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Comparative effectiveness of low, moderate and high molecular weight hyaluronic acid injections in delaying time to knee surgery

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Abstract

Background—We compared the effectiveness of low molecular weight (LMWHA), moderate molecular weight (MMWHA), and high molecular weight (HMWHA) hyaluronic acid for prevention or delay of knee surgery in patients with knee osteoarthritis (OA).

Methods—An observational cohort study using Lifelink Plus claims (2006-2015) was used. The primary outcome measure of the study included all surgical interventions of the knee. The secondary outcome measures were 1) unicompartmental (UKR) or total knee replacement (TKR) and 2) TKR only. A high dimensional propensity score (hdPS) using 1:1 matching was used to adjust for confounding. The likelihood of each outcome was assessed using Cox proportional hazard models.

Results—A cohort of 30,417 incident HA users with knee OA met our inclusion-exclusion criteria. There was no difference in the likelihood of composite surgical events between LMWHA users (HR: 0.939; 95%CI: 0.870-1.013) and MMWHA users (HR: 1.032; 95%CI: 0.952-1.119) when compared to HMWHA users in a matched hdPS analysis. However, a significantly lower likelihood for all outcome measures was demonstrated in LMWHA and MMWHA users compared to HMWHA users when hdPS was not used.

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Ethical review Committee Statement: The study protocol was reviewed and approved by the University of Arkansas for Medical Sciences Institutional Review Board, Little Rock, AR, USA.

Conflicts of Interest: No external funding was received for this study.

Conclusion—There was no significant difference in the likelihood of surgical interventions between LMWHA, MMWHA and HMWHA users after accounting for empirically derived confounders.

Keywords

hyaluronic acid; knee osteoarthritis; arthroplasty; Synvisc; Hyglan; knee surgery; comparative effectiveness; high dimensional propensity score

Introduction

Osteoarthritis is a degenerative joint disease in which the cartilage that cushions the bones wears off and the bones rub against each other resulting in pain and stiffness.[1] Hyaluronic acid (HA) is naturally present in the knee joint and it binds to intracellular fluid to provide flexibility and compressibility to the cartilage.[2] HA not only acts as a chondroprotective agent but also has anti-inflammatory, anabolic, and analgesic actions.[3] In OA, synovial inflammation increases the concentration of proteolytic enzymes, cytokines and free radicals as well as increases the permeability of HA through the synovial membrane.[4,5] This inflammation causes reduction in both, the concentration as well as the molecular weight of HA in the joints.[4–6]

Replacing reduced HA in synovial joints through intra-articular administration of HA is called viscosupplementation.[7] Various low molecular weight (LMWHA), moderate molecular weight (MMWHA), and high molecular weight (HMWHA) hyaluronic acid injections are now available in the market for viscosupplementation. The LMWHA include Hyglan (MW: 0.5-0.7 million Daltons) and Supartz (MW: 0.6-1.2 million Daltons); MMWHA includes Euflexxa (MW: 2.4-3.6 million Daltons), Orthovisc (MW: 1-2.9 million Daltons), and Monovisc (MW: 1-2.9 million Daltons); and HMWHA include Synvisc and Synvsic–One (MW: 6 million Daltons).[8] There is conflicting biologic evidence to support use of LMWHA, MMWHA or HMWHA. Based on in-vitro studies, the optimum molecular weight of HA to have a high binding affinity and to stimulate production of endogenous HA is 0.5-4 million Dalton, which supports the use of LMWHA and MMWHA formulations.[8,9] Conversely, others postulated that HMWHA would restore the rheological properties of synovial fluid by increasing its elastoviscosity.[8,10] However, limited data exist to support either of these theories. Very few randomized controlled trials compare the efficacy of different molecular weight hyaluronic acids. Of those that exist, there is lack of consistency in the results. For example, one of the trials reported that HMWHA was more efficacious in pain reduction than LMWHA.[11] Whereas two other trials found no significant difference between the efficacies of HMWHA and LMWHA [12], [8]. In practice, similar rates of use have been observed for different molecular weight HA products; with HMWHA being the most commonly used HA (40%), followed by MMWHA (30%) and LMWHA (30%) .[13]

In order to address the lack of evidence comparing different molecular weight HA products, we compared the effectiveness of LMWHA, MMWHA, and HMWHA for the management of knee OA. The primary outcome measure was receipt of any knee surgical (composite) intervention, which is generally considered if non-surgical interventions, including HA

injections, fail to manage knee OA. We also assessed the effectiveness of these injections using two additional secondary outcome measures which are more invasive surgical interventions: 1) Unicompartmental (UKR) and total knee replacement (TKR) and 2) TKR only.

