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

Seung-Beom Han  
Korea University College of Medicine and School of Medicine

Jung-Ro Yoon  
Veterans Health Service Medical Center

Ji-Young Cheong  
Korea University College of Medicine and School of Medicine

Sang-Soo Lee  
Hallym University College of Medicine

Young-Soo Shin (✉️ sysoo3180@naver.com)  
Veterans Health Service Medical Center  https://orcid.org/0000-0003-1030-9979

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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 | Standardised difference |
|---------------------------------------|----------------|-------------------------|-------------------------|
|                                       | Unilateral TKA, n=210 | Bilateral TKA, n=163 719 | PS Unilateral TKA, n=163 719 | Bilateral TKA, n=163 719 |
|                                       | 128            |                         |                         |
| **Demographics**                      |                |                         |                         |
| Stroke type, n (%)                    |                |                         |                         |
| 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 (%)                 |                |                         |                         |
| < 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) | 18.1 ± 9.3 (23.7) | 17.7 ± 8.3 (100) | 18.1 ± 9.3 (23.7) | 0.728 | 0.746 |
| Age distribution, n (%)               |                |                         |                         |
| 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)  | 79 694 (48.3)           | 78 980 (48.2)           | 79 694 (48.3)            |
| ≥ 80                                  | 16 077 (7.7)   | 9 205 (5.6)             | 9 342 (2.7)             | 9 205 (5.6)              |
| Sex, n (%)                            |                |                         |                         |
| 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 (%)                       |                |                         |                         |
| 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 (%)                  |                |                         |                         |
| 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 (%)                 |                |                         |                         |
| No 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 comorbidities in previous year** |                |                         |                         |
| NSAIDs, n (%)                         |                |                         |                         |
| 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 (%)                   |                |                         |                         |
| 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)             | 2 930 (1.8)             | 3 173 (1.9)              |
| Antiplatelet drugs, n (%)             |                |                         |                         |
| No                                    | 208 039 (99.0) | 162 635 (99.3)          | 162 712 (99.4)          | 162 635 (99.3)           |
| Yes                                   | 2088 (1.0)     | 1 084 (0.7)             | 1 007 (0.6)             | 1 084 (0.7)              |
| Aspirin, n (%)                        |                |                         |                         |
| 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 (%)          |                |                         |                         |
| 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 (%)           |                |                         |                         |
| 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 |

