Risk of stroke after unilateral or bilateral TKA (simultaneous and staged without discharge) in 327,438 matched patients using data from the National Health Insurance Claims for South Korea

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Abstract

Purpose 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).

Conclusion 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.

Keywords Knee arthroplasty · Unilateral · Bilateral · Risk factors · Epidemiology

Introduction

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...
used, which can lead to reduced statistical power [4, 9].

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.

Materials and 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 more than 6 months after discharge of index TKA. This is because the planned-staged cohort (more than 6 months) does not appear to be directly related to the index TKA for the risk of cardiovascular complication [6, 13]. 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.

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 Comorbidity Index was calculated for all patients [14]; those with no comorbidities received
a score of 0 points. Information on the use of drugs was based on a 3-month period within 1 year before the index date because, in South Korea, drugs are generally prescribed for 3 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).

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.

Propensity score (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 [15]. PS matching is a method of 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. 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 [16, 17]. 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. Sub-group 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 modeling 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

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. The details of the cohort selection process are summarized in Fig. 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 Fig. 2, indicating that the incidence of stroke decreased steadily regardless of the type of surgery.

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, 1411 (0.86%) developed stroke; 1168 (82.8%) cases were ischemic and the remaining 243 (17.2%) were hemorrhagic stroke, whereas 1120 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 2 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 0.73–0.85). 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 0.69–0.84), female sex (HR 0.75, 95% CI 0.71–0.86), rural area (HR 0.77, 95% CI 0.70–0.86), small- or medium-sized hospital (HR 0.75, 95% CI 0.68–0.83), health insurance (HR 0.77, 95% CI 0.71–0.84), history of hypertension drug use (HR 0.75, 95% CI 0.54–1.04), CHF (HR 0.70, 95% CI 0.51–0.97), connective tissue disease (HR 0.71, 95% CI 0.54–0.92), diabetes (HR 0.77, 95% CI 0.67–0.89), and diabetes with complications (HR 0.76, 95% CI 0.59–0.98).

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 0.73–0.86). 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 previous studies that showed no significant difference between unilateral TKA and bilateral TKA with respect to postoperative stroke evaluated in a single institution and patients undergoing bilateral TKA were almost three times more likely to develop acute ischemic stroke compared with unilateral TKA patients in population-based study using the Nationwide Inpatient Sample [9, 18]. 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 [19]. 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 [20, 21]. 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.
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 | Standardized difference | PS | Standardized difference |
|----------------|----------------|------------------------|----|------------------------|
|                | Unilateral TKA, n = 210 719 | 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, day (%) | SiB 18.1 ± 9.3 (23.7)/ | 0.728 | SiB 18.1 ± 9.3 (23.7)/ | 0.746 |
| Mean age ± SD, year | 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 | 1217 (0.6) | 415 (0.3) | 400 (0.2) | 415 (0.3) |
| 50–59 | 17,566 (8.4) | 64,163 (39.2) | 63,617 (38.9) | 64,163 (39.2) |
| 60–69 | 77,086 (36.7) | 79,094 (48.3) | 78,980 (48.2) | 79,094 (48.3) |
| 70–79 | 98,182 (46.7) | 9205 (5.6) | 9205 (5.6) |
| ≥ 80 | 16,077 (7.7) | 150,794 (92.1) | 150,794 (92.1) |
| 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) | 79,931 (48.2) | 78,931 (48.2) |
| Rural | 127,683 (60.8) | 84,788 (51.8) | 84,788 (51.8) |
| Hospital size, n (%) | 0.056 | 0.012 |  |                           |
| Large | 81,706 (38.9) | 59,232 (36.2) | 59,232 (36.2) |
| Small or medium | 128,422 (61.1) | 104,487 (63.8) | 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) | 12,992 (7.9) |
| History of drug use and comorbidities in 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 | 6291 (3.0) | 3173 (1.9) | 3173 (1.9) |
| Antiplatelet drugs, n (%) | 0.037 | 0.006 |  |                           |
| No | 208,030 (99.0) | 162,635 (99.3) | 162,712 (99.4) | 162,635 (99.3) |
| Yes | 2098 (1.0) | 1084 (0.7) | 1084 (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) | 2074 (1.3) | 2074 (1.3) |
Table 1 (continued)

