)	162 931 (99.5)		162 962 (99.5)	162 931 (99.5)	
Yes	1 203 (0.6)	788 (0.5)		757 (0.5)	788 (0.5)	
Hypothyroidism, n (%)			0.003			0.002
No	202 566 (96.4)	157 928 (96.5)		157 988 (96.5)	157 928 (96.5)	
Yes	7 562 (3.6)	5 791 (3.5)		5 731 (3.5)	5 791 (3.5)	

TKA, total knee arthroplasty; PS, propensity score; SD, standard deviation; ~~SB~~ SiB, simultaneous bilateral; StB, staged bilateral; NSAIDs, non-steroidal anti-inflammatory drugs; AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular disease; TIA, transient ischemic attack

Table 2

Subgroup analyses of risk of stroke with bilateral total knee arthroplasty, compared to unilateral total knee arthroplasty, in PS matched cohort.

Subgroup	Sum of person years	Number of events	Incidence rate per 1000000 person years (95% CI)*	95% CI lower	95% CI upper	HR	95% CI lower	95% CI upper	*p* value	*p* value for interaction
Overall	487 273 006	2 531	5.19	4.99	5.40	0.79	0.73	0.85	< 0.001	
unilateral TKA	235 758 899	1 411	5.98	5.68	6.31					
bilateral TKA	251 514 107	1 120	4.45	4.20	4.72					
Age										0.368
40–49	1 538 293	1	0.65	0.02	3.62	NA	NA	NA	NA	
50–59	37 380 596	70	1.87	1.46	2.37	1.17	0.73	1.88	0.504	
60–69	199 119 148	651	3.27	3.02	3.53	0.81	0.69	0.94	0.007	
70–79	226 804 347	1 556	6.86	6.52	7.21	0.76	0.69	0.84	< 0.001	
≥ 80	22 430 622	253	11.28	9.93	12.76	0.84	0.66	1.07	0.164	
Sex										0.657
Male	35 445 002	258	7.28	6.42	5.24	0.79	0.59	0.96	0.022	
Female	451 828 004	2 273	5.03	4.83	8.22	0.75	0.71	0.86	< 0.001	
Location										0.463
Urban	226 829 869	1 078	4.75	4.47	5.04	0.82	0.73	0.93	0.001	
Rural	260 443 137	1 453	5.58	5.30	5.87	0.77	0.70	0.86	< 0.001	
Hospital size										0.098
Large	175 297 445	976	5.57	5.22	5.93	0.86	0.76	0.97	0.018	
Small or medium	311 975 561	1 555	4.98	4.74	5.24	0.75	0.68	0.83	< 0.001	
Insurance type										0.101
Health insurance	448 017 058	2 236	4.99	4.79	5.20	0.77	0.71	0.84	< 0.001	
Medical aid	39 255 948	295	7.51	6.68	8.42	0.94	0.75	1.19	0.623	
History of drug use and comorbidities in previous year										
NSAIDs										0.732
No	133 406 439	669	5.01	4.64	5.41	0.77	0.66	0.90	0.001	
Yes	353 866 567	1 862	5.26	5.03	5.51	0.80	0.73	0.87	< 0.001	
Statin drugs										0.533
No	478 764 990	2 458	5.13	4.93	5.34	0.79	0.73	0.86	< 0.001	
Yes	8 508 016	73	8.58	6.73	10.79	0.68	0.43	1.08	0.106	

