Knee Surgery, Sports Traumatology, Arthroscopy (2019) 27:2082–2089
https://doi.org/10.1007/s00167-018-5333-4

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The use of bisphosphonates after joint arthroplasty is associated with lower implant revision rate

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Received: 14 August 2018 / Accepted: 7 December 2018 / Published online: 13 December 2018

Abstract

Purpose This study hypothesized that the use of bisphosphonates (BPs) after total joint arthroplasty (TJA) is associated with a lower implant revision rate. This study aimed (1) to investigate the association between BP use and the revision rate of TJA and (2) to determine the relationship between the medication period and the revision rate of TJA.

Methods National Health Insurance Service data on surgeries, medications, diagnoses, and screenings of 50 million Koreans were reviewed. People who underwent TJA in the period from 2002 to 2012 were identified and followed until 2016. During that period, 331,660 patients underwent total knee arthroplasty (TKA), and 56,043 patients underwent total hip arthroplasty (THA). Among them, 8447 knee patients (2.5%) and 2851 hip patients (5.0%) required revision surgery due to aseptic loosening. Demographic data, the duration of BP medication, and comorbidities were identified. The rate of revision surgery according to BP medication was investigated. The extended Cox proportional hazard model was used to evaluate the effect of the medication period.

Results The rate of TKA revision was 1.4% for BP users and 2.9% for BP non-users ($p < 0.001$). The THA revision rate was 2.8% and 5.3% for BP users and non-users, respectively ($p < 0.001$). The hazard ratio (HR) of revision was significantly lower in patients who took BP medication for more than one year (TKA HR = 0.472, 95% CI [0.350–0.637]; THA HR = 0.490, 95% CI [0.247–0.972]) compared to that in short-term users (less than 1 year).

Conclusions The use of BPs after TJA was associated with a lower revision rate. The use of BPs for more than one year further reduced the risk of revision. Bisphosphonate use can be highly recommended to reduce the revision rate of TJA.

Level of evidence Retrospective cohort study, Level III.

Keywords Arthroplasty · Revision · Bisphosphonate · National registry

Abbreviations

BP	Bisphosphonate
TJA	Total joint arthroplasty
NHIS	National Health Insurance Service
TKA	Total knee arthroplasty
THA	Total hip arthroplasty
HR	Hazard ratio
ICD	International classification of diseases
RCT	Randomized controlled trial

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Introduction

Total joint arthroplasty (TJA) is a popular surgical procedure to relieve pain and correct joint deformities. Annually, total knee arthroplasty (TKA) and total hip arthroplasty (THA) procedures are performed more than 400,000 and 200,000 times in the United States, respectively [8]. During the same period, 32,700 cases of revision TKA and 36,000 cases of revision THA are performed. As the number of primary cases and the population age increases, revision burdens are expected to grow rapidly [8, 13]. Among the causes of revision, aseptic loosening, which includes mechanical loosening and osteolysis by polyethylene wear, is the most common cause of implant failure [5, 22]. Despite advances in techniques and implants, revisions still occur in approximately 1–2% of primary TJA patients [8, 13].

The mechanism of aseptic loosening is complex and includes physical and biological responses [1, 12]. However, regardless of these factors, it is well known that enhanced osteoclast recruitment and activity adjacent to bone–implant interfaces leads to osteolysis and, ultimately, the loosening of implants [1, 12].

Bisphosphonates (BPs), a family of pharmacological compounds that strongly inhibit osteoclast activity, have recently garnered attention [4]. Several investigations, including meta-analyses and randomized controlled trials (RCTs), have suggested that BPs can increase periprosthetic bone mineral density and reduce periprosthetic bone loss and prosthetic migration [10]. However, these studies are limited by short- to mid-term follow-up, and they did not address clinically relevant outcomes, e.g., revision rate. There have also been several observational studies that investigated the association between bisphosphonate use and the risk of implant revision after TJA [7, 15, 20, 21]. However, the outcomes are inconsistent, and the quality of the studies varies. Therefore, current evidence regarding the use of BPs after TJA is not convincing.