Methods

Study design

The effectiveness of LMWHA, MMWHA, and HMWHA for management of knee OA was compared using an observational cohort study design. A random 10% sample of Lifelink Plus claims data (2006-2015) comprising 150 million commercially insured enrollees was used for the study. Enrollment information, prescription claims, and inpatient and outpatient claims were collected. A detailed description of the data source is described previously.[13,14]

Study subjects

Incident users of HA with a diagnosis of knee OA (ICD-9-CM code 715.x6) were identified between July 1, 2006 and February 28, 2015. Baseline characteristics and knee OA diagnosis were obtained using claims during the six-month period prior to or on the index date (date of first HA claim). The operational definitions used for case findings in the inclusion and exclusion criteria are presented in Appendix A.

Definition of Exposure

HA use was defined based on the presence of a claim in which there was a knee OA diagnosis, and a procedure code for an intra-articular injection and a code for a HA product defined below.[15] The molecular weight categorization of HA was defined as; HMWHA: Synvisc and Synvisc-One, (HCPCS codes: J7320, J7322, J7325, and Q4084, Manufacturer: Genzyme Biosurgery, Ridgefield, NJ, USA); MMWHA: Orthovisc (HCPCS codes: Q4086 and J7324; Manufacturer: Anika Therapeutics, Woburn, MA, USA), Euflexxa (HCPCS codes: Q4085 and J7323, Manufacturer: Ferring Pharmaceuticals, Parsippany, NJ, USA), Monovisc (HCPCS code: J7327, Manufacturer: Anika Therapeutics, Woburn, MA, USA), or Gel-one (HCPCS code: J7326, Manufacturer: Zimmer Inc. IN, USA); LMWHA Hyglan (HCPCS codes: J7317, Q4083, and J7321, Manufacturer: Fidia Pharma Inc., Parsippany, NJ, USA) or Supartz (HCPCS codes: J7317, Q4083, and J7321, Manufacturer: Bioventus, Durham, NC, USA).[16,17]

Outcome measures

Any surgical intervention, which included arthroscopic knee procedures, osteotomy, free-floating interpositional devices, and UKR and TKR were considered together as a composite surgical intervention and used as the primary outcome measure. Two secondary outcome measures: 1) UKR/TKR and 2) TKR were investigated. The rationale for choosing these as outcome measures has been described previously.[18] The operational definitions were based on previously published studies[19–23] or reimbursement codes used by insurance companies. (Appendix B) A licensed medical coder at our university hospital verified the definitions used for the outcome measures. For each outcome, patients were followed from 4

weeks after an HA injection (so that we can attribute the effect to HA exposure) until the date of the first outcome event, the study end date, or until the subject was no longer enrolled. The 4-week time point was chosen based on the minimum cut off time beyond which the HA injections have demonstrated either superiority or non-inferiority in the clinical trials.[24]

Other covariates

Age, sex, patient region, year of injection, Charlson comorbidity index score, cerebrovascular disease, neoplasms, cardiac dysrhythmias, deep vein thrombosis, sleep disorders, other diseases of the musculoskeletal system and connective tissues, fatigue, back pain, cervical pain, fibromyalgia, painful neuropathic disorders, hypertension, ischemic heart disease, valve disease, hyperlipidemia, diabetes mellitus, obesity, depressive disorders, anxiety disorders, migraine, congestive heart failure, arthritis (other than osteoarthritis), diseases of the musculoskeletal system and connective tissues, other body/joint pain, headache, chest pain, abdominal pain, sprains and strains, dislocation, fractures, use of corticosteroids (CS), NSAIDs, opioids, anticoagulants, antidiabetics, antimigraine, antipsychotics, loop diuretics, and conservative interventions were a-priori identified as potential confounders and used to characterize patients (Appendices C and D). [19,25–27]

Analysis

T-test, anova and chi-square tests were used to compare the characteristics of LMWHA, MMWHA, and HMWHA users. A hdPS matching approach was used to reduce the residual confounding between the three HA users by using a large number of empirical covariates (n=500). [28] Because hdPS can only be estimated for two groups, the most commonly used HA formulation (HMWHA) was used as a reference and estimated hdPS for two cohorts: LMWHA vs. HMWHA users and MMWHA vs. HMWHA users. The hdPS for each cohort was based on predefined covariates described above and 500 empirically derived covariates. (Appendices E and F) A 1:1 greedy matching approach within a predefined caliper (0.2 of the pooled standard deviation of the logit of the hdPS) was used. Characteristics of the two group comparisons were compared for both unmatched and hdPS-matched samples using a standardized difference (SD) with a cut-off value of 10. [29]