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| Condition                        | No                  | Yes       | 0.077   | 0.006   |
|---------------------------------|---------------------|-----------|---------|---------|
| Hypertension drugs, n (%)       |                     |           |         |         |
| No                              | 210 113 (100.0)     | 163 710 (100) | 163 709 (100) | 163 710 (100) |
| Yes                             | 15 (0.0)            | 9 (0.0)   | 10 (0.0) | 9 (0.0) |
| AIDS, n (%)                     |                     |           |         |         |
| 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)  |
| CHF, n (%)                      |                     |           |         |         |
| No                              | 210 119 (100.0)     | 163 713 (100) | 163 711 (100) | 163 713 (100) |
| Yes                             | 9 (0.0)             | 6 (0.0)   | 8 (0.0)  | 6 (0.0) |
| CKD, n (%)                      |                     |           |         |         |
| 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 (%)                     |                     |           |         |         |
| No                              | 201 807 (96.0)      | 157 694 (98.8) | 157 776 (98.4) | 157 694 (98.8) |
| Yes                             | 8 321 (4.0)         | 6 025 (3.7)  | 5 943 (3.6)  | 6 025 (3.7)  |
| Connective tissue disease, n (%)|                     |           |         |         |
| No                              | 188 530 (89.7)      | 147 356 (90.9) | 147 158 (90.9) | 147 356 (90.9) |
| Yes                             | 21 598 (10.3)       | 16 363 (9.1)  | 16 197 (9.1)  | 16 363 (9.1)  |
| CVA or TIA, n (%)               |                     |           |         |         |
| No                              | 187 245 (89.1)      | 148 357 (90.6) | 148 271 (90.6) | 148 357 (90.6) |
| Yes                             | 22 883 (10.9)       | 15 484 (9.4)  | 15 326 (9.4)  | 15 484 (9.4)  |
| Dementia, n (%)                 |                     |           |         |         |
| No                              | 204 127 (97.1)      | 160 313 (97.9) | 160 310 (97.9) | 160 313 (97.9) |
| Yes                             | 6 001 (0.3)         | 4 000 (0.2)   | 3 999 (0.2)   | 4 000 (0.2)   |
| Hemiplegia, n (%)               |                     |           |         |         |
| No                              | 209 716 (99.8)      | 163 529 (99.9) | 163 551 (99.9) | 163 529 (99.9) |
| Yes                             | 412 (0.2)           | 190 (0.1)    | 190 (0.1)    | 190 (0.1)    |
| Myocardial infarction n (%)     |                     |           |         |         |
| 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 (%)     |                     |           |         |         |
| No                              | 133 184 (63.4)      | 106 698 (65.2) | 106 168 (64.8) | 106 698 (65.2) |
| Yes                             | 76 944 (36.6)       | 57 021 (33.8) | 57 551 (35.2) | 57 021 (33.8) |
| Peripheral vascular disease, n (%)|                     |           |         |         |
| 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 (%)            |                     |           |         |         |
| 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 (%)     |                     |           |         |         |
| No                              | 209 610 (99.8)      | 163 365 (99.8) | 163 375 (99.8) | 163 365 (99.8) |
| Yes                             | 58 610 (2.7)        | 43 888 (26.8) | 44 115 (26.9) | 43 888 (26.8) |
| Cancer, n (%)                   |                     |           |         |         |
| No                              | 199 631 (95.6)      | 15 670 (95.6)  | 15 681 (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 (%)        |                     |           |         |         |
| 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 (%)                 |                     |           |         |         |
| 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 (%)|                     |           |         |         |
| No                              | 209 610 (99.8)      | 163 365 (99.8) | 163 375 (99.8) | 163 365 (99.8) |
| Yes                             | 58 610 (2.7)        | 43 888 (26.8) | 44 115 (26.9) | 43 888 (26.8) |
| Charlson comorbidity score, mean ± SD | 5.25 ± 1.70 | 5.12 ± 1.59 | 5.13 ± 1.59 | 5.12 ± 1.59 |
|--------------------------------------|--------------|--------------|--------------|--------------|
| Atrial fibrillation, n (%)           | 0.027        | <0.001       | 0.002        | 0.002        |
| Valvular heart disease, n (%)        |              |              |              |              |
| Carotid artery disease, n (%)        |              |              |              |              |
| Hypothyroidism, n (%)                |              |              |              |              |