This study aimed (1) to investigate the association between BP use and the revision rate of TJA, and (2) to determine the relationship between the medication period and the revision rate of TJA. This study hypothesized that the use of BPs after total joint arthroplasty (TJA) is associated with a lower implant revision rate. To test the hypothesis, national registry data from a population of 50 million were investigated.

Materials and methods

The study protocol was approved by the Institutional Review Board (Protocol No. E-1708-001-872).

National Health Insurance Service (NHIS) data are based on national health insurance claim data and include health care utilization, health screening, socio-demographic variables, medication, operation codes, and mortality data for more than 99% of Koreans (approximately 50 million). In this study, we utilized NHIS data to investigate whether BP intake in TKA and THA patients was associated with revision surgery by following patients until 2016. Patients who underwent primary TKA or THA from January 2002 to December 2012 were identified using the operation code classification system of the NHIS (Fig. 1). Subjects with operation codes N2072 and N2077 were defined as TKA patients, and those with N0711 and N2070 were defined as THA patients. TKA and THA patients were excluded if they satisfied any of the following conditions: less than 30 years of age; prior fracture or traumatic arthritis (International Classification of Diseases (ICD) code: S82 and M17.3); history of Paget's disease, rheumatoid arthritis, crystal-induced arthritis (ICD code: M10, M11, M12, M13, M14, M45, and M88), infective arthritis, reactive arthritis (ICD code: M00-M03), or osteonecrosis (ICD code: M87). We found that some patients had undergone bilateral surgeries, and the date of their first surgery was considered as the index date for our Cox regression. According to these criteria, 331,660 TKA patients and 56,043 THA patients were identified and

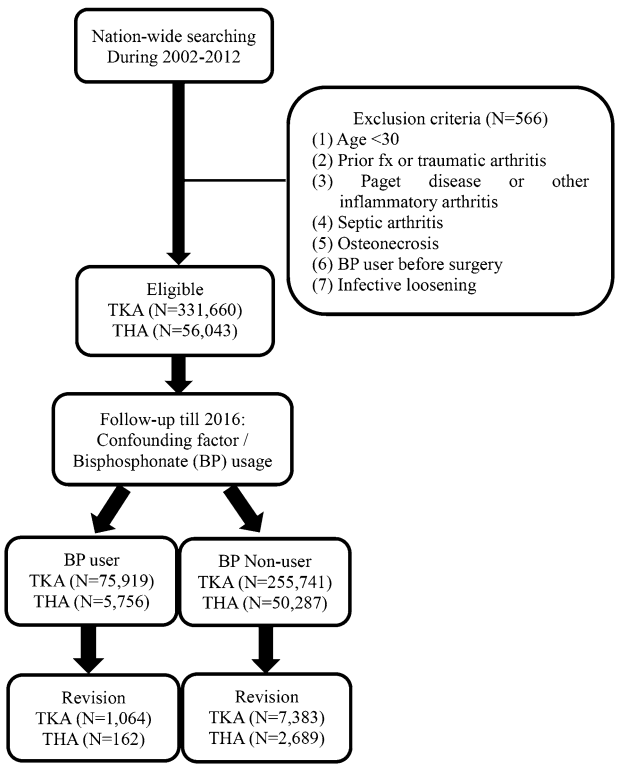

Fig. 1 Study flowchart

followed to determine whether they required revision surgery up to 2016 (Table 1).

The main objective was to identify the effect of oral or intravenous BP use on implant loosening. Medication codes were used to determine BP use in THA/TKA patients through December 2016. Regarding the medication codes for BP use, we defined M05BA for BP drugs and M05BB for combinations of BP drugs with calcium. Patients who used BPs before THA/TKA surgery were excluded from the analysis. Patients were considered to be BP users if they had received at least 1 WHO-defined daily defined dose of oral BP before THA/TKA revision surgery; otherwise, they were classified as BP non-users. There were 75,919 and 5756 BP users among the TKA and THA patients, respectively. The loosening of implants was identified through revision surgeries. Operation codes N3722, N3727, N4722, and N4727 for TKA and N1721, N1725, and N3720 for THA were used to identify revision surgeries. Patients were considered to have infectious loosening and excluded from the revisions for analysis if they had a simultaneous infection code (T85.7, T84.7, T84.5, M00-M03). Patients were censored for any follow-up loss.