Subgroup	Sum of person years	Number of events	Incidence rate per 1000000 person years (95% CI)*	95% CI		HR	95% CI		*p* value	*p* value for interaction
				lower	upper		lower	upper		
Antiplatelet drugs										0.578
No	484 349 186	2 504	5.17	4.97	5.38	0.79	0.73	0.86	< 0.001	
Yes	2 923 820	27	9.23	6.09	13.44	0.63	0.29	1.37	0.246	
Aspirin										0.941
No	481 724 149	2 480	5.15	4.95	5.35	0.79	0.73	0.85	< 0.001	
Yes	5 548 857	51	9.19	6.84	12.08	0.77	0.45	1.34	0.361	
Vitamin K antagonists										0.330
No	486 788 236	2 525	5.19	4.99	5.39	0.79	0.73	0.85	< 0.001	
Yes	484 770	6	12.38	4.54	26.94	1.83	0.34	10.00	0.484	
Factor Xa inhibitor										0.973
No	487 137 787	2 530	5.19	4.99	5.40	0.79	0.73	0.85	< 0.001	
Yes	135 219	1	7.40	0.19	41.20	NA	NA	NA	NA	
Direct thrombin inhibitor										1.000
No	487 264 451	2 531	5.19	4.99	5.40	0.79	0.73	0.85	< 0.001	
Yes	8 555	0	0.00	0.00	431.20	NA	NA	NA	NA	
Hypertension drugs										0.753
No	471 886 519	2 383	5.05	4.85	5.26	0.79	0.73	0.86	0.082	
Yes	15 386 487	148	9.62	8.13	11.30	0.75	0.54	1.04	< 0.001	
AIDS										1.000
No	487 254 281	2 531	5.19	4.99	5.40	0.79	0.73	0.85	< 0.001	
Yes	18 725	0	0.00	0.00	197.00	NA	NA	NA	NA	
CHF										0.467
No	469 984 045	2 378	5.06	4.86	5.27	0.79	0.73	0.86	< 0.001	
Yes	17 288 961	153	8.85	7.50	10.37	0.70	0.51	0.97	0.032	
CKD										0.622
No	482 451 662	2 490	5.16	4.96	5.37	0.79	0.73	0.86	< 0.001	
Yes	4 821 344	41	8.50	6.10	11.54	0.68	0.36	1.26	0.217	
COPD										0.909
No	302 399 164	1 624	5.37	5.11	5.64	0.79	0.71	0.87	< 0.001	
Yes	184 873 842	907	4.91	4.59	5.24	0.79	0.70	0.91	0.001	
Connective tissue disease										0.391
No	435 853 149	2 308	5.30	5.08	5.52	0.80	0.73	0.87	< 0.001	

Subgroup	Sum of person years	Number of events	Incidence rate per 1000000 person years (95% CI)*	95% CI		HR	95% CI		*p* value	*p* value for interaction
				lower	upper		lower	upper		
Yes	51 419 857	223	4.34	3.79	4.94	0.71	0.54	0.92	0.010	
CVA or TIA										0.727
No	441 509 488	2 133	4.83	4.63	5.04	0.78	0.72	0.85	< 0.001	
Yes	45 763 518	398	8.70	7.86	9.59	0.82	0.67	0.99	0.043	
Dementia										0.606
No	478 938 862	2 447	5.11	4.91	5.32	0.79	0.73	0.86	< 0.001	
Yes	8 334 144	84	10.08	8.04	12.48	0.71	0.46	1.09	0.118	
Hemiplegia										0.229
No	486 728 204	2 524	5.19	4.99	5.39	0.79	0.73	0.85	< 0.001	
Yes	544 802	7	12.85	5.17	26.47	2.16	0.42	11.11	0.359	
Myocardial infarction										0.544
No	483 269 362	2 496	5.16	4.96	5.37	0.79	0.73	0.86	< 0.001	
Yes	4 003 644	35	8.74	6.09	12.16	0.64	0.33	1.26	0.196	
Peptic ulcer disease										0.493
No	309 899 308	1 636	5.28	5.03	5.54	0.77	0.70	0.85	< 0.001	
Yes	177 373 698	895	5.05	4.72	5.39	0.82	0.72	0.93	0.003	
Peripheral vascular disease										0.136
No	432 394 256	2 182	5.05	4.84	5.26	0.77	0.71	0.84	< 0.001	
Yes	54 878 750	349	6.36	5.71	7.06	0.92	0.74	1.13	0.411	
Liver disease										0.202
No	474 611 698	2 481	5.23	5.02	5.44	0.80	0.73	0.86	< 0.001	
Yes	12 661 308	50	3.95	2.93	5.21	0.54	0.31	0.97	0.059	
Severe liver disease										0.806
No	485 959 159	2 525	5.20	5.00	5.40	0.79	0.73	0.85	< 0.001	
Yes	1 313 847	6	4.57	1.68	9.94	0.96	0.19	4.76	0.961	
Cancer										0.492
No	468 096 910	2 444	5.22	5.02	5.43	0.79	0.73	0.85	< 0.001	
Yes	19 176 096	87	4.54	3.63	5.60	0.91	0.60	1.39	0.674	
Metastatic cancer										0.800
No	486 212 605	2 526	5.20	4.99	5.40	0.79	0.73	0.85	< 0.001	

