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Prevalence and Perioperative Outcomes of Off-Label Total Hip and Knee Arthroplasty in the United States, 2000–2010

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Abstract

“Off-label use” refers to medical device utilization for purposes or subpopulations other than those approved by the United States Food and Drug Administration. The primary goal of this study was to determine the current epidemiology of off-label total hip and knee arthroplasty (THA and TKA, respectively) in the United States and to project further off-label use through 2040. Over the past decade, the prevalence of off-label THA and TKA was 30.4% and 37.0%, respectively, growing ~70% from 2000–2010. By 2040, the majority of THA (86.1%) and TKA (91.5%) could be off-label. The high prevalence of off-label arthroplasty and the dramatically shifting patient profile illustrated by these results highlight the need for continued medical device surveillance among on- and off-label patients.

INTRODUCTION

Utilization of a medical device or drug outside the scope of indications or population subgroups specifically approved by the United States (US) Food and Drug Administration (FDA) is considered “off-label use.”¹ This legal usage is documented in many treatments across health specialties (e.g., cardiology, pediatrics, orthopaedics, etc.) and is typically considered acceptable if the physician is prescribing or caring for patients in a well-informed, medically appropriate manner based on scientific rationale.²⁵ Scrutiny of off-label use in orthopaedics, has increased in recent years, with many orthopaedic conferences and journals now requiring transparency of off-label usage when presenting research.⁶

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Over the last few decades, the surgeon's definition of an appropriate total hip and knee arthroplasty (THA and TKA, respectively) patient has expanded. The current and projected prevalence of primary THA and TKA in the US^{7,8} reflects not just the growing arthritic population, but also an increasingly heterogeneous total joint patient population. With significant improvements in bearing surfaces, fixation techniques, surgical approaches, and postoperative care practices, THA and TKA are becoming increasingly offered to what was once considered non-traditional patients (e.g., young, multiple comorbidities, history of solid organ transplant, etc.).^{8–11}

While indications of total joint arthroplasty have evolved, implant labeling has largely remained unchanged. Rapid advancements in technology, manufacturer-driven device labeling, and sparse financial incentive have led most orthopaedic implants to be cleared for marketing and sale through the 510(k) process. The 510(k) pathway offers a quicker, less burdensome, and cheaper alternative to premarket approval for eligible devices.¹² Rather than submitting a premarket approval application that contains detailed information about the device's design, manufacturing process, safety, and efficacy,¹³ the 510(k) process requires device manufacturers to only provide evidence of substantial equivalence in materials, purpose, and mechanism of action to a predicate device previously approved for use.¹² With the 510(k) process, the predicate device labeling is conserved, causing today's implant indications and contraindications to mirror those from decades ago. Contraindicated total joint reconstruction criteria include conditions inherently predisposed to falling, infection, implant loosening, noncompliance, and inadequate fixation (Appendix 1).

After decades of arthroplasty evolution and relatively fixed FDA-approved indications, off-label implant usage is believed to be common in primary THA and TKA. However, there are no documented studies that examine and quantify the national impact of off-label use in this orthopaedic population. The objectives of this study were to characterize the current prevalence, resource utilization (i.e., length of stay [LOS] and cost), perioperative complication risk, and inpatient facility discharge rate of off-label THA and TKA in the US. Additionally, we sought to estimate future off-label primary total joint reconstruction usage rates through 2040.

METHODS

The Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP) (US Agency for Healthcare Research and Quality) was utilized in this cross-sectional secondary data analysis. This national administrative database is the largest all-payer inpatient care database, representing a 20% stratified sample of discharges from US non-Federal, short-term, general, and other specialty hospitals.¹⁴ Our institutional review board deemed this study exempt from approval as it used non-identifiable information obtained from a public source.

