Research Article

Trends in Deep Vein Thrombosis Prophylaxis and Deep Vein Thrombosis Rates After Total Hip and Knee Arthroplasty

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Abstract

Introduction: Patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) are at high risk of deep vein thrombosis (DVT) postoperatively, necessitating the use of prophylaxis medications. This investigation used a large claims database to evaluate trends in postoperative DVT prophylaxis and rates of DVT within 6 months after THA or TKA.

Methods: Truven Health MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases were reviewed from 2004 to 2013 for patients who underwent THA or TKA. Data were collected on patient age, sex, Charlson Comorbidity Index, and hypercoagulability diagnoses. Postoperative medication claims were reviewed for prescribed aspirin, warfarin, enoxaparin, fondaparinux, rivaroxaban, and dabigatran.

Results: A total of 369,483 patients were included in the analysis, of which 239,949 patients had prescription medication claims. Warfarin was the most commonly prescribed anticoagulant. Patients with a hypercoagulable diagnosis had markedly more DVTs within 6 months after THA or TKA. More patients with a hypercoagulable diagnosis were treated with warfarin or lovenox than other types of anticoagulants. A multivariate regression analysis was performed, showing that patients prescribed aspirin, fondaparinux, and rivaroxaban were markedly less likely than those prescribed warfarin or enoxaparin to have a DVT within 6 months after THA or TKA.

Conclusion: After THA and TKA, warfarin is the most commonly prescribed prophylaxis. Patients with hypercoagulability diagnoses are at a higher risk of postoperative DVT. The likelihood of DVT within 6 months of THA and TKA was markedly higher in patients treated with warfarin and lovenox and markedly lower in those treated with aspirin, fondaparinux, and rivaroxaban.

Level of Evidence: Level III

More than 1 million total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures are performed in the United States each year.[1] Patients undergoing these procedures are at an increased risk of thromboembolic complications.[2–4] The most common complication is deep vein thrombosis (DVT) because patients are placed at a higher risk as a result of venous stasis with leg positioning, increased risk of

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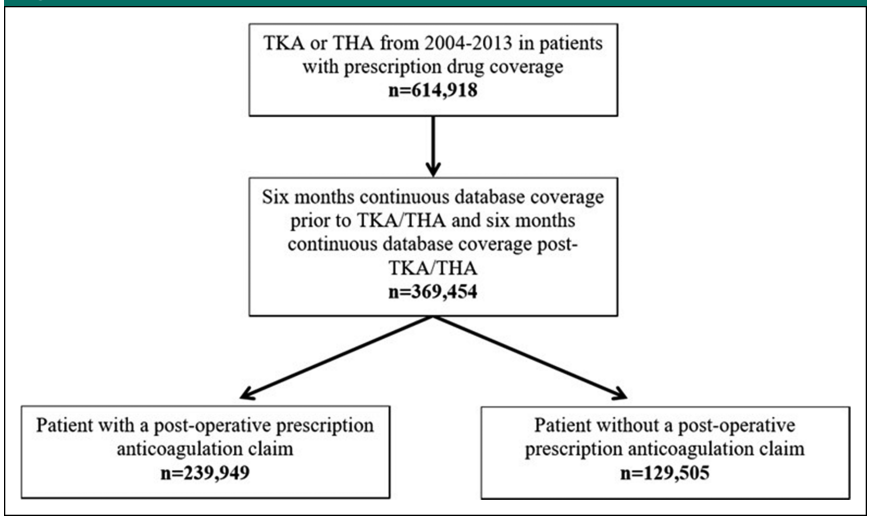
endothelial injury, and aberrant activation of the clotting cascade.[4,5] Prophylaxis after THA and TKA is recommended by both the American Academy of Orthopaedic Surgeons and American College of Chest Physicians; however, no consensus exists on the optimal prophylactic regimen.[6] Anticoagulation after THA or TKA can pose unique challenges because anticoagulation medications must balance the reduction in blood clot formation, with the risk of postoperative bleeding, hematoma formation, revision surgery, and infection.[7-10] The vitamin K antagonist warfarin has been shown to be effective in reducing the rate of proximal DVTs and pulmonary embolisms.[11,12] The major advantage of warfarin is that it can be reversed if bleeding complications arise or if patients require urgent surgical intervention.[13,14] Warfarin's most notable disadvantage is that it is only effective within a narrow therapeutic window, necessitating frequent laboratory monitoring and dose adjustments. These drawbacks have led to the use of alternative methods of chemoprophylaxis.