Subgroup	Sum of person years	Number of events	Incidence rate per 1000000 person years (95% CI)*	95% CI		HR	95% CI		*p* value	*p* value for interaction
				lower	upper		lower	upper		
Yes	1 060 401	5	4.72	1.53	11.00	0.64	0.11	3.81	0.622	
Diabetes										0.684
No	359 206 894	1 734	4.83	4.60	5.06	0.80	0.73	0.88	< 0.001	
Yes	128 066 112	797	6.22	5.80	6.67	0.77	0.67	0.89	< 0.001	
Diabetes with complication										0.757
No	454 116 703	2 288	5.04	4.83	5.25	0.79	0.73	0.86	< 0.001	
Yes	33 156 303	243	7.33	6.44	8.31	0.76	0.59	0.98	0.034	
Atrial fibrillation										0.936
No	483 244 151	2 453	5.08	4.88	5.28	0.79	0.73	0.85	< 0.001	
Yes	4 028 855	78	19.36	15.30	24.16	0.80	0.51	1.26	0.337	
Valvular heart disease										0.973
No	487 184 407	2 530	5.19	4.99	5.40	0.79	0.73	0.85	< 0.001	
Yes	88 599	1	11.29	0.29	62.89	NA	NA	NA	NA	
Carotid artery disease										0.385
No	485 545 773	2 509	5.17	4.97	5.37	0.79	0.73	0.85	< 0.001	
Yes	1 727 233	22	12.74	7.98	19.28	1.15	0.50	2.66	0.749	
Hypothyroidismm										0.786
No	471 135 808	2 466	5.23	5.03	5.44	0.79	0.73	0.85	< 0.001	
Yes	16 137 198	65	4.03	3.11	5.13	0.84	0.52	1.38	0.497	

TKA, total knee arthroplasty; PS, propensity score; HR, hazard ratio; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular disease; TIA, transient ischemic attack

*****Incidecnce rate=(No of events/sum of person years)x1000000; 95% CI calculated assuming Poisson distribution.

Table 3

Association between unilateral TKA and bilateral TKA

	Univariable analysis				Multivariable analysis				Sensitivity analysis			
	Crude HR	95% CI lower	upper	*p* value	Adjusted HR*	95% CI lower	upper	*p* value	Adjusted HR†	95% CI lower	upper	*p* value
Surgery												
Unilateral	reference				reference				reference			
Bilateral	0.789	0.730	0.854	< 0.001	0.793	0.733	0.858	< 0.001	0.792	0.732	0.857	< 0.001

TKA, total knee arthroplasty; HR, hazard ratio; CI, confidence interval.

*Adjusted by age, sex, location, hospital size, NSAIDs, statin drugs, antiplatelet drugs, aspirin drugs, vitamin K antagonists, hypertension drugs, CHF, CKD, COPD, connective tissue disease, CVA or TIA, dementia, hemiplegia, myocardial infarction, peripheral vascular disease, cancer, diabetes, diabetes with complication, Charlson comorbidity score, atrial fibrillation, carotid artery disease, hypothyroidism.