Study Population

Diagnosis and procedure information was captured using *International Classification of Disease, 9th Revision, Clinical Modification* (ICD-9-CM) codes. NIS data from 2000 to 2010 were retrospectively queried for all primary THA and TKA cases, defined as

discharges with a primary or secondary procedure of 81.51 (THA) or 81.54 (TKA). No exclusion criteria were applied, resulting in a final weighted study cohort of 7,769,863. Study subjects were grouped according to operative joint (hip, knee) and label status (off-label, on-label). The term “off-label” is defined as the implantation of any hip or knee prosthesis in settings not specifically identified in the labeled indications cleared by the US FDA. Patient conditions not cleared for use were collected from package inserts approved by the FDA of multiple hip and knee prostheses (Appendix 1). The designation of “off-label” was assigned if the inpatient record included at least one off-label diagnosis, as defined by the ICD-9-CM diagnosis codes listed in Table 1: obesity, neurological or mental disorder, and/or derangement of metabolism or bony integrity. All remaining subjects were classified as “on-label.” Not all off-label conditions could be identified using NIS data (e.g., moderate to severe limb deformity, highly active patients, mixture of prosthetic components from different manufacturers, etc.). However, the conditions defined as off-label in these analyses are exceedingly common and therefore, as an aggregate, likely provide a relatively accurate overall portrayal of off-label primary adult total joint reconstruction in the US.

Outcomes

Our primary outcome of interest was annual trends in the national rate of off-label THA and TKA. Secondary outcomes included hospital LOS, admission cost, perioperative complication rate, and inpatient facility discharge rate (as opposed to discharge directly home) by label status. Additionally, the frequency of in-hospital mortality was noted for patient cohorts. Perioperative complications were recorded as a single binary variable and coded as positive according to the presence of the secondary diagnosis codes (DX2 - DX25 columns) listed in Appendix 2. Complications included a variety of procedure, systemic, and medical care complications, as well as in-hospital death, lower extremity venous thrombotic events, pulmonary embolism, respiratory complications, urinary tract infection, and transient mental disorders. Discharge to inpatient facility (defined as discharges or transfers to a skilled nursing facility, intermediate care facility, short-term hospital, or any other type of facility; DISPUiform = 2 or 5) was included to represent a surrogate marker of additional cost as inpatient rehabilitation has been previously reported as more expensive than home-based rehabilitation following total joint surgery.¹⁵

Statistical Analysis

The distribution of data and descriptive statistics of demographic, hospital, and outcome variables were examined by procedure type cohort (THA and TKA) and label status. Data were further analyzed by off-label subgroups. Associations between each variable and off-label status were tested using the Pearson’s Chi-square test for categorical variables and Student’s t-test for continuous variables. The annual hospital-specific cost-to-charge ratios provided by HCUP were used to convert charge data to cost data.¹⁶ Due to the stratified sampling format of the NIS, all frequencies and analyses were converted to national estimates using weights.

The annual prevalence and rate of off-label procedures were studied across the 2000–2010 timeframe. Multiple linear and logistic regression models were used to measure the effect of off-label status on linear (LOS, admission cost) and dichotomous (perioperative

complications, inpatient facility discharge) secondary outcome variables, respectively. These analyses were adjusted for demographics (age, gender, race), primary payer, hospital characteristics (region of the US, bed size, location, and teaching status), and bilateral status (defined as an additional primary THA or TKA procedure in the hospital admission). Since approximately 25% of the discharge records did not have a race value, we created an additional race category and captured it as “Unknown Race.”

National arthroplasty projections through 2040 were executed using methodology similar to that established by Kurtz et al.⁷ The annual prevalence of arthroplasty was modeled using Poisson regression models with year, age, race, and gender as covariates. Two-way interactions between year and age, race, and gender were also included. The log-transformed population data for each age-race-sex-year subgroup was used as the offset term. THA and TKA were modeled separately. Logistic regression was used to estimate the proportion of future THA and TKA procedures that will be off-label. A second set of logistic regression models were used to estimate the proportion of off-label procedures that would be attributed to each of the three off-label subgroups. These results were considered an upper bound for estimated projections. The previously described projection models were sensitive to annual changes in the proportion of surgeries that were off-label from 2001 to 2010. It is possible that these increases in off-label prevalence (particularly obesity) will reach an inflection point in the future and growth will slow. We therefore conducted a sensitivity analysis, where we assumed a constant prevalence of off-label surgeries at the 2010 levels, the last year of our data, would continue into the future. These results were considered a lower bound for estimated projections. The predicted probabilities from the Poisson and logistic regression models were multiplied by the projected population of each age-race-sex subgroup per year through 2040. The projected population data were obtained from the 2012 National Population Projections file created by the US Census Bureau.¹⁷ All analyses were performed using SAS, v 9.3 (SAS Institute, Cary, NC).