TKA, total knee arthroplasty; PS, propensity score; SD, standard deviation; 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)* | HR | 95% CI | p value | p value for interaction |
|----------|---------------------|------------------|-----------------------------------------------|----|--------|---------|---------------------|
| Overall  | 487 273 2 531       | 273 006          | 5.19 4.99 5.40 0.79 0.73 0.85 < 0.001 |    |        |         |        |
| unilatera l TKA | 235 758 1 411     | 899              | 5.98 5.68 6.31                                |    |        |         |        |
| bilateral TKA | 251 514 1 120     | 107              | 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         | 119              | 3.27 3.02 3.53 0.81 0.69 0.94 0.007         |    |        |         |        |
| 70–79      | 226 804 347         | 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 2 273 004   | 137              | 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         | 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 561 | 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 0.08 | 448 017 4058      | 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 0.732 |                      |                  |                                                |    |        |         |        |
| NSAIDs No 0.533 | 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        |    |        |         |        |
| Subgroup                  | Sum of person years | Number of events | Incidence rate per 1000000 person years (95% CI)* | HR       | 95% CI       | p value for interaction |
|--------------------------|---------------------|------------------|-------------------------------------------------|----------|--------------|-------------------------|
|                          |                     |                  | lower | upper | lower | upper |         |                       |
| No                       | 478 764 | 2 458 | 990      | 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 |
| Antiplatelet drugs       |                     |                  |       |       |       |       | 0.578 |                       |
| No                       | 484 349 | 2 504 | 186      | 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 | 2 480 | 149      | 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 | 2 525 | 236      | 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 | 2 530 | 787      | 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 | 2 531 | 451      | 5.19 | 4.99 | 5.40 | 0.79 | 0.73 | 0.85 | < 0.001 |
| Yes                      | 8 555 0 | 0       | 0.00 | 0.00 | 431.20 | NA | NA | NA | NA |
| Hypertension drugs       |                     |                  |       |       |       |       | 0.753 |                       |
| No                       | 471 886 | 2 383 | 519      | 5.05 | 4.85 | 5.26 | 0.79 | 0.73 | 0.86 | 0.082 |
| Yes                      | 15 386 | 148 | 487      | 9.62 | 8.13 | 11.30 | 0.75 | 0.54 | 1.04 | < 0.001 |
| AIDS                     |                     |                  |       |       |       |       | 1.000 |                       |
| No                       | 487 254 | 2 531 | 281      | 5.19 | 4.99 | 5.40 | 0.79 | 0.73 | 0.85 | < 0.001 |
| Yes                      | 18 725 0 | 0         | 0.00 | 0.00 | 197.00 | NA | NA | NA | NA |
| CHF                      |                     |                  |       |       |       |       | 0.467 |                       |
| No                       | 469 984 | 2 378 | 045      | 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 | 2 490 | 662      | 5.16 | 4.96 | 5.37 | 0.79 | 0.73 | 0.86 | < 0.001 |
| Subgroup                              | Sum of person years | Number of events | Incidence rate per 1000000 person years (95% CI)* | HR | 95% CI | p value for interaction |
|---------------------------------------|---------------------|------------------|------------------------------------------------|----|--------|-------------------------|
|                                       | lower              | upper            | lower                                      | upper | lower | upper | lower | upper |   |
| Yes                                   | 4 821              | 344              | 8.50                                       | 6.10  | 11.54  | 0.68 | 0.36 | 1.26 | 0.217 |
| COPD                                  |                     |                  |                                            |       |        |       |      |      | 0.909 |
| No                                    | 302 399            | 1 624            | 5.37                                       | 5.11  | 5.64  | 0.79 | 0.71 | 0.87 | < 0.001 |
| Yes                                   | 184 873            | 907              | 4.91                                       | 4.59  | 5.24  | 0.79 | 0.70 | 0.91 | 0.001 |
| Connective tissue disease             |                     |                  |                                            |       |        |       |      |      | 0.391 |
| No                                    | 435 853            | 2 308            | 5.30                                       | 5.08  | 5.52  | 0.80 | 0.73 | 0.87 | < 0.001 |
| Yes                                   | 51 419             | 223              | 4.34                                       | 3.79  | 4.94  | 0.71 | 0.54 | 0.92 | 0.010 |
| CVA or TIA                            |                     |                  |                                            |       |        |       |      |      | 0.727 |
| No                                    | 441 509            | 2 133            | 4.83                                       | 4.63  | 5.04  | 0.78 | 0.72 | 0.85 | < 0.001 |
| Yes                                   | 45 763             | 398              | 8.70                                       | 7.86  | 9.59  | 0.82 | 0.67 | 0.99 | 0.043 |
| Dementia                              |                     |                  |                                            |       |        |       |      |      | 0.606 |
| No                                    | 478 938            | 2 447            | 5.11                                       | 4.91  | 5.32  | 0.79 | 0.73 | 0.86 | < 0.001 |
| Yes                                   | 8 334              | 84               | 10.08                                      | 8.04  | 12.48 | 0.71 | 0.46 | 1.09 | 0.118 |
| Hemiplegia                            |                     |                  |                                            |       |        |       |      |      | 0.229 |
| No                                    | 486 728            | 2 524            | 5.19                                       | 4.99  | 5.39  | 0.79 | 0.73 | 0.85 | < 0.001 |
| Yes                                   | 544 802            | 7 128            | 12.85                                      | 5.17  | 26.47 | 2.16 | 0.42 | 11.11 | 0.359 |
| Myocardial infarction                 |                     |                  |                                            |       |        |       |      |      | 0.544 |