†*Adjusted by the same variables as in multivariable analysis and insurance type.

Figures

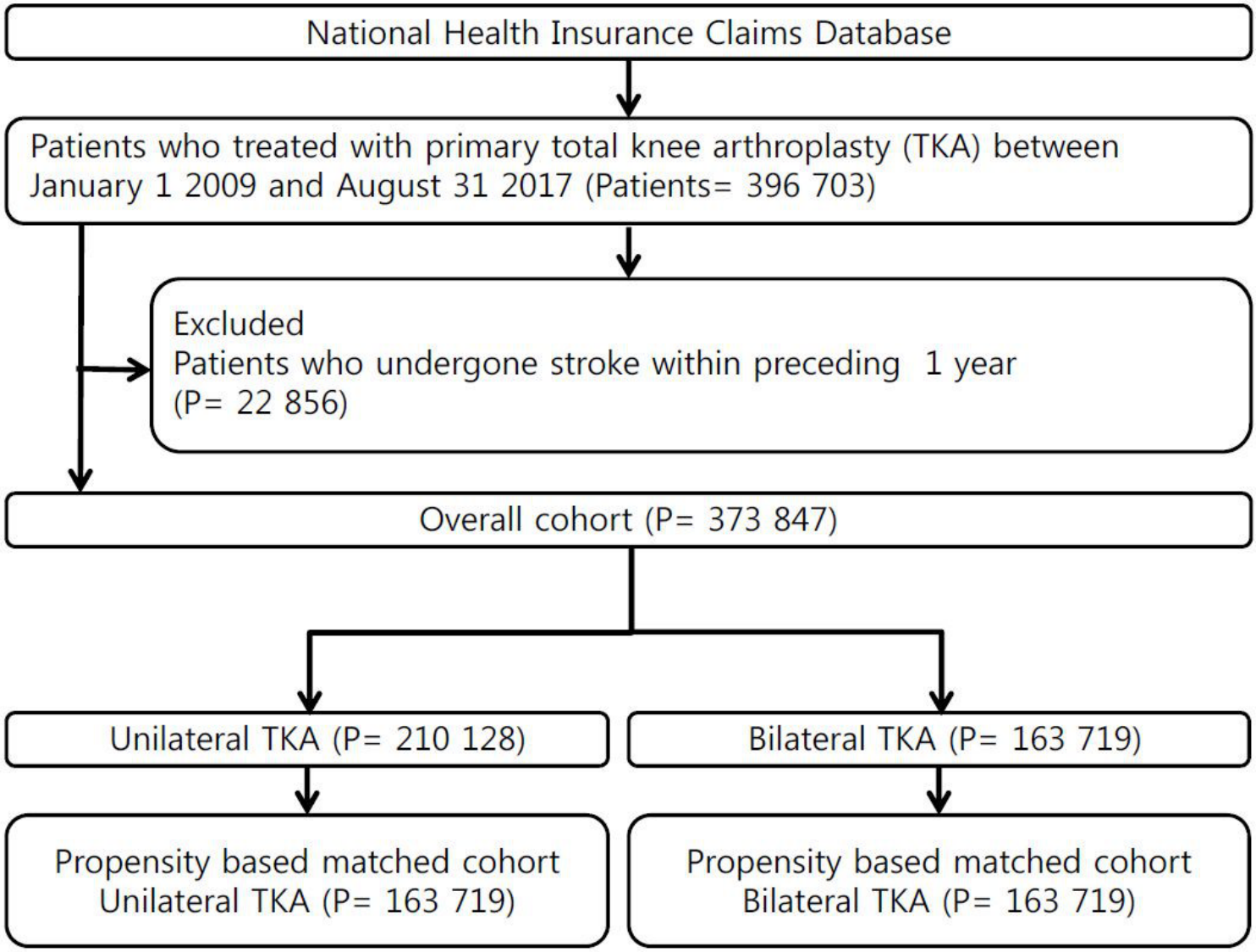

Figure 1

Selection of study participants from National Health Insurance Claims Database in restrospective cohort design.