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RESULTS

From 2000 to 2010, there were an estimated 2,566,523 THA and 5,203,340 TKA admissions in the US. Of these 7,769,863 admissions, 2,705,697 (34.8%) were categorized as off-label based on the study definitions, corresponding to a national off-label prevalence of 30.4% (n=780,639) and 37.0% (n=1,925,058) for THA and TKA, respectively (Table 2). During this decade, the off-label rate rose annually for each procedure type. By 2010, at least 37.3% and 44.6% of THA and TKA procedures, respectively, were off-label.

Patient demographics and hospital characteristics by off-label and on-label status are shown in Table 3. From 2000 to 2010, off-label THA and TKA patients were most often white

women in their mid-sixties affected by metabolic or bone disease and serviced at large urban hospitals in the South. There was slight predilection for off-label practice in TKA compared to THA due to higher rates of obesity (15.3% vs. 9.8%) and metabolic/bone disease (23.7% vs. 19.4%) among TKA patients.

Table 4 presents the results of the regression models, illustrating the differences in resource utilization, perioperative complication risk, and inpatient facility discharge rate between off-label and on-label patients after adjusting for patient and hospital characteristics. These results indicate that off-label THA and TKA patients stayed an average of 0.30 and 0.11 days longer ($p<0.001$) and had admission costs averaging \$1139 and \$816 higher ($p<0.001$), respectively, than their on-label peers (reference values in Table 4). Additionally, off-label status was associated with increased likelihood of one or more defined perioperative complication(s) (adjusted odds ratio [aOR], THA=1.34 (95% confidence interval [CI], 1.31 1.36), TKA=1.19 (95% CI, 1.17 1.21); $p<0.001$) as well as discharge to an inpatient facility (aOR, THA=1.57 (95% CI, 1.55 1.59), TKA=1.44 (95% CI, 1.42 1.45); $p<0.001$). Off-label subgroups followed parallel patterns, albeit with obese patients often exhibiting resource utilization most similar to on-label patients. Patients with neurological or mental disorders had the worst outcomes of the off-label subgroups relative to their on-label peers (Table 4). Analysis of the individual off-label diagnoses from Table 1 revealed that patients with vertical column fractures, severe alcohol dependence, and hemiplegia were among the most expensive to treat ($> \$20,000$) and at greatest risk for complications (27% – 52% complication rate) in both THA and TKA patients (results not shown). Additionally, off-label THA patients had a slightly elevated inpatient mortality rate (0.3%) compared to their on-label peers (0.2%) ($p<0.001$). In-hospital mortality rates were similar between off-label and on-label TKA patients (0.1%; $p=0.029$).

Figure 1 displays the upper and lower bounds for estimated projections of off-label primary THA and TKA through 2040. By 2040, most total joint arthroplasty of the hip and knee may be off-label (THA, 86.1%; TKA, 91.5%). Allowing growth patterns seen from 2000 to 2010, the number of off-label THA and TKA procedures is projected to increase over 9- and 21-fold, respectively, from 2010 to 2040 (Figure 1). Affecting an estimated 6.1 million THA and TKA patients in 2040, obesity is projected to be the most common off-label diagnosis over the next three decades. Growth rates of obesity are the most robust, followed by neurological/mental disorders and lastly metabolic/bone diseases. However, it is important to note these projections are affected by large off-label rate increases in obesity and neurological/mental disorders during this decade and could likely reach an inflection point in the future and growth will slow. Lower bound estimated projections are presented, which show more modest off-label projections (THA, 30.9%; TKA, 37.6%). However, due to the volume burden expected in the future for the total joint arthroplasty patient population, these lower bound estimates still depict a large national off-label annual volume by 2040 (THA, $n=374,355$; TKA, $n=2,549,664$).

DISCUSSION

Off-label use is well acknowledged in orthopaedic surgery, but has been typically associated with special patient populations and products, such as pediatrics and bone morphogenetic

protein.^{2,3} THA and TKA are regularly performed procedures. As of 2009, TKA was the 14th most highly performed inpatient procedure nationwide, and the top procedure among those 65 to 84 years of age.^{14,18} Additionally, in 2009, THA and TKA were among the fastest growing inpatient procedures, with rates having increased 33% and 84%, respectively, since 1997.^{14,18} Our results show that even for commonplace procedures, off-label use is relatively routine and trending up, which is not surprising given the fact that labeling criteria is based on decades old indications.