| Characteristic                          | Overall cohort | Standardized difference | PS          | Standardized difference | Standardized difference |
|-----------------------------------------|----------------|-------------------------|-------------|-------------------------|-------------------------|
|                                         | Overall cohort | Standardized difference | PS          | Standardized difference | Standardized difference |
|                                         | Unilateral TKA, n = 210 | 128 | 0.024 | 0.003 | 0.024 |
|                                         | Bilateral TKA, n = 163 | 719 | 0.024 | 0.003 | 0.024 |
| 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 (%)       | 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 (%)               | No             | 200,082 (95.2) | 158,365 (96.7) | 158,549 (96.8) | 158,365 (96.7) |
|                                         | Yes            | 10,046 (4.8) | 5354 (3.3) | 5170 (3.2) | 5354 (3.3) |
| AIDS, n (%)                             | No             | 210,119 (100.0) | 163,713 (100) | 163,711 (100.0) | 163,713 (100.0) |
|                                         | Yes            | 9 (0.0) | 6 (0.0) | 8 (0.0) | 6 (0.0) |
| CHF, n (%)                              | No             | 201,807 (96.0) | 157,694 (96.3) | 157,776 (96.4) | 157,694 (96.3) |
|                                         | Yes            | 8321 (4.0) | 6025 (3.7) | 5943 (3.6) | 6025 (3.7) |
| CKD, n (%)                              | No             | 206,392 (92.2) | 161,763 (98.8) | 161,820 (98.8) | 161,763 (98.8) |
|                                         | Yes            | 3736 (1.8) | 1956 (1.2) | 1899 (1.2) | 1956 (1.2) |
| COPD, n (%)                             | 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 (%)        | No             | 188,530 (89.7) | 147,356 (90.0) | 147,158 (89.9) | 147,356 (90.0) |
|                                         | Yes            | 21,589 (10.3) | 16,363 (10.0) | 16,561 (10.1) | 16,363 (10.0) |
| 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) | 15,362 (9.4) | 15,448 (9.4) | 15,362 (9.4) |
| Dementia, n (%)                         | No             | 204,127 (97.1) | 160,313 (97.9) | 160,310 (97.9) | 160,313 (97.9) |
|                                         | Yes            | 6001 (2.9) | 3406 (2.1) | 3409 (2.1) | 3406 (2.1) |
| 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) | 168 (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            | 2326 (1.1) | 1358 (0.8) | 1329 (0.8) | 1358 (0.8) |
| Peptic ulcer disease, n (%)             | No             | 133,184 (63.4) | 106,698 (65.2) | 106,168 (64.8) | 106,698 (65.2) |
|                                         | Yes            | 6694 (26.6) | 4798 (26.8) | 4792 (26.8) | 4798 (26.8) |
Table 1 (continued)

| Characteristic                      | Overall cohort | Standardized difference | PS Unilateral TKA, n = 210 | Standardized difference | PS Bilateral TKA, n = 163 |
|------------------------------------|----------------|-------------------------|-----------------------------|-------------------------|---------------------------|
|                                    |                |                         | Unilateral TKA, n = 163     |                         | Bilateral TKA, n = 163    |
|                                    |                |                         | 719                         |                         | 719                        |
| Yes                                | 76,944 (36.6)  | 57,021 (34.8)           | 57,551 (35.2)               | 57,021 (34.8)           |                           |
| 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                                | 6059 (2.9)     | 4000 (2.4)              | 3899 (2.4)                  | 4000 (2.4)              |                           |
| Severe liver disease, n (%)        |                |                         |                              |                         |                           |
| 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 (%)                      |                |                         |                              |                         |                           |
| No                                 | 199,631 (95.0) | 15,670 (95.6)           | 156,681 (95.7)              | 15,670 (95.6)           |                           |
| Yes                                | 10,497 (5.0)   | 7149 (4.4)              | 7038 (4.3)                  | 7149 (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                                 | 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)            |                           |
| Charlson comorbidity score, mean ± SD |            | 5.25 ± 1.70             | 5.12 ± 1.59                 | 5.13 ± 1.59             | 5.12 ± 1.59               |
| Atrial fibrillation, n (%)         |                |                         |                              |                         |                           |
| No                                 | 207,033 (98.5) | 161,818 (98.8)          | 161,822 (98.8)              | 161,818 (98.8)          |                           |
| Yes                                | 3095 (1.5)     | 1901 (1.2)              | 1897 (1.2)                  | 1901 (1.2)              |                           |
| Valvular heart disease, n (%)      |                |                         |                              |                         |                           |
| 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 (%)      |                |                         |                              |                         |                           |
| No                                 | 208,925 (99.4) | 162,931 (99.5)          | 162,962 (99.5)              | 162,931 (99.5)          |                           |
| Yes                                | 1203 (0.6)     | 788 (0.5)               | 757 (0.5)                   | 788 (0.5)               |                           |
| Hypothyroidism, n (%)              |                |                         |                              |                         |                           |
| No                                 | 202,566 (96.4) | 157,928 (96.5)          | 157,988 (96.5)              | 157,928 (96.5)          |                           |
| Yes                                | 7562 (3.6)     | 5791 (3.5)              | 5731 (3.5)                  | 5791 (3.5)              |                           |

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
of prophylactic anticoagulant agents during the postoperative period compared with patients with unilateral 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 [22].