Statistical analysis

The association between TKA/THA revision surgeries and the hazards of BP use on revision surgeries was estimated using the Cox regression model. Bisphosphonate use was coded using two different strategies: the absence/presence of BP use; and the duration of BP use from the first to last date of the BP prescription. We assumed that BP use may decrease the hazards of revision surgery and that the risk of revision surgery changed after BP use. The effect of BP use was estimated using an extended Cox regression model, where the time-varying coefficient for BP use of subject i was defined as $\beta \cdot I(t < t_i)$ or $\beta \cdot \delta_i I(t < t_i)$, where t_i indicates the time point when BP medication was started, and δ_i represents the duration of BP use.

Several covariates, such as smoking, alcohol intake, osteoporosis, and type of hospital setting, were considered to be potential confounders, and their effects were adjusted. Baseline age, sex, and BMI were also considered to be confounders. Hypertension was identified by ICD codes I10 and I15, and cardiovascular disease by ICD code I25. Diabetes was defined by ICD codes E10, E11, and E14. Smoking status was coded as 1 if the pack-years were greater than 10 or coded as 0 otherwise. Alcohol intake was coded as 1 if it was greater than or equal to twice a week or coded as 0 otherwise. Osteoporosis was identified by ICD codes M80, M81, and M82. Osteoporosis was coded as 1 if it was detected before TKA/THA, otherwise it was coded as 0. Hospitals were categorized into three different types: general hospital, hospital, and clinic. A general hospital is defined, by healthcare law, as a healthcare institution with more than 100 hospital beds. A clinic is defined as a healthcare institution with less than 30 hospital beds. A hospital is defined as a healthcare institution with more than 30 and less than 100 hospital beds. There can be differences in patient characteristics between the hospital types. It was assumed that the type of hospital was influenced by patient socioeconomic status and medical comorbidities, and their effects were adjusted by including them as covariates. All statistical analyses were conducted using SAS version 9.3 (SAS 9.3, SAS Institute, Cary, NC).

Results

In both TKA and THA, the revision rate was significantly lower in BP users (both $p < 0.001$) (Table 2). Regarding TKA, among the 75,919 BP users, 1064 underwent revision surgery, accounting for 1.4% of the total primary cases. However, in BP non-users, 7383 of 255,741 patients underwent revision surgery, accounting for approximately 2.9% of the total primary cases. In regard to THA, among 5756 patients classified as BP users, 162 underwent

Table 1 Clinical characteristics of the study subjects

	Total knee arthroplasty	Total hip arthroplasty
Primary arthroplasty (no. of patients)[a]	331,660	56,043
Revision arthroplasty (no. of patients)[b]	8447 (2%)	2851 (5%)
Age (years)[a]	68.8 ± 7.0	59.1 ± 12.6
Body mass index (kg/m^2)[a]	25.9 ± 3.3	24.0 ± 3.2
Female[a]	292,311 (88%)	25,682 (45%)
Bisphosphonate[b]		
User	75,919 (23%)	5756 (10%)
Non-user	255,741 (77%)	50,287 (90%)

SD standard deviation

[a]Baseline: 2002–2012

[b]Follow-up: 2016

Table 2 Revision rates and characteristics of bisphosphonate (BP) users and non-BP users after TJA