The now mainstream practice of off-label prosthesis implantation brings into question the way medical devices are monitored after introduction to the market. Postmarket surveillance was largely catalyzed with establishment of the medical device reporting system by the Safe Medical Device Act of 1990.¹⁹ Section 522, added by the FDA Amendments Act of 2007, enabled the FDA to mandate postmarket surveillance studies from medical device manufacturers.²⁰ The FDA has since made several new propositions calling for unique numerical identification of all medical devices, national/international medical device registry development, and modernized surveillance and analysis of adverse events and evidence.²¹ Postmarket surveillance as sponsored by device manufacturers is complicated by the tenuous border between off-label reporting and off-label promotion. While off-label reporting is allowed by the FDA, off-label promotion is not and has resulted in billion dollar losses for medical drug and device companies.²² There is now a significant trend among manufacturing companies to refrain from sponsoring research whereby participants harbor contraindicated comorbidities. This may lead to the bias toward positive results among studies at least partially sponsored by pharmaceutical or medical device companies versus not.^{23–25} Within the orthopaedic surgery literature, Leopold et al. found studies with commercial sponsorship 25% more likely to demonstrate a positive result.²³ Outcomes and challenges associated with many off-label conditions (e.g., obesity, diabetes, substance abuse, neurologic impairment, etc.) are independently documented in the literature.^{26–29} Previously reported poor surgical outcomes associated with many off-label conditions may further incentivize the preclusion of off-label patients in industry-sponsored research. With off-label rates nearing 50% and growing, the exclusion of TJA patients from future studies according to label status may be impractical and associated with extremely skewed, inaccurate data (risk of complication, treatment-specific outcome, cost, etc.)

Especially in orthopaedics, for many devices the extent of clinically appropriate use exceeds what the device can feasibly be approved for. As patient care systemically advances, the occurrence of off-label use is an expected phenomenon both now and in the future. However, with acknowledgment of the necessity of off-label use, a concerted effort on behalf of manufacturers, physicians, and healthcare systems is also necessary in assessing and addressing inherent risks, and costs of off-label use. NIS data show elevated LOS, admission costs, perioperative complication risk, and inpatient facility discharge likelihood among off-label patients compared to on-label total joint arthroplasty patients. While these increases are statistically significant due to the large number of cases analyzed, the clinical significance is relatively minimal for the individual patient and is not cause for alarm. LOS is minimally increased and elevated perioperative complication rates have been previously associated with many off-label diagnoses.^{26–29} However, the especially high costs and complication rates associated with specific conditions (e.g., hemiplegia, severe alcohol

dependence, etc.) highlight the importance of cautious patient selection. These findings are corroborated by previous reports of high rates of infections (i.e., superficial wound infections, urinary tract infections) and psychoses following surgery among THA patients with neurodegenerative disease or a history of substance abuse, respectively.^{28–30}

The results of this study suggest for most patients, label status alone may have minimal perioperative clinical consequence thereby supporting off-label use per physician discretion. Off-label THA and TKA patients have greater odds of being discharged to inpatient facilities, lending to higher total costs in this group compared to the on-label group. The long-term results, which could not be directly addressed in the present study, have the potential for substantial impact. Diabetes and uncontrolled diabetes have independently been shown to correlate with poor functional outcomes 2 and 5 years following TKA.³¹ Young TKA patients are at a higher risk for revision surgery, a finding often attributed to higher activity levels associated with this population.^{32,33} Osteoporotic patients undergoing non-cemented THA have been shown to experience more pain and functional limitations at mid-term follow-up than non-osteoporotic controls.³⁴ Obesity has been identified as an independent risk factor for periprosthetic infection.³⁵ Patients with Parkinson's disease experience much higher complication rates (26% – 68%) and 6-month mortality rates (5.6% – 21%) after primary THA than those patients without Parkinson's disease.^{28,30} Mental disability has been associated with longer LOS, greater inpatient costs, and higher rates of complications.³⁶ Revision arthroplasty is a clinically complex endeavor often resulting in net institutional financial losses.³⁷ Costs of revision hip arthroplasty due to aseptic and infectious causes are estimated 1.4 and 3.6 times more than primary arthroplasty.³⁸ Projections and data from this study, together with reports from the literature, illustrate the increasing clinical complexity of TJA patients; accompanying this shift in patient profile has been an increase in cost and likelihood of poor outcomes long after surgery. These results support long-term investigations of off-label practice and outcomes outside of the inpatient hospital stay; such analyses may render some off-label diagnoses clinically irrelevant while others useful criteria for risk stratification.