Recent studies have demonstrated the effectiveness of aspirin prophylaxis after TKA or THA. In a trial of 13,356 patients undergoing THA, low-dose aspirin reduced the rate of DVT by 29%, PE by 43%, and fatal pulmonary embolism by 58% compared with placebo.[15] Low-molecular-weight heparin agents, such as enoxaparin, have also been shown to be effective; however, they must be administered through subcutaneous injection.[16] Other therapies such as factor Xa and direct thrombin inhibitors are appealing because they can be delivered orally, do not require monitoring, and have constant dosing for most patients. Unfortunately, this group of medications is costly and requires fresh frozen plasma for reversal.[5,17,18]

Although DVT prophylaxis after THA and TKA is assumed to be the standard of care, given the high likelihood of thromboembolic events without prophylaxis, a paucity of data exists on surgeon practice patterns and changes over time. In addition, few studies have evaluated postoperative DVT rates by anticoagulants at a large-scale population level. The purpose of this investigation was to use a large claims database to evaluate trends over time in national practice patterns of postoperative DVT prophylaxis and rates of DVT within 6 months after THA or TKA procedures.

Figure 1



Flowchart showing the cohort selection. TKA = total knee arthroplasty, THA = total hip arthroplasty

Methods

Data Source

A retrospective review was conducted using the Truven Health MarketScan Commercial Claims and Encounters (commercial insurance) and Medicare Supplemental and Coordination of Benefits (Medicare with commercial supplement) databases (Truven Health Analytics). The databases contain deidentified, integrated, person-specific claims data for approximately 17 to 51 million individuals per year. The commercial insurance database includes healthcare claims for individuals with insurance through a commercial provider or a self-insuring employer under fee-for-service, fully capitated, or partially capitated health plans. The Medicare with commercial supplement database includes claims information for individuals who have both Medicare and commercial employer-sponsored coverage. All claims from the Medicare with commercial supplement database reflect the coordination of benefits between the commercial insurer and Medicare such that all payments made by either entity are captured within the database. The age distribution in the Medicare with commercial supplement database is representative of the overall Medicare population. These databases, when combined, constitute approximately 20% of the overall insurance market. *International Classification of Disease* (*ICD-9*) diagnoses codes and Current Procedure Terminology (CPT) codes can be identified in individual claims. The data include claims made from both inpatient and outpatient clinical encounters and prescription medications. National Drug Codes (NDCs) are used to organize prescription medication claims. The NDCs specify

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Table 1

Demographics of Patient Deep Vein Thrombosis Prophylaxis After Total Hip Arthroplasty or Total Knee Arthroplasty Procedures

Factor	Prescription Aspirin	Warfarin	Enoxaparin	Fondaparinux	Rivaroxaban	Dabigatran	No Anticoagulation Claim
Age	61.9	64.9	62.5	61.8	61.3	70.2	66.0
% Female	56.6	57.7	56.0	55.9	56.7	41.9	61.4
% Hypercoagulability diagnosis	1.8	3.0	2.9	1.8	1.7	2.5	0.9
CCI	0.043	0.081	0.085	0.081	0.043	0.067	0.089
Percent of total population (%)	0.44	38.0	20.8	3.4	5.1	0.3	35.1

CCI = Charlson Comorbidity Index

Table 2

Postoperative Deep Vein Thrombosis Prophylaxis Trends by Drug Type

Postoperative Medication	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Prescription aspirin	0.03%	0.02%	0.03%	0.00%	0.03%	0.08%	0.20%	1.04%	1.59%	2.91%
Warfarin	75.02%	72.29%	68.04%	63.18%	61.65%	60.36%	58.92%	54.77%	45.51%	41.17%
Enoxaparin	25.26%	28.46%	30.91%	33.81%	35.65%	37.21%	37.94%	36.88%	26.19%	24.63%
Fondaparinux	2.72%	3.33%	5.21%	7.27%	7.09%	7.14%	7.18%	5.85%	2.98%	2.15%
Rivaroxaban	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	5.30%	27.89%	33.58%
Dabigatran	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.25%	1.39%	1.25%	1.05%

both the type and dosage of the medication prescribed.