		BP users	Non-BP users	*P* value
TKA	Revision/primary (no. of patients)	1064/75,919 (1.4%)	7383/255,741 (2.9%)	< 0.001
	Age (years)	70.2 ± 6.1	68.3 ± 7.2	< 0.001
	Body mass index (kg/m^2)	25.4 ± 3.2	26.0 ± 3.3	< 0.001
	Female	72,103 (95%)	220,208 (86%)	< 0.001
	Diagnosis of osteoporosis at primary TKA	17,417 (23%)	21,652 (8%)	< 0.001
	Revision/primary (no. of patients)	162/5756 (2.8%)	2689/50,287 (5.3%)	< 0.001
THA	Age (years)	67.3 ± 9.4	58.1 ± 12.6	< 0.001
	Body mass index (kg/m^2)	23.6 ± 3.3	24.1 ± 3.2	< 0.001
	Female	4207 (73%)	21,475 (43%)	< 0.001
	Diagnosis of osteoporosis at primary THA	1072 (19%)	2213 (4%)	< 0.001

TKA total knee arthroplasty, *THA* total hip arthroplasty

revision surgery (2.8%). Of the 50,287 BP non-users, a significantly higher number of THA patients ($n = 2689$) underwent revision surgery (5.3%, $p < 0.001$). The average age was higher in the BP user group.

The Kaplan–Meier plot showed a decrease in implant survival over time, with both THA and TKA patients showing better survival in the BP group ($p < 0.001$) (Fig. 2).

A Cox proportional hazard analysis was performed to determine the hazard ratios (HRs) for the defined risk factors (Table 3). In regard to TKA, the HR of BP use was 0.752 compared to BP non-use ($p < 0.001$). The HR was further reduced if the medication period exceeded 1 year ($p < 0.001$, Fig. 3). The HR was lower in females compared to males ($p < 0.001$). Osteoporosis at the time of TKA showed an HR of 0.713 ($p < 0.001$), and THA demonstrated the same pattern. The HR of BP use was 0.693 ($p < 0.001$); it was further reduced to 0.490 if the medication period exceeded 1 year ($p = 0.043$).

Cox regression hazard models that included the type of hospital, drinking, and smoking are presented in a separate table because of the large number of missing values. Despite the missing values, the effect of BP use on revision surgery was the same for both THA and TKA patients (Table 4).

Discussion

The most important findings of this study were that BP use after TJA was associated with a lower revision rate, and taking BPs for more than 1 year further reduced the risk of revision. The hazard ratio of aseptic revision was reduced to 0.752 and 0.693 in TKA and THA patients, respectively. In addition, if the medication period exceeded 1 year, it

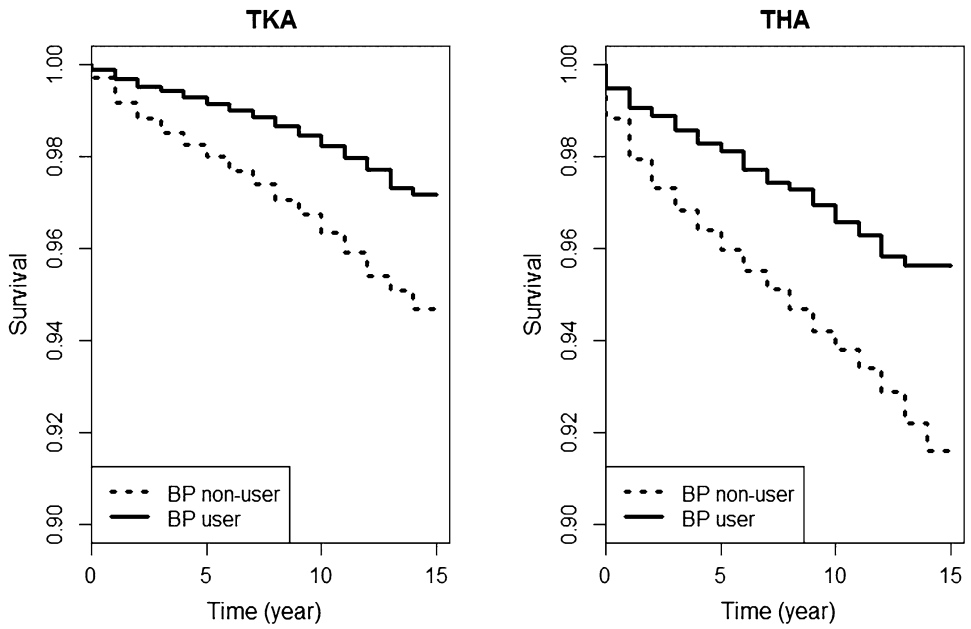

Fig. 2 Kaplan–Meier estimate by bisphosphonate (BP) use. BP users showed significantly reduced revision rates compared to BP non-users in both TKA and THA (both $p < 0.001$)