This study has some notable limitations. The use of an administrative inpatient database precludes long-term follow-up and functional data acquisition, which is a major concern for off-label outcomes. Also, exact estimates of nationwide off-label use cannot be made from this database due to a lack of granularity in off-label conditions (Appendix 1) and inaccuracies in coding.³⁹ Given the inherent limitations of this study, the primary goal was to identify trends of off-label hip and knee arthroplasty on a national scale. Liu et al.^{40,33} reported off-label use in 154 of 225 (68%) of THA and TKA patients at a single, academic tertiary medical center. Despite potential inadequacies in identification, our results confirm widespread off-label use nationwide. The prevalence of off-label total joint arthroplasty identified in this study during the 2000–2010 time period is not unreasonable, but likely represents a low-end estimate of the true value, thereby supporting the increasing prominence of its use. Obesity is likely a large contributor to the low-end off-label prevalence estimates of this study. Obesity has been noted to be largely underreported within inpatient databases.³⁹ A diagnosis of obesity was recorded in only 13.5% of arthroplasty patients in this cohort, while it is estimated to affect approximately one third of

all adults nationwide.^{41,42} Fehring et al.²⁶ reported obesity having institutional prevalence of 52.1% in primary THA and TKA patients.

The projections presented are based on historical data and therefore entail an inherent degree of uncertainty, especially as these predictions are made further into the future. Our models were based on data during a period of rapid increase in THA and TKA procedures and obesity rates, which may not continue into the future. Other unknown factors, such as changes in technology, the health care system, or the economy could also impact the accuracy of these projections. The dramatic increases in off-label arthroplasty predicted by these models may be overestimates; if so, future rates of off-label arthroplasty are more likely a compromise of estimates expecting prevalence growth and sensitivity analysis estimates. Nonetheless, these crude projections are useful for policymakers and manufacturers to estimate future demand for off-label use of devices.

CONCLUSION

The national occurrence of THA and TKA on patients with at least one currently defined off-label condition is relatively common and is projected to increase in the future. The results from this study and the literature, demonstrate off-label patients have greater length of stay, admission costs, long-term complication risks, and inpatient facility discharge likelihood than on-label patients. As the practice of total joint arthroplasty continues to evolve both technically (e.g., bearing surface design, device fixation, operative technique, etc.) and in patient profile (e.g., expanding indications for surgery, increasing burden of comorbid disease, etc.), so must the way outcomes are monitored and reported. Accurate and up-to-date data are increasingly essential in preoperative risk-benefit stratification and patient selection. The results of this study support a need for continued medical device observation by manufacturers, doctors, and healthcare systems; such an endeavor is necessary to accurately assess and stratify risk, especially given our industry-wide movement to more accountable care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a

Figure 1b

Figure 1.

Current (2000–2010) and projected prevalence through 2040 (solid line, upper bound estimate; dashed line, lower bound estimate) of off-label primary (a) total hip arthroplasty and (b) total knee arthroplasty. Vertical dotted line marks boundary between recorded past NIS and future projected data points.