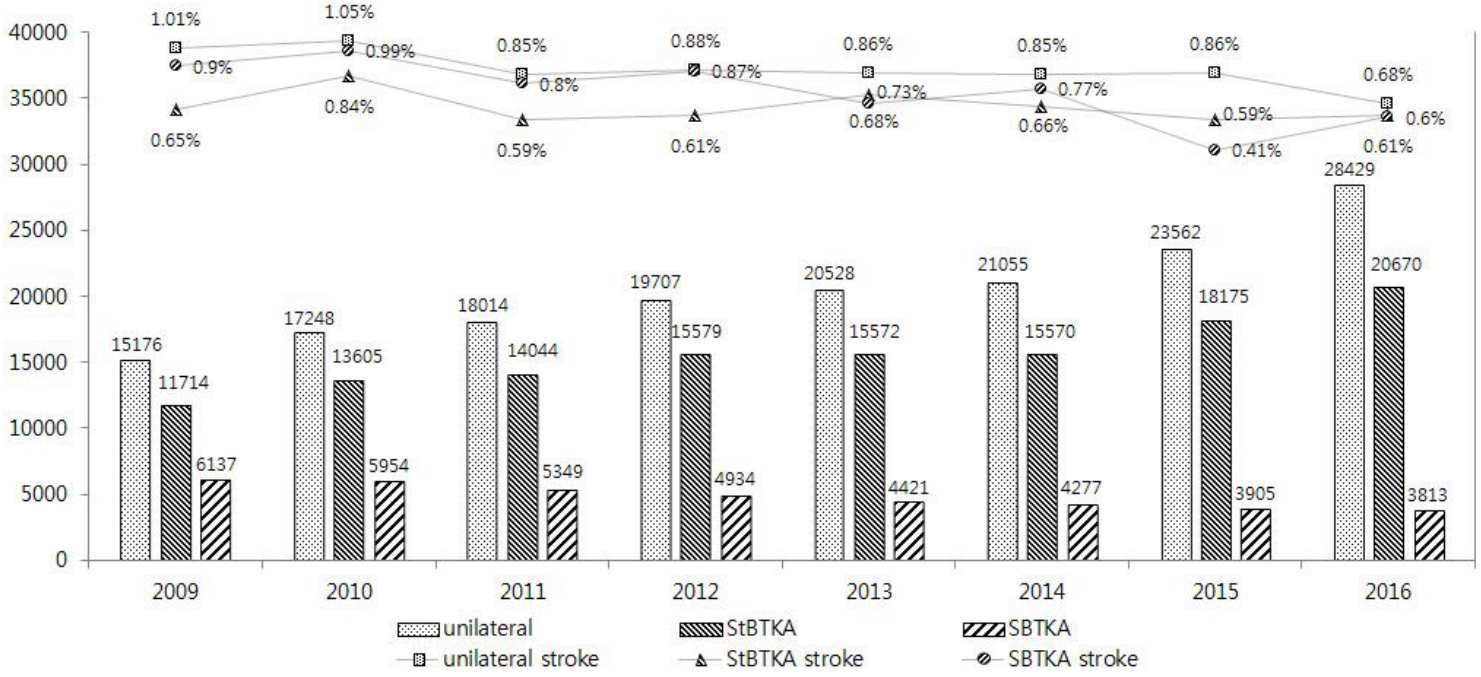

Figure 2

The association of incidence of stroke and annual procedure volume after unilateral TKA or bilateral TKA in South Korea during the study period.