Table 3 Cox proportional hazard analysis

Model	Variable	HR (95% CI)	*P* value
TKA	BP	0.752 (0.704, 0.804)	< 0.001
	BP medication period (more than 1 year)	0.472 (0.350, 0.637)	< 0.001
	Sex		
	Male	1 (Referent)	
	Female	0.751 (0.705, 0.800)	< 0.001
	Age	1.091 (1.053, 1.132)	< 0.001
	Age^2	0.998 (0.998, 0.999)	< 0.001
	Osteoporosis		
	No	1 (Referent)	
	Yes	0.713 (0.661, 0.769)	< 0.001
THA	BP	0.693 (0.587, 0.818)	< 0.001
	BP medication period (more than 1 year)	0.490 (0.247, 0.972)	0.041
	Sex		
	Male	1 (Referent)	
	Female	0.682 (0.630, 0.738)	< 0.001
	Age	1.093 (1.063, 1.123)	< 0.001
	Age^2	0.999 (0.999, 0.999)	< 0.001
	Osteoporosis		
	No	1 (Referent)	
	Yes	0.817 (0.691, 0.964)	0.017

further reduced the risk of aseptic revision in TKA and THA patients to 0.472 and 0.490, respectively. These findings suggest that BP use after TJA can reduce the risk of aseptic loosening. Furthermore, extended BP use (> 1 year) can further reduce the risk of revision.

The correlation between BP use and the implant revision rate has been previously reported. To date, three cohorts and one case–control study have been reported. Prieto-Alhambra et al. reported a twofold increase in implant survival time and a 59% reduced risk of revision surgery with the use of BPs [14, 15]. Namba et al. reported that BP use was associated with low risk of revision regardless of osteoporosis [11]. Teng et al. reported the results of a meta-analysis in 2015 [20]. The adjusted relative risk for THA and TKA implant revisions was 0.47 and 0.45, respectively. They concluded that BP use was associated with a reduction in revisions [20].

However, different results have also been reported. Aro et al. reported randomized controlled trial (RCT) results for THA patients [2]. The test group received zoledronate, while the control group received a placebo, and both groups were followed for 4 years. The authors concluded that BP use had a partial effect in preventing periprosthetic bone loss but failed to show an increase in stability of the cementless femoral stem. Skoldenberg et al. reported similar results in THA patients [18]. Ren et al. reported a meta-analysis based on four RCTs and concluded that BP use could reduce periprosthetic bone resorption, but failed to show the results for more clinically relevant outcomes such as loosening or revision rate [16].