Study Sample

The databases were reviewed from 2004 to 2013 for subjects with a CPT code for THA (CPT = 27,130) or TKA (CPT = 27,447). Patients were required to be enrolled in the database continuously for 6 months before and 6 months immediately after the THA or TKA procedure. Data were collected on patient age and sex. We identified a group of patients who were hypercoagulable, defined as subjects with a previous DVT (ie, *ICD-9* code 453.40) or who had an *ICD-9* code for primary hypercoagulable state (ie, *ICD-9* 289.81, 289.82, 286.53, and 795.79), which includes diagnoses of factor V leiden, antiphospholipid antibody, lupus anticoagulant, and protein C/S deficiency. Prescription medication claim information was collected based on NDCs on prescribed aspirin, warfarin, enoxaparin, fondaparinux, rivaroxaban, and dabigatran. Patients were excluded if they were on any prescription anticoagulation medications >2 months before the THA or TKA procedure. In addition, patients with no claims for a prescription anticoagulant are presented as a separate group. Data were gathered on all anticoagulation prescription claims in the 6-month period after THA and TKA procedures. Postoperative DVTs were identified in the 6 months after THA and TKA procedures using the *ICD-9* code for DVT (453.40). We excluded any anticoagulation prescription claims that occurred after a DVT. Charlson Comorbidity Index (CCI) scores were calculated for each subject using *ICD-9* codes for comorbidities, as described in previous studies.[19]

Statistical Analysis

Mean age, percent female, percent of population with the hypercoagulable group, and CCI were calculated for each type of anticoagulant studied. Trends of utilization by year for each anticoagulant were compared. Rates of DVT in the 6-month period after THA and TKA were calculated by each type of prescription anticoagulant using the *ICD-9* code for DVT (ie, 453.40). DVT rates by year were also calculated over the course of the study period to analyze trends in DVT rates over time. A best fit line was used to calculate the R^2 value and statistical significance of the yearly trend.

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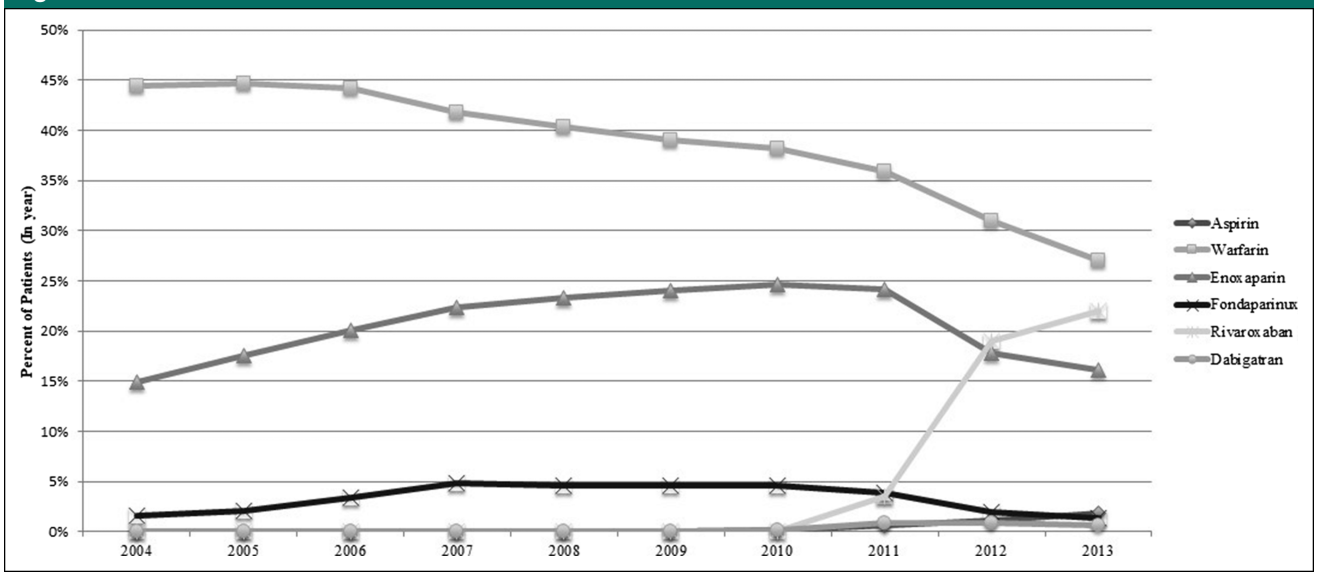
Figure 2



Graph showing yearly trends in deep vein thrombosis prophylaxis after total hip arthroplasty and total knee arthroplasty procedures.