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 [23, 24]. Conversely, in previous studies with relatively small cohorts, significant differences were not reported in terms of cardiac complications between unilateral TKA and bilateral TKA [25, 26]. The large difference 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 because part of those subjects come from candidates for SiBTKA through a selective preoperative screening process. 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 (non-cardioselective β-blockers), not surprisingly, had a higher incidence of postoperative stroke resulting from inhibition of β2-mediated cerebral vasodilation [27]. 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 non-cardio-selective 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...
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 1000,000 person-years (95% CI)| 95% CI HR | 95% CI | p value | 95% CI p value for interaction |
|------------------------------|---------------------|------------------|-----------------------------------------------|-----------|--------|---------|---------------------------------
| Overall                      | 487,273,006         | 2531             | 5.19                                          | 4.99      | 5.40   | 0.79    | 0.73 0.85 < 0.001               |
| Unilateral TKA               | 235,758,899         | 1411             | 5.98                                          | 5.68      | 6.31   |         |                                |
| Bilateral TKA                | 251,514,107         | 1120             | 4.45                                          | 4.20      | 4.72   |         |                                |
| Age                          |                     |                  |                                               |           |        |         |                                |
| 40–49                        | 1,538,293           | 1                | 0.65                                          | 0.02      | 3.62   | NA      | 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         | 1536             | 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                          |                     |                  |                                               |           |        |         |                                |
| Male                         | 35,445,002          | 258              | 7.28                                          | 6.42      | 5.24   | 0.79    | 0.59 0.96 0.022               |
| Female                       | 451,828,004         | 2273             | 5.03                                          | 4.83      | 8.22   | 0.75    | 0.71 0.86 < 0.001            |
| Location                     |                     |                  |                                               |           |        |         |                                |
| Urban                        | 226,829,869         | 1078             | 4.75                                          | 4.47      | 5.04   | 0.82    | 0.73 0.93 0.001              |
| Rural                        | 260,443,137         | 1453             | 5.58                                          | 5.30      | 5.87   | 0.77    | 0.70 0.86 < 0.001           |
| Hospital size                |                     |                  |                                               |           |        |         |                                |
| 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         | 1555             | 4.98                                          | 4.74      | 5.24   | 0.75    | 0.68 0.83 < 0.001            |
| Insurance type               |                     |                  |                                               |           |        |         |                                |
| Health insurance             | 448,017,058         | 2236             | 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                       |                     |                  |                                               |           |        |         |                                |
| No                           | 133,406,439         | 669              | 5.01                                          | 4.64      | 5.41   | 0.77    | 0.66 0.90 0.001              |
| Yes                          | 353,866,567         | 1862             | 5.26                                          | 5.03      | 5.51   | 0.80    | 0.73 0.87 < 0.001            |
| Statin drugs                 |                     |                  |                                               |           |        |         |                                |
| No                           | 478,764,990         | 2458             | 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           |                     |                  |                                               |           |        |         |                                |
| No                           | 484,349,186         | 2504             | 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                      |                     |                  |                                               |           |        |         |                                |
| No                           | 481,724,149         | 2480             | 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        |                     |                  |                                               |           |        |         |                                |
| No                           | 486,788,236         | 2525             | 5.19                                          | 4.99      | 5.39   | 0.79    | 0.73 0.85 < 0.001            |
| Yes                          |                     |                  |                                               |           |        |         |                                |

Note: HR = Hazard Ratio; CI = Confidence Interval; p value for interaction is calculated using the cox proportional hazards model.
Table 2 (continued)