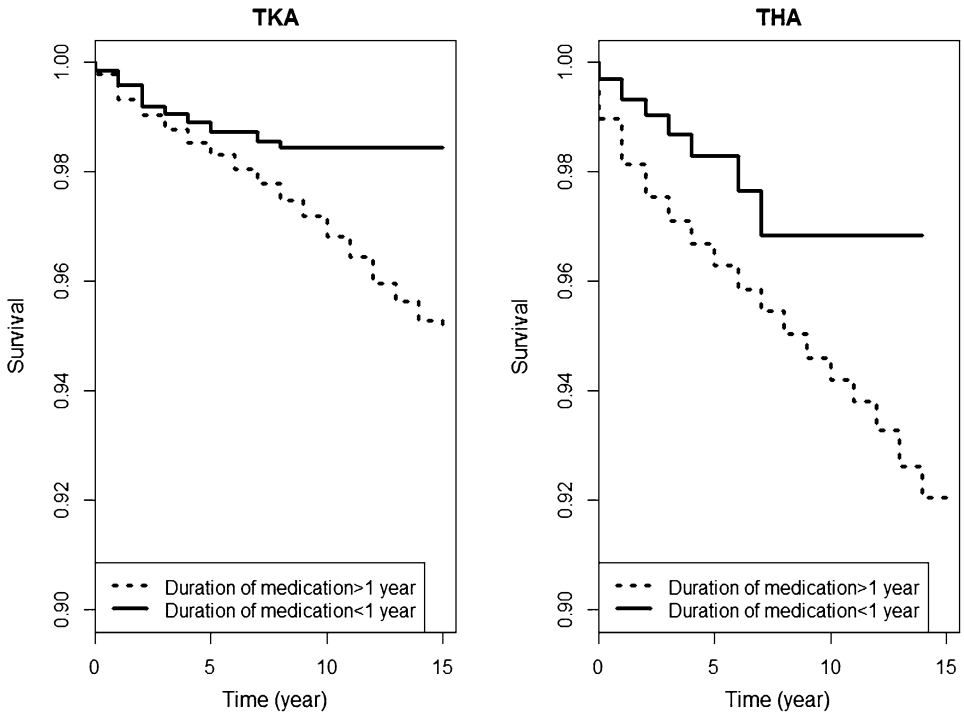

Fig. 3 Kaplan–Meier estimate by the duration of medication. A longer medication period (more than 1 year) further reduced the revision rate in both TKA and THA (both $p < 0.001$)

Table 4 Cox proportional hazard analysis including all variables

Model	Variable	HR (95% CI)	*P* value
TKA (*N* = 98,259)	BP	0.785 (0.679, 0.909)	0.001
	BP medication period (more than 1 year)	0.233 (0.088, 0.614)	0.003
	Sex		
	Male	1 (Referent)	
	Female	0.608 (0.533, 0.693)	< 0.001
	Age	1.077 (0.979, 1.186)	ns
	Age^2	0.999 (0.998, 0.999)	0.012
	BMI	0.998 (0.984, 1.013)	ns
	Osteoporosis		
	No	1 (Referent)	
	Yes	0.828 (0.705, 0.971)	0.021
	Hospital		
	General hospital	1 (Referent)	
	Hospital	0.792 (0.717, 0.876)	< 0.001
	Clinic	0.996 (0.827, 1.199)	ns
	Drinking	0.818 (0.664, 1.009)	ns
	Smoking	0.564 (0.454, 0.701)	< 0.001
THA (*N* = 12,024)	BP	0.788 (0.531, 1.166)	ns
	BP medication period (more than 1 year)	0.000 (0.000, Infinity)	ns
	Sex		
	Male	1 (Referent)	
	Female	0.612 (0.502, 0.744)	< 0.001
	Age	1.120 (1.031, 1.213)	0.007
	Age^2	0.999 (0.998, 0.999)	0.011
	BMI	1.000 (0.975, 0.103)	ns
	Osteoporosis		
	No	1 (Referent)	
	Yes	0.785 (0.530, 1.160)	ns
	Hospital		
	General hospital	1 (Referent)	
	Hospital	1.100 (0.907, 1.345)	ns
	Clinic	2.070 (1.283, 3.328)	0.003
	Drinking	0.712 (0.569, 0.891)	0.003
	Smoking	0.920 (0.735, 1.150)	ns

Such conflicting findings are possibly due to the small numbers of patients. Revision due to aseptic loosening is infrequent and occurs over time. Most RCT studies have shown differences in bone resorption but exhibit no clinically meaningful differences in loosening or revision. Therefore, evidence regarding differences in variables such as loosening could be considered weak. For this reason, a study that enrols a large number of patients followed for an extended period of time is necessary.

In this respect, two advantages are present in our study: (1) A total of 50 million patients were examined, and 387,000 joints were followed for 14 years. This is a large population size with a longer follow-up period than the existing report, which had only 30,000 patients. The entire Korean population is represented in this study, and there was no dropout other than immigration issues. Therefore, this study was more reliable compared to previous studies. (2) The computerization system of insurance claims made it possible to accurately evaluate the relevant variables.