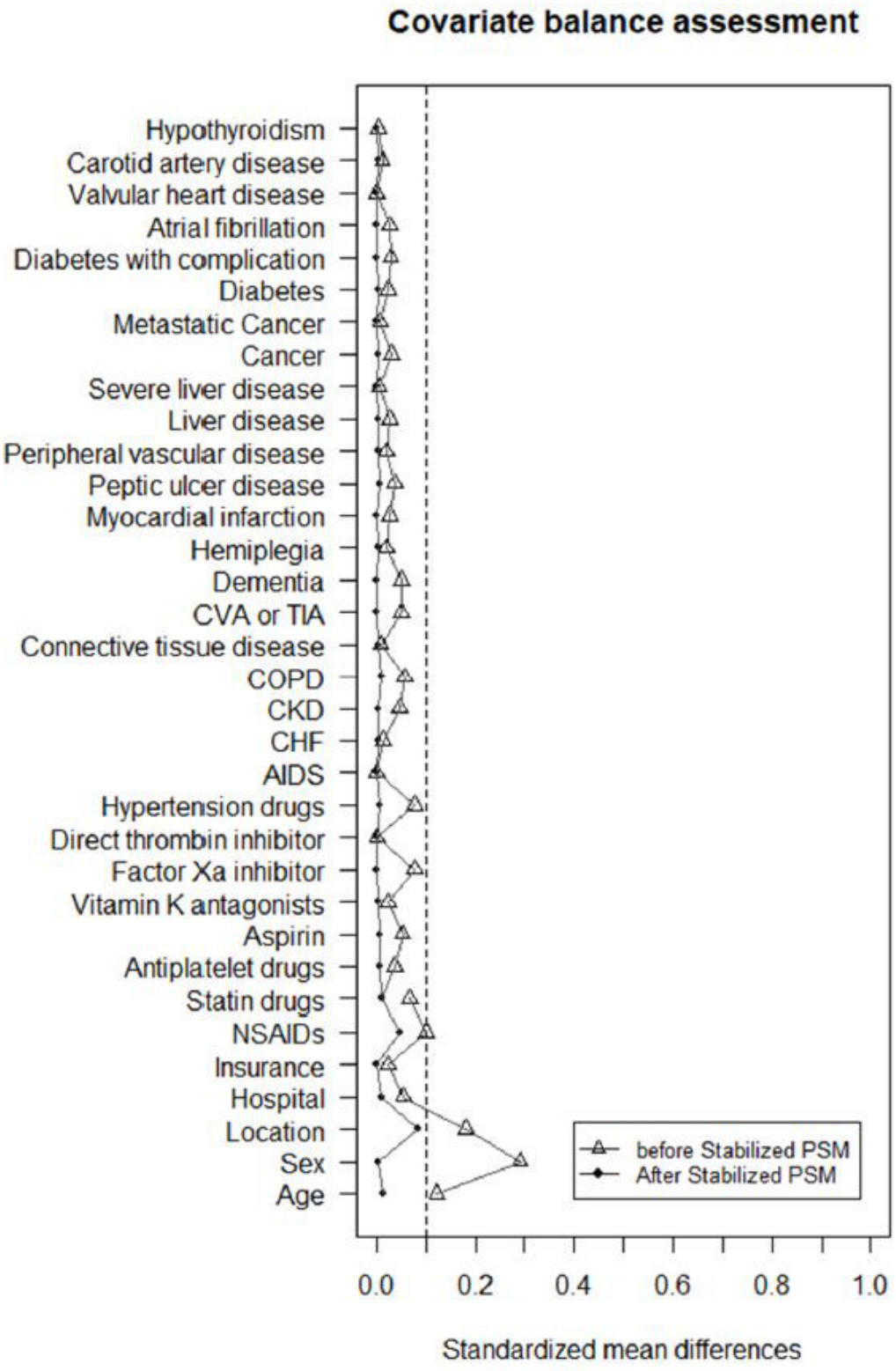

Figure 3

Standardized differences in key baseline characteristics for the unmatched dataset and the dataset weighted by the stabilized PSM.

Supplementary Files

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- IRBdocument.pdf