| No                                    | 483 269            | 2 496            | 5.16                                       | 4.96  | 5.37  | 0.79 | 0.73 | 0.86 | < 0.001 |
| Yes                                   | 4 003              | 644              | 8.74                                       | 6.09  | 12.16 | 0.64 | 0.33 | 1.26 | 0.196 |
| Peptic ulcer disease                  |                     |                  |                                            |       |        |       |      |      | 0.493 |
| No                                    | 309 899            | 1 636            | 5.28                                       | 5.03  | 5.54  | 0.77 | 0.70 | 0.85 | < 0.001 |
| Yes                                   | 177 373            | 895              | 5.05                                       | 4.72  | 5.39  | 0.82 | 0.72 | 0.93 | 0.003 |
| Peripheral vascular disease           |                     |                  |                                            |       |        |       |      |      | 0.136 |
| No                                    | 432 394            | 2 182            | 5.05                                       | 4.84  | 5.26  | 0.77 | 0.71 | 0.84 | < 0.001 |
| Yes                                   | 54 878             | 349              | 6.36                                       | 5.71  | 7.06  | 0.92 | 0.74 | 1.13 | 0.411 |
| Liver disease                         |                     |                  |                                            |       |        |       |      |      | 0.202 |
| No                                    | 474 611            | 2 481            | 5.23                                       | 5.02  | 5.44  | 0.80 | 0.73 | 0.86 | < 0.001 |
| Subgroup                                      | Sum of person years | Number of events | Incidence rate per 1000000 person years (95% CI)* | HR | 95% CI lower | 95% CI upper | p value for interaction |
|-----------------------------------------------|---------------------|------------------|-----------------------------------------------|----|--------------|--------------|-------------------------|
| Yes                                           | 12 661              | 50               | 3.95                                         | 2.93 | 5.21 | 0.54 | 0.31 | 0.97 | 0.059 |
| Severe liver disease                          |                     |                  |                                               |     |         |         | 0.806 |
| No                                            | 485 959            | 2 525            | 5.20                                         | 5.00 | 5.40 | 0.79 | 0.73 | 0.85 | <0.001 |
| Yes                                           | 1 313              | 6                | 4.57                                         | 1.68 | 9.94 | 0.96 | 0.19 | 4.76 | 0.961 |
| Cancer                                        |                     |                  |                                               |     |         |         | 0.492 |
| No                                            | 468 096            | 2 444            | 5.22                                         | 5.02 | 5.43 | 0.79 | 0.73 | 0.85 | <0.001 |
| Yes                                           | 19 176             | 87               | 4.54                                         | 3.63 | 5.60 | 0.91 | 0.60 | 1.39 | 0.674 |
| Metastatic cancer                             |                     |                  |                                               |     |         |         | 0.800 |
| No                                            | 486 212            | 2 526            | 5.20                                         | 4.99 | 5.40 | 0.79 | 0.73 | 0.85 | <0.001 |
| Yes                                           | 1 060              | 5                | 4.72                                         | 1.53 | 11.00 | 0.64 | 0.11 | 3.81 | 0.622 |
| Diabetes                                      |                     |                  |                                               |     |         |         | 0.684 |
| No                                            | 359 206            | 1 734            | 4.83                                         | 4.60 | 5.06 | 0.80 | 0.73 | 0.88 | <0.001 |
| Yes                                           | 128 066            | 797              | 6.22                                         | 5.80 | 6.67 | 0.77 | 0.67 | 0.89 | <0.001 |
| Diabetes with complication                    |                     |                  |                                               |     |         |         | 0.757 |
| No                                            | 454 116            | 2 288            | 5.04                                         | 4.83 | 5.25 | 0.79 | 0.73 | 0.86 | <0.001 |
| Yes                                           | 33 156             | 243              | 7.33                                         | 6.44 | 8.31 | 0.76 | 0.59 | 0.98 | 0.034 |
| Atrial fibrillation                           |                     |                  |                                               |     |         |         | 0.936 |
| No                                            | 483 244            | 2 453            | 5.08                                         | 4.88 | 5.28 | 0.79 | 0.73 | 0.85 | <0.001 |
| Yes                                           | 4 028              | 855              | 19.36                                        | 15.30 | 24.16 | 0.80 | 0.51 | 1.26 | 0.337 |
| Valvular heart disease                        |                     |                  |                                               |     |         |         | 0.973 |
| No                                            | 487 184            | 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            | 2 509            | 5.17                                         | 4.97 | 5.37 | 0.79 | 0.73 | 0.85 | <0.001 |
| Yes                                           | 1 727              | 233              | 12.74                                        | 7.98 | 19.28 | 1.15 | 0.50 | 2.66 | 0.749 |
| Hypothyroidism                                |                     |                  |                                               |     |         |         | 0.786 |
### Table 3
Association between unilateral TKA and bilateral TKA

| Subgroup | Sum of person years | Number of events | Incidence rate per 1000000 person years (95% CI)* | HR | 95% CI | p value | p value for interaction |
|----------|---------------------|-----------------|--------------------------------------------------|----|--------|---------|------------------------|
| No       | 471 135 2 466 808   | 135 2 466 808   | 5.23 5.03 5.44 0.79 0.73 0.85 < 0.001           |     |        |         |                        |
| Yes      | 16 137 65 198       | 137 65 198      | 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.

*Incidence rate = (No of events/sum of person years) x 1000000; 95% CI calculated assuming Poisson distribution.

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**Figures**
Figure 1

Selection of study participants from National Health Insurance Claims Database in retrospective 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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