Table 1

Definition of Off-Label Status by ICD-9-CM Diagnosis Codes

Off-Label Subgroup	Variable	ICD-9-CM Diagnosis Codes & Descriptions
Obesity	<i>Obesity</i>	<ul style="list-style-type: none"> 278.00: obesity, unspecified 278.01: morbid obesity
	<i>Elevated BMI</i>	<ul style="list-style-type: none"> V85.3: BMI between 30 and 39, adult V85.4: BMI 40 and over, adult V85.54: BMI, pediatric, 95th percentile
Neurological/Mental Disorder	<i>Neurological Disease</i>	<ul style="list-style-type: none"> 330 – 332, 333.0, 333.2, 333.4 – 333.9, 334 – 336: hereditary and degenerative diseases of the CNS (i.e. cerebral degenerations, Alzheimer's disease, Parkinson's disease, spinal cord diseases) (autonomic nervous system disorders, tics, benign tremor not included) 340 – 345, 347: other disorders of the CNS (i.e. multiple sclerosis, epilepsy, narcolepsy) 353.1, 353.3 – 353.5, 355 – 359: disorders of the peripheral nervous system (i.e. lumbar and thoracic neuropathies) (cranial nerve neuropathies, cervical neuropathies, upper limb mononeuritis not included) 806: fracture of vertebral column with spinal cord injury 094.0 – 094.2, 094.8 – 094.9: symptomatic neurosyphilis
	<i>Mental Disorders</i>	<ul style="list-style-type: none"> 290: dementias 291: alcoholic psychoses 294: persistent mental disorders due to conditions classified elsewhere 303.00 – 303.02, 303.90 – 303.92: alcohol dependence syndrome 304.00 – 304.02, 304.10 – 304.12, 304.20 – 304.22, 304.30 – 304.32, 304.40 – 304.42, 304.50 – 304.52, 304.60 – 304.62, 304.70 – 304.72, 304.80 – 304.82, 304.90 – 304.92: drug dependence 317 – 319: mental retardation
Metabolic/Bone Disease	<i>Diabetes Mellitus</i>	<ul style="list-style-type: none"> 249 – 250: diabetes mellitus (including secondary)
	<i>Osteoporosis</i>	<ul style="list-style-type: none"> 733.0: osteoporosis
	<i>Osteomalacia</i>	<ul style="list-style-type: none"> 268.2, 275.3: osteomalacia and resistance to vitamin D
	<i>Pathologic Fracture</i>	<ul style="list-style-type: none"> 733.1: pathologic fracture
	<i>Immunosuppression</i>	<ul style="list-style-type: none"> V42.0, V42.1, V42.6, V42.7, V42.83: history of solid organ (kidney, heart, lung, liver, pancreas) transplant V58.65: long-term (current) use of steroids 042, 079.53, 795.71, V08: human immunodeficiency virus
	<i>Neuropathic Joint</i>	<ul style="list-style-type: none"> 713.5: arthropathy associated with neurological disorders

Three- and four-digit codes include all respective four- and five-digit codes, unless otherwise specified. BMI, body mass index; CNS, central nervous system

Table 2

Annual Prevalence of Off-Label Primary Total Hip and Knee Arthroplasty, 2000–2010

	Hip	Knee
2000	35,950 (21.8%)	70,868 (25.1%)
2001	43,465 (23.5%)	85,704 (27.3%)
2002	50,144 (24.8%)	103,416 (29.5%)
2003	53,223 (26.3%)	119,828 (31.5%)
2004	61,142 (27.0%)	142,572 (33.0%)
2005	69,672 (29.3%)	174,955 (35.1%)
2006	71,704 (31.3%)	186,160 (37.5%)
2007	82,434 (32.6%)	221,322 (40.1%)
2008	98,162 (35.4%)	258,004 (41.8%)
2009	101,674 (35.6%)	268,352 (43.2%)
2010	113,069 (37.3%)	293,877 (44.6%)
TOTAL	780,639 (30.4%)	1,925,058 (37.0%)

Values are adjusted to the weighted national frequencies (percentage of respective hip/knee cohort annual total).

Primary Total Hip and Knee Arthroplasty Patient Demographics and Hospital Characteristics, 2000–2010