It is shown in our report that for both TKA and THA, the revision rate was significantly lower in BP users (both $p < 0.001$). This is in line with previous observational studies, with an HR for BP use of 0.752 compared to BP non-use ($p < 0.001$) [11, 14, 15, 20]. It is biologically plausible that bisphosphonates have an anti-resorptive effect, by preventing osteoclast-mediated periprosthetic bone loss and osteolysis [3, 4]. Our report also supports this idea by showing the reduction of aseptic revisions in a large population. In addition, we also showed the effect of the medication period. In this study, a longer medication period (> 1 year)

further reduced the risk of revision ($p < 0.001$), which was observed equally in TKA and THA patients. The interesting and unique findings of this study were not reflected in previous studies. This may suggest that osteolysis induced by osteoclastic activity occurs over a long period of time. However, it should be noted that aseptic loosening is caused by a variety of factors, such as mechanical loosening and osteolysis by polyethylene wear. We think that the relationship between BP use and aseptic loosening is one of several pieces of the puzzle.

This study showed that males had a higher risk of revision surgery than females in both TKA and THA. The results were the same after including all variables and are consistent with most of the previous studies [6]. However, one study had an opposite conclusion, which may be related to the small sample size or use of mobile bearing TKA [19].

This study presents some limitations. First, although it is a cohort of the entire population, the causality cannot be evaluated because of the limitations of a retrospective cohort study. This can be proven through long-term, prospective studies of large populations. However, this study demonstrates the effect of the medication period for the reduction of revisions and can be considered as indirect evidence of causality. Second, aseptic loosening can be attributed to various factors, such as type of surgical implant, surgical technique, and general condition of the patient. In this study, we could not obtain a detailed evaluation of these factors. However, as shown in the supplemental data, even if more variables were considered, the influence of BP use would most likely remain the same in terms of decreasing the risk of revision. Third, to analyse large-scale data, the following definitions and assumptions were used: (1) it was impossible to distinguish between left and right sides through the codes. Therefore, even if both knees were operated on at different times, it was assumed that the first operation was revised first. (2) In the case of both TKA and THA revisions, there is a limitation that the case can be interpreted as only one index case. In a small number of samples, this assumption could cause a large error, but in a large cohort with 50 million samples, the probability that this assumption will cause an error is relatively constant between the groups. Therefore, it is unlikely that this would have caused a biased conclusion. Fourth, Table 4 should be interpreted with caution. Correction of the covariates in Table 4 significantly reduced the number of subjects. Because revisions happen with a very low incidence, the statistical power significantly decreases when the number of subjects is reduced. For example, the relationship between BP use and THA was insignificant. Smoking also reduced revision significantly in TKA but not in THA. Although not consistent with previous studies, direct comparisons are inadequate because the previous literature includes all causes of revision and focuses on postoperative complications [9, 17]. Hence, the results in Table 4 should be interpreted with caution and future studies are needed.

By observing the entire Korean population from 2002 to 2016, this study showed that BP medication was associated with a reduction in the aseptic loosening of TJA implants. Bisphosphonate use can be highly recommended to reduce the revision rate of TJA.

Conclusions

This study found that BP use after TJA was associated with a lower revision rate. In addition, taking BP medication for more than 1 year further reduced the risk of revision. Bisphosphonate use can be highly recommended to reduce the revision rate of TJA.

Author contributions DHR: Design, data acquisition, data interpretation, and drafting manuscript. HJ: Data acquisition and analysis and drafting manuscript. JYP: Data acquisition, analysis and interpretation. MCL: Data acquisition and data interpretation. SW: Data acquisition and analysis, data interpretation, drafting manuscript. HSH: Design, data acquisition, data interpretation, manuscript revision.

Funding This study was funded by a grant from the Seoul National University Hospital Research Fund (04-2017-0710).

Compliance with ethical standards

Conflict of interest The authors certify that they have no commercial associations that might pose a conflict of interest in connection with this article.

Ethical approval The study protocol was approved by the Institutional Review Board (Protocol No. E-1708-001-872).

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