Cox proportional hazard models were used to assess the likelihood of each outcome (composite surgical outcome measure, UKR/TKR, and TKR only) among LMWHA users, MMWHA users, and HMWHA users (reference group). Four models for each outcome definition were constructed: 1) unmatched sample using an unadjusted analysis without controlling for any covariates, 2) unmatched sample using an adjustment for Charlson co-morbidity index score and predefined potential confounders, 3) hdPS-matched sample and 4) inverse probability weighting (IPW using the inverse of hdPS).

Sensitivity Analyses

Four additional sensitivity analyses were conducted to assess the robustness of the study findings. Literature suggests that HA injections may provide pain relief for up to six months. [30–32], a separate analysis wherein patients were followed until the date of their first event, six months after the last dose of HA injection, the study end date, cessation of insurance

benefits, or a switch to the alternate HA treatment, whichever came first, was conducted. An additional analysis to account for time varying effect of HA exposure was performed. Patient-time was classified into five treatment windows: LMWHA, MMWHA, HMWHA, no exposure widow, and combination of two or more HA injections of different molecular weights. Third, because the secondary outcome definitions (UKR/TKR and TKR) may have other surgical interventions competing with outcome event, competitive risk models were used, as these models account for patients who are censored due to competing events. [33,34] Finally, we conducted a sensitivity analysis restricting the analysis to patients who received at least the minimum number of recommended LMWHA (3 injections), MMWHA (3 injections) and HMWHA (1 injection) injections. Patients were followed until the date of their first event, the study end date, or until a patient was no longer enrolled, whichever came first. Two falsification tests were performed to determine if two identified variables (asthma and intracranial hemorrhage) that are highly unlikely to be causally related to receipt of different HA formulations actually were related to HA formulation receipt.

Results

Baseline Characteristics

A cohort of 30,417 incident HA users with knee OA met the inclusion-exclusion criteria, (Appendix G) which included 12,410 HMWHA users, 9,127 MMWHA users, and 8,526 LMWHA users (Table 1). LMWHA use was more prevalent prior to 2010, HMWHA more prevalent from 2010 to 2012 and MMWHA more prevalent after 2012 (Table 2). The three groups did not differ in terms of Charlson co-morbidity index score and all pain conditions except MMWHA were less likely to have chest pain (13.16% vs. 14.35%; p value =0.002) and more likely to have dislocations compared to HMWHA (16.51% vs. 14.16%; p value < 0.001; Appendix H). MMWHA users (61.94%; p value < 0.001) were more likely to use CS injections than LMWHA (57.1%; p value < 0.001) and HMWHA (60.4%). We were able to match 84.8% (n=7,235) of LMWHA users and 85.4% (n=7,796) of MMWHA users with HMWHA users using the hdPS algorithm. After matching, no statistically significant difference in any characteristics between LMWHA-HMWHA users and MMWHA-HMWHA users existed (standardized difference less than 10; Appendix I).

Base Case Analysis

In the base case analysis, LMWHA users (HR: 0.885; 95% CI: 0.840-0.932) and MMWHA users (HR: 0.904; 95% CI: 0.857-0.953) demonstrated a significantly lower likelihood of composite surgical events compared to HMWHA before adjusting for any confounders (Table 3). After adjusting for the potential confounders using standard cox models, LMWHA and MMWHA use still demonstrated significantly a lower likelihood of the composite endpoint compared to HMWHA users. The difference in the likelihood of composite surgical events disappeared when LMWHA use (HR: 0.939; 95% CI: 0.870-1.013) and MMWHA use (HR: 1.032; 95% CI: 0.952-1.119) were matched 1:1 with HMWHA use using the hdPS. Further, LMWHA (HR: 0.990; 95% CI: 0.941-1.041) and MMWHA use (HR: 0.987; 95% CI: 0.937-1.045) also failed to demonstrate any benefit over HMWHA use when inverse proportional weighting was used. Restricting the outcome definition to UKR/TKR yielded results consistent with the base case analysis. Similarly,

LMWHA and MMWHA use demonstrated a significantly lower likelihood of TKR compared to HHWHA use in unadjusted and adjusted analyses but failed to demonstrate any benefit when hdPS or inverse proportional weighting analyses were performed.