| Subgroup                  | Sum of person-years | Number of events | Incidence rate per 1000,000 person-years (95% CI) | 95% CI          | HR     | 95% CI          | p value | p value for interaction |
|---------------------------|---------------------|------------------|---------------------------------------------------|-----------------|--------|-----------------|---------|------------------------|
|                           |                     |                  |                                                   | HR              |        | HR              |         |                        |
|                           |                     |                  |                                                   | Lower           | Upper  | Lower           |         |                        |
| **Factor Xa inhibitor**   |                     |                  |                                                   |                 |        |                 |         |                        |
| Yes                       | 484,770             | 6                | 12.38                                             | 4.54            | 26.94  | 1.83            | 0.34    | 10.00                  | 0.484   | 0.973                  |
| No                        | 487,137,787         | 2530             | 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      | 1.000                  |
| **Direct thrombin inhibitor** |                 |                  |                                                   |                 |        |                 |         |                        |
| No                        | 487,264,451         | 2531             | 5.19                                              | 4.99            | 5.40   | 0.79            | 0.73    | 0.85                   | < 0.001 |
| Yes                       | 8555                | 0                | 0.00                                              | 0.00            | 431.20 | NA              | NA      | NA                     | NA      | 0.753                  |
| **Hypertension drugs**    |                     |                  |                                                   |                 |        |                 |         |                        |
| No                        | 471,886,519         | 2383             | 5.05                                              | 4.85            | 5.26   | 0.79            | 0.73    | 0.86                   | 0.082   | 0.467                  |
| Yes                       | 15,386,487          | 148              | 9.62                                              | 8.13            | 11.30  | 0.75            | 0.54    | 1.04                   | < 0.001 |
| **AIDS**                  |                     |                  |                                                   |                 |        |                 |         |                        |
| No                        | 487,254,281         | 2531             | 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      | 1.000                  |
| **CHF**                   |                     |                  |                                                   |                 |        |                 |         |                        |
| No                        | 469,984,045         | 2378             | 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   | 0.622                  |
| **CKD**                   |                     |                  |                                                   |                 |        |                 |         |                        |
| No                        | 482,451,662         | 2490             | 5.16                                              | 4.96            | 5.37   | 0.79            | 0.73    | 0.86                   | < 0.001 |
| Yes                       | 4821,344            | 41               | 8.50                                              | 6.10            | 11.54  | 0.68            | 0.36    | 1.26                   | 0.217   | 0.909                  |
| **COPD**                  |                     |                  |                                                   |                 |        |                 |         |                        |
| No                        | 302,399,164         | 1624             | 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   | 0.391                  |
| **Connective tissue disease** |                 |                  |                                                   |                 |        |                 |         |                        |
| No                        | 435,853,149         | 2308             | 5.30                                              | 5.08            | 5.52   | 0.80            | 0.73    | 0.87                   | < 0.001 |
| Yes                       | 51,419,857          | 223              | 4.34                                              | 3.79            | 4.94   | 0.71            | 0.54    | 0.92                   | 0.010   | 0.727                  |
| **CVA or TIA**            |                     |                  |                                                   |                 |        |                 |         |                        |
| No                        | 441,500,488         | 2133             | 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   | 0.606                  |
| **Dementia**              |                     |                  |                                                   |                 |        |                 |         |                        |
| No                        | 478,938,862         | 2447             | 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   | 0.229                  |
| **Hemiplegia**            |                     |                  |                                                   |                 |        |                 |         |                        |
| No                        | 486,728,204         | 2524             | 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   | 0.544                  |
| **Myocardial infarction** |                     |                  |                                                   |                 |        |                 |         |                        |
### Table 2 (continued)

| Subgroup                          | Sum of person-years | Number of events | Incidence rate per 1000,000 person-years (95% CI)<sup>a</sup> | 95% CI         | HR | 95% CI       | p value | p value for interaction |
|----------------------------------|---------------------|------------------|---------------------------------------------------------------|----------------|----|--------------|---------|------------------------|
|                                  |                     |                  |                                                              | Lower | Upper | Lower | Upper |                      |
| No                               | 483,269,362         | 2496             | 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             |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 309,899,308         | 1636             | 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      |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 432,394,256         | 2182             | 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                    |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 474,611,698         | 2481             | 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             |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 485,959,159         | 2525             | 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                           |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 468,096,910         | 2444             | 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                |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 486,212,605         | 2526             | 5.20                                                          | 4.99  | 5.40  | 0.79  | 0.73  | 0.85  | <0.001 |
| Yes                              | 1,060,401           | 5                | 4.72                                                          | 1.53  | 11.00 | 0.64  | 0.11  | 3.81  | 0.622  |
| Diabetes                         |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 359,206,894         | 1734             | 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       |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 454,116,703         | 2288             | 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              |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 483,244,151         | 2453             | 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           |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 487,184,407         | 2530             | 5.19                                                          | 4.99  | 5.40  | 0.79  | 0.73  | 0.85  | <0.001 |
| Yes                              | 88,599              | 1                | 11.29                                                         | 0.29  | 26.89 | NA    | NA    | NA    | NA     |
| Carotid artery disease           |                     |                  |                                                              |       |       |       |       |       |        |
| No                               | 485,545,773         | 2509             | 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  |
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 1-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.

### Conclusion

The risk of stroke was lower in patients treated with bilateral TKA (simultaneous and staged without discharge) 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. This is precisely what the guidelines will implement by South Korea for patient selection aim to do and our data show that the risk of stroke is not increased in selected patients undergoing SiBTKA and StBTKA without discharge.
Table 3  Association between unilateral TKA and bilateral TKA

| Surgery     | Univariable analysis | Multivariable analysis | Sensitivity analysis |
|-------------|----------------------|------------------------|---------------------|
|             | Crude HR 95% CI p value | Adjusted HR95% CI p value | Adjusted HR95% CI p value |
|             | Lower | Upper | Adjusted Lower | Adjusted Upper | Lower | Upper | Lower | Upper |
| Unilateral  | 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

*a* 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 with complication, Charlson comorbidity score, atrial fibrillation, carotid artery disease, hypothyroidism

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

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