Table 3

	Obese			Neuro/Mental			Metabolic/Bone			Total Off-Label			On-Label		
	Hip	Knee		Hip	Knee		Hip	Knee		Hip	Knee		Hip	Knee	
N	252,470	797,529		155,603	286,445		497,812	1,235,595		780,639	1,925,058		1,785,885	3,278,281	
% of Respective Cohort ^a	9.8%	15.3%		6.1%	5.5%		19.4%	23.7%		30.4%	37.0%		69.6%	63.0%	
Mean Age, years (SD)	61.3 (11.1)	62.6 (9.4)		62.5 (13.8)	63.8 (10.9)		67.9 (12.6)	67.4 (10.0)		64.9 (13.2)	65.6 (10.4)		66.0 (12.9)	67.6 (10.5)	
Gender ^b															
Male	40.8%	28.4%		40.7%	35.9%		36.1%	32.7%		38.0%	31.8%		44.9%	38.7%	
Female	59.2%	71.6%		59.3%	64.1%		63.9%	67.3%		62.0%	68.2%		54.6%	60.9%	
Race ^b															
White	64.1%	61.8%		69.1%	67.7%		64.2%	60.6%		64.9%	61.9%		65.4%	64.4%	
Black	7.1%	7.9%		4.4%	4.2%		6.3%	6.7%		6.1%	6.6%		4.3%	4.3%	
Hispanic	2.7%	4.2%		2.0%	2.9%		3.0%	5.1%		2.7%	4.5%		2.1%	3.3%	
Other/Unknown Race ^c	26.1%	26.1%		24.5%	25.2%		26.5%	27.6%		26.3%	27.0%		28.2%	28.0%	
Primary Payer ^b															
Medicare	42.1%	44.8%		69.1%	67.6%		67.0%	63.7%		60.3%	57.9%		52.1%	57.0%	
Medicaid	4.1%	3.7%		4.0%	2.9%		3.1%	3.1%		3.5%	3.1%		3.0%	2.3%	
Private Insurance	50.3%	47.1%		24.3%	26.7%		27.4%	29.8%		33.4%	35.3%		41.4%	36.7%	
Other/Missing ^d	3.5%	4.4%		2.7%	2.8%		2.5%	3.4%		2.8%	3.6%		3.5%	4.1%	
Hospital Region ^b															
Northeast	18.8%	15.8%		18.7%	15.1%		20.1%	16.7%		19.8%	16.4%		20.8%	17.0%	
Midwest	29.3%	30.2%		27.0%	29.6%		27.5%	28.8%		27.7%	29.2%		26.0%	27.7%	
South	30.2%	34.8%		33.8%	36.4%		34.5%	38.1%		33.2%	36.8%		31.9%	36.2%	
West	21.7%	19.1%		20.5%	19.0%		17.8%	16.4%		19.3%	17.6%		21.2%	19.1%	
Hospital Bed Size ^b															
Small	14.2%	14.6%		13.8%	14.8%		13.9%	14.9%		14.1%	15.0%		15.4%	15.7%	
Medium	24.7%	25.4%		24.0%	24.6%		24.4%	25.0%		24.4%	25.0%		23.5%	24.6%	
Large	60.7%	59.6%		61.7%	60.1%		61.3%	59.6%		61.2%	59.6%		60.9%	59.4%	
Hospital Location ^b															

	<u>Obese</u>		<u>Neuro/Mental</u>		<u>Metabolic/Bone</u>		<u>Total Off-Label</u>		<u>On-Label</u>	
	Hip	Knee	Hip	Knee	Hip	Knee	Hip	Knee	Hip	Knee
Rural										
Urban Non-Teaching	9.9%	11.5%	12.2%	13.3%	11.9%	13.6%	11.5%	13.0%	11.3%	13.5%
Urban Teaching	43.1%	46.2%	44.8%	47.0%	44.3%	47.2%	44.0%	46.8%	43.5%	47.1%
	46.6%	41.9%	42.5%	39.2%	43.4%	38.8%	44.1%	39.8%	45.0%	39.1%

^aValues reflect percentage of respective hip (n=2,566,524) or knee (n=5,203,339) total cohort, 2000–2010.

^bValues reflect percentage of column total.

^cOther Race includes Asian/Pacific Islander, Native American, and Other categories.

^dOther Primary Payer includes Self-Pay, No Charge, and Other categories.

For total hip arthroplasty, overall percentage of missing values for Gender, Hospital Bed Size, and Hospital Location were 0.35%, 0.30%, 0.30%, respectively.

For total knee arthroplasty, overall percentage of missing values for Gender, Hospital Bed Size, and Hospital Location were 0.26%, 0.33%, 0.33%, respectively.

Missing values for Race and Primary Payer were combined with respective “Other” category for statistical models. No missing values for Hospital Region.