Sensitivity Analyses

When additional censoring criteria (180 days after last HA exposure or switch to alternate HA) were applied, LMWHA use was associated with a lower likelihood of the primary outcome measure (adjusted HR: 0.898; 95% CI: 0.823-0.979) but not with any secondary outcome compared to HMWHA (Appendix J). After adjusting for potential confounders, MMWHA did not demonstrate risk reduction for any outcome measure. However, in the time varying exposure analysis both LMWHA (adjusted HR: 0.824; 95% CI: 0.763-0.891) and MMWHA use (adjusted HR: 0.911; 95% CI: 0.845-0.981) were associated with a lower likelihood of composite surgical outcomes compared to HMWHA (Appendix K). But again, MMWHA use failed to demonstrate a significantly different benefit from HMWHA use when the outcome definitions were restricted to UKR and TKR (adjusted HR: 0.922; 95% CI: 0.840-1.011) or TKR (adjusted HR: 0.915; 95% CI: 0.832-1.006) with the time varying exposure approach. Accounting for competing events for secondary outcome measure or restricting to patients who receive at least minimum number of HA injections resulted in findings consistent with the base case analyses that did not incorporate hdPS demonstrating a significant risk reduction of all outcome measures among LMWHA and MMWHA users compared to HMWHA users (Appendices L and M). The falsification test assessments did not detect significant relationships between the molecular weight of HA and the risks of asthma or intracranial hemorrhage (Appendix N) indicating that residual confounding is less likely to account for reported differences in treatment groups.

Discussion

The likelihood of surgical interventions did not vary between LMWHA, MMWHA, and HMWHA use in a cohort of knee OA patients when we accounted for known confounders and a broad range or empirically derived confounders using hdPS scores in the matched and IPW analyses. This was true for the primary outcome measure that included any surgical intervention as well as secondary outcome measures that were restricted to UKR/TKR and TKR only. Using the hdPS minimizes the potential for residual confounding by empirically identifying potential proxies available in our datasets that may be the best approximation to large randomized clinical trials. [8,12,35] For example, severity of knee OA cannot be directly measured in the current dataset but the empirical confounders identified by hdPS algorithm such as number of X-ray exams, physical therapy and nerve block injections may be proxy measures for the severity of knee OA. When hdPS scores were not used, LMWHA and MMWHA use demonstrated a significantly lower likelihood of surgical interventions suggesting that standard analysis may be biased due to residual confounding.

Though our study is one of few to test for the differences between HA formulations on knee OA surgeries, the preponderance of clinical trial literature which most often focuses on functioning and symptom relief is consistent with our main findings which did not detect differences between HA formulations. A systematic review of randomized controlled trials

that evaluated the efficacy of LMWHA, HMWHA, and placebo only found one out of 4 trials that suggested efficacy was different between the medication classes.[36] No significant differences between LMWHA and HMWHA in pain, stiffness, or physical function assessed by The Western Ontario and McMaster University Osteoarthritis (WOMAC) index were found in the review. Caution is warranted when interpreting pooled and summarized results of multiple trials because most of the trials comparing an HA product with another HA formulation or placebo only were powered to assess the agents' impact on primary outcome measures that differed between trials, used different classification systems to assess the severity of knee OA, and had varying follow-up periods. [36,37] Different outcome measures and different time points at which the outcomes were measured could explain heterogeneity in the trial findings.[37] However, there are exceptions to note. One of the trials concluded that HMWHA was significantly more efficacious ($p < 0.05$) than LMWHA for all the primary outcome measures (pain and knee movement) and overall treatment assessment.[11] Limitations of this trial included its small sample size (n=32) and short follow-up period (12 weeks) and the use of non-recommended dosing frequencies. [11]

Conversely, there are also observational studies that have compared HA formulations that compared time to TKR, that allows for a direct comparison to one of our secondary outcome measures. One used the same data source (Lifelink Plus claims) and they found LMWHA and MMWHA use was associated with longer delays in TKR compared to HMWHA use. [38] Another observational study compared the effectiveness of Euflexxa (MMWHA) with other HA products (Orthovisc, Monvisc, Hyglan and Synvisc) and found that Euflexxa delayed receipt of a TKR (1.8 months; 95% CI: 0.3-3.3 months).[39] Inadequate control of residual confounding and introduction of potential bias (selective loss to follow up) in the previous studies [38], [39] could explain the difference in our study findings. In both of these studies, all patients were required to have received a TKR in an attempt to restrict their analyses to patients with severe knee OA. [38], [39]. This may result in biased estimates if the proportion of patients losing enrollment or receiving TKR outside the study period is not balanced across the comparison groups. In order to avoid the bias due to potential loss to follow up, we accounted for person follow-up time of patients who did not undergo TKR in the study period as well. Along with the severity of knee OA, other factors such as physician preference, patient preference, or health plan benefit could impact the timing and receipt of a TKR [40] and thus may result in residual confounding if not adequately controlled. Rather than restricting our study to patients with TKA, we used the high dimensional propensity scores to account for pre-defined and empirical confounders to account for most of the potential confounders and could be a reason for the differences in our hdPS adjusted estimates and those from the observational studies. [38], [39] Also the previous observational studies did not consider other surgical knee interventions which could complete with TKR and delay the time-to-TKR [38], [39] whereas our composite outcome measures included all the types of surgical knee interventions.

In our study sample, the median number of injections per treatment for LMWHA (5 injections per treatment) and MMWHA (3 injections per treatment) injections were higher compared to HMWHA (2 injections per treatment), which may have resulted in a longer “wait and see” period before patients opted for a surgical intervention, often the final

management strategy. The longer “wait and see” period with LMWHA followed by MMWHA and then HMWHA could be one of the reasons why we found a lower likelihood of composite outcome measure among LMWHA users when additional censoring criteria (censor 180 days after last injection) or a time varying approach was included in the sensitivity analyses.

Our study findings should be interpreted in light of the following limitations. First, we used surgical intervention as a proxy for changes in disease progression, pain, discomfort, and stiffness to assess the effectiveness of HA injections. We selected these outcome measures because they are events that are reliably recorded in the data source and have been used as outcome measures in other knee OA comparative studies. [38, 39] This may not be the most accurate indicator to assess the effectiveness but we used a broad and sensitive definition of primary outcome to detect any indication of treatment failure. Second, we did not have direct indicators to measure the severity of knee OA or pain scores. There may be factors that are not strongly associated with disease progression, pain, discomfort, or stiffness (for example patient preference, physician practice, or insurance plan coverage), which could also influence the decision to undergo a surgical intervention. In light of these limitations and the potential for treatment groups to not be comparable, an hdPS was developed to account for residual confounding inherent in unmeasured factors in the LifeLink Plus claims database. Third, we were also not able to control for over-the-counter medication interventions (for example, acetaminophen, NSAIDs) and non-pharmacological interventions (for example, exercise and weight loss programs) used for knee OA management that were not available in the LifeLink Plus claims database. Fourth, we also did not compare the effectiveness of HA formulations from different sources (avian versus non-avian). Fifth, approximately 70% of our included subjects were less than 65 years old and our findings may not be applicable for an older population. Lastly, we did not compare the effectiveness of HA injections over other interventions (for example, intra-articular corticosteroid injections) or no intervention, which by itself remains a controversial question.[18] In spite of these limitations, our study findings may help clinicians and payers choose between different HA injections based on the other product attributes (for example, one-dose injections versus multi-dose injections) and cost; given that there is no difference in their effectiveness to delay knee surgeries.

Conclusion

There were no significant differences in the likelihood of surgical interventions between LMWHA, MMWHA, and HMWHA users with knee OA after accounting for the baseline characteristics of patients using an hdPS algorithm. Based on these findings, factors other than time to knee surgery should be used in selecting an HA formulation by payers or clinicians.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Event rates among LMWHA, MMW HA and HMWHA users with knee OA

Exposure	N	Person years	Composite event rate/1000 PY	UKR/TKR rate/1000 PY	TKR rate/1000 PY
LMWHA	8526	17422	136.55	97.64	94.36
MMWHA	9127	14348	150.33	103.71	98.83
HMWHA	12410	22357	159.59	116.34	111.06

Note: Data represents events rates expressed in events per 1000person years. LMWHA users: Intra-articular low molecular weight hyaluronic acid injection users, MMWHA users: Intra-articular moderate molecular weight hyaluronic acid injection users, HMWHA users: Intra-articular high molecular weight hyaluronic acid users, OA: Osteoarthritis, Composite: includes any surgical interventions arthroscopic procedures, osteotomy, free floating interpostinal device, unicompartmental or total knee replacement, UKR/TKR: includes unicompartmental or total knee replacement, TKR: total knee replacement