SD, standard deviation

Table 4

Adjusted Effect of Off-Label Arthroplasty (vs. On-Label) on LOS, Admission Cost, Perioperative Complication, and Inpatient Facility Discharge

	Obese			Neuro/Mental			Metabolic/Bone			Total Off-Label			On-Label Adjusted Means (ref values)		
	Hip	Knee		Hip	Knee		Hip	Knee		Hip	Knee		Hip	Knee	
LOS, days ^a	-0.01	+0.05		+0.84	+0.33		+0.33	+0.12		+0.30	+0.11		4.27 days	3.91 days	
Admission Cost, USD ^a	+964	+929		+1,880	+1,432		+1,205	+820		+1,139	+816		\$14,727	\$13,886	
Complication, aOR (95% CI) ^b	1.17 (1.13 – 1.21)	1.18 (1.16 – 1.20)		1.83 (1.77 – 1.88)	1.50 (1.46 – 1.54)		1.32 (1.29 – 1.34)	1.18 (1.16 – 1.20)		1.34 (1.31 – 1.36)	1.19 (1.17 – 1.21)		9.7%	8.2%	
Discharge to Inpatient Facility, aOR (95% CI) ^b	1.52 (1.49 – 1.55)	1.51 (1.49 – 1.53)		2.21 (2.16 – 2.25)	1.86 (1.83 – 1.89)		1.55 (1.52 – 1.58)	1.46 (1.44 – 1.47)		1.57 (1.55 – 1.59)	1.44 (1.42 – 1.45)		42.7%	40.4%	

^aResults of linear regression analyses.^bResults of logistic regression analyses.

Bolded values are significant at p<0.001.

All analyses adjusted for age, gender, race, primary payer, hospital characteristics (region, bed size, location, teaching status), and bilateral status.

LOS, length of stay; USD, United States Dollar; aOR, adjusted odds ratio; CI, confidence interval

Appendix 1

Full List of Off-Label Conditions & Availability in NIS Database

Off-Label Criteria	Joint	Condition
Included	Hip and Knee	<ul style="list-style-type: none"> Obesity Alcohol or drug addiction Neurological disorders or conditions that may cause patient to be incapable of following instructions (i.e., paraplegia, cerebral palsy, Parkinson's disease) Charcot or neuropathic arthropathy Metabolic disorders or systemic pharmacological treatments leading to progressive deterioration of solid bone support for the implant (i.e., diabetes mellitus, steroid therapies, immunosuppressive therapies) Rheumatoid arthritis patients using steroids or with history of recurrent breakdown of skin Osteoporosis, marked osteomalacia, and metabolic disorders which may impair bone formation (i.e., pathologic fracture)
		<ul style="list-style-type: none"> High likelihood of falls Osteochondral, muscle, or vascular compromise or deficiency in the affected limb that cannot provide adequate support and/or fixation of the implanted devices Inadequate soft tissue coverage or support Active or recent joint sepsis Active local or systemic infection Sensitivity or allergic reactions to implant materials (i.e., metal, bone cement, polyethylene) Tissue reactions to implant corrosion or implant wear debris Severe deformities leading to impaired fixation or improper positioning of the implant Active sports classification or high levels of patient activity Mixing implants from different manufacturers or implant systems Disabilities of other lower limb joints (knees, hips, ankles) Skeletal immaturity
Not Included	Hip Only	<ul style="list-style-type: none"> Congenital dysplasia of the hip Ceramic heads used with metal liners Hydroxyapatite coated implants used with cement
	Knee Only	<ul style="list-style-type: none"> Severe tibial bone loss or deformity over 15 degrees varus Severe instability secondary to advanced loss of osteochondral structure or absence of collateral ligament integrity Previous arthrodesis

Off-label conditions represent general contraindications, warnings, and precautions according to multiple FDA-approved manufacturers inserts (Stryker, Zimmer, DePuy, Smith & Nephew).

"Not Included" conditions are either not or not satisfactorily defined by ICD-9-CM codes and therefore could not be used to define label status.

Appendix 2

Definition of Perioperative Complications by ICD-9-CM Secondary Diagnosis Codes

Complication	ICD-9-CM Diagnosis Codes
• Surgical and medical care complications	996 – 999
• Transient mental disorders/delirium	293
• Lower extremity venous thrombotic events	451.1, 451.2, 451.81, 453.2, 453.4
• Pulmonary embolism and infarction	415.1
• Respiratory complications (i.e., iatrogenic pneumothorax, postoperative pulmonary insufficiency, transfusion related acute lung injury, tracheostomy complications)	512.1, 518.5, 518.7, 519.0
• Urinary tract infection	595.0, 599.0
• In-hospital death	DIED column: 1

Three- and four-digit codes include all respective four- and five-digit codes, unless otherwise specified.