Table 2
Demographic characteristics of LMWHA, MMWHA and HMWHA users

Characteristics	LMWHA	MMWHA	HMWHA
N, %	8526 (28.36)	9127 (30.36)	12410 (41.28)
Age (mean, SD)	59.36 (9.46)	59.00 (9.57)	59.43 (9.45)
Age: 40-54 years	2651 (31.09) *	3017 (33.06) *	3869 (31.18)
55- 64 years	3830 (44.92)	3993 (43.75)	5446 (43.88)
65-74 years	1234 (14.47)	1354 (14.84)	1998 (16.10)
75 or more	811 (9.51)	763 (8.36)	1097 (8.84)
Female	5111 (59.95)	5552 (60.83) *	7382 (59.48)
Region: East	1811 (21.24) *	2284 (25.02) *	3132 (25.24)
South	2739 (32.13)	2764 (30.28)	3403 (27.42)
West	924 (10.84)	1086 (11.90)	1440 (11.60)
Midwest	2932 (34.39)	2584 (28.31)	4356 (35.10)
Unknown	120 (1.41)	409 (4.48)	79 (0.64)
Index year: 2006	280 (3.28) *	0 (0.00) *	290 (2.34)
2007	1031 (12.09)	431 (4.72)	1085 (8.74)
2008	1471 (17.25)	755 (8.27)	1408 (11.35)
2009	1451 (17.02)	935 (10.24)	1121 (9.03)
2010	1147 (13.45)	988 (10.83)	1926 (15.52)
2011	975 (11.44)	1221 (13.38)	1823 (14.69)
2012	790 (9.27)	1398 (15.32)	1702 (13.71)
2013	720 (8.44)	1499 (16.42)	1494 (12.04)
2014	506 (5.93)	1499 (16.42)	1220 (9.83)
2015	155 (1.82)	401 (4.39)	341 (2.75)

Note: LMWHA: Low molecular weight hyaluronic acid injection user, MMWHA: Moderate molecular weight hyaluronic acid injection user, HMWHA: High molecular weight hyaluronic acid injection use. Data compares LMWHA to HMWHA and MMWHA to HMWHA.

* indicates p value <0.05

Table 3

Risk surgical intervention among LMWHA, MMWHA and HMWHA users

Event	Exposure	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	hdPS matched HR (95% CI)	Inverse hdPS wt. HR (95% CI)
Composite	LMWHA (n= 8526)	0.885 (0.840-0.932)	0.882 (0.836-0.929)	0.939 (0.870-1.013)	0.990 (0.941-1.041)
	MMWHA (n=9127)	0.904 (0.857-0.953)	0.901 (0.853-0.951)	1.032 (0.952-1.119)	0.987 (0.937-1.045)
	HMWHA (n=12410)	*Reference*	*Reference*	*Reference*	*Reference*
UKR or TKR	LMWHA (n= 8526)	0.861 (0.810-0.916)	0.866 (0.814-0.921)	0.941 (0.858-1.031)	0.998 (0.940-1.059)
	MMWHA (n=9127)	0.863 (0.810-0.920)	0.873 (0.818-0.931)	1.072 (0.970-1.184)	0.996 (0.937-1.060)
	HMWHA (n=12410)	*Reference*	*Reference*	*Reference*	*Reference*
TKR	LMWHA (n= 8526)	0.872 (0.819-0.928)	0.879 (0.825-0.936)	0.967 (0.881-1.062)	1.016 (0.957-1.080)
	MMWHA (n=9127)	0.862 (0.808-0.921)	0.873 (0.817-0.933)	1.074 (0.970-1.190)	1.006 (0.944-1.072)
	HMWHA (n=12410)	*Reference*	*Reference*	*Reference*	*Reference*

Note: LMWHA: Low molecular weight hyaluronic acid injection user, MMWHA: Moderate molecular weight hyaluronic acid injection user, HMWHA: High molecular weight hyaluronic acid injection user, hdPS: high dimensional propensity score, Composite: Includes arthroscopic procedures, osteotomy, freefloating interpositional devices, partial and total knee replacement, UKR or TKR: Partial or total knee replacement, TKR: Total knee replacement. , Adjusted: These models account for age, sex, patient region, physician type, year of index diagnosis, cerebrovascular disease, neoplasms, cardiac dysrhythmias, obesity, deep vein thrombosis, use of anticoagulants, hypertension, ischemic heart disease, valve disease, hyperlipidemia, diabetes mellitus, congestive heart failure, chest pain back pain, cervical pain, fibromyalgia, painful neuropathic disorders, other body/joint pain, other diseases of the musculoskeletal system and connective tissues, trauma (sprains and strains), dislocations and fracture, fatigue and Charlson comorbidity scores