DVT rates were compared in patients in the hypercoagulable group versus patients not in the hypercoagulable group using chi-squared tests. All statistical analysis were performed with SAS software, version 9.3 (SAS).

Comparison of Deep Vein Thrombosis Rates by Anticoagulants

Further analysis was conducted to attempt to compare the rate of DVT observed within 6 months after THA or TKA procedures by the anticoagulant type after controlling for confounding variables. Multivariate logistic regression analysis was performed controlling for the effects of age, sex, hypercoagulability, and CCI. Odds ratios >1.0 signified the increased risk of DVT in relation to the other forms of prescription anticoagulation studied.

Results

A total of 369,483 patients were included in the analysis, of which 239,949 patients had prescription anticoagulant information. A flowchart of patient selection is presented in Figure 1. The average age of the cohort was 66.7 years, 58.7% were female, 1.8% were in the hypercoagulable group, 28.3% underwent THA, and 71.7% underwent TKA. Demographics by anticoagulant type and for patients without anticoagulation claims are presented in Table 1. Warfarin was the most commonly prescribed anticoagulant within the cohort at a rate of 58.44%.

At the beginning of the study period in 2004, 0.03% of patients had claims for prescribed aspirin, 75.02% warfarin, 25.26% enoxaparin, 2.72% fondaparinux, zero rivaroxaban, and zero dabigatran. Throughout the study period, the most notable changes included a decrease in warfarin claims and increase in rivaroxaban claims. In 2013, 2.19% of patients had claims for prescribed aspirin, 41.17% warfarin, 24.63% enoxaparin, 2.15% fondaparinux, 33.58% rivaroxaban, and 1.05% dabigatran. The prescription medication claims per year are presented in Table 2. Figure 2 demonstrates the change in postoperative

Table 3

Deep Vein Thrombosis Rates Within 6 Months of Total Hip Arthroplasty or Total Knee Arthroplasty Procedures by Drug Type

Postoperative Anticoagulation	Percent w/DVT
Prescription aspirin	2.20
Warfarin	4.74
Enoxaparin	3.73
Fondaparinux	2.69
Rivaroxaban	1.86
Dabigatran	3.83
No anticoagulation claim	2.16

DVT = deep vein thrombosis

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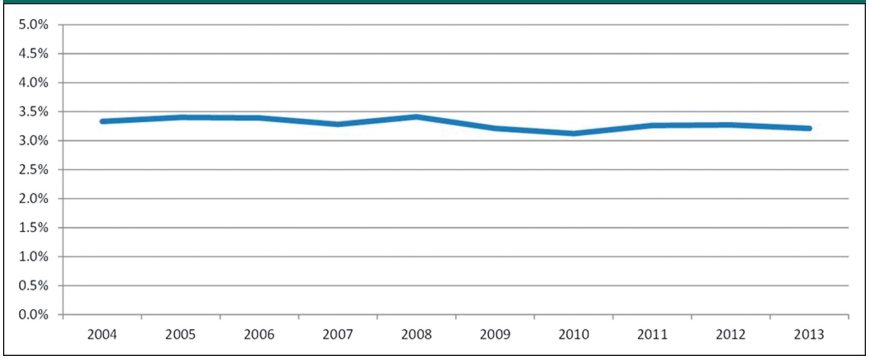
Table 4

Deep Vein Thrombosis Rate Within 6 Months After Total Hip Arthroplasty or Total Knee Arthroplasty Procedures by Year

Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Annual DVT rate	3.33%	3.40%	3.39%	3.28%	3.41%	3.21%	3.12%	3.26%	3.27%	3.21%

DVT = deep vein thrombosis

Figure 3



Graph showing the annual rate of deep vein thrombosis within 6 months after total hip arthroplasty and total knee arthroplasty procedures.

Table 5

Deep Vein Thrombosis Rates Within 6 Months of Total Hip Arthroplasty or Total Knee Arthroplasty Procedures Based on Hypercoagulable Diagnosis

Postoperative Anticoagulation	Hypercoagulable Diagnosis*	No Hypercoagulable Diagnosis	*P* value
Prescription aspirin	0.45%	0.44%	0.98
Warfarin	64.26%	37.48%	<0.001
Enoxaparin	34.75%	20.55%	<0.001
Fondaparinux	3.41%	3.35%	0.76
Rivaroxaban	4.81%	5.10%	0.29
Dabigatran	0.47%	0.32%	0.05
No anticoagulation claim	18.54%	35.35%	<0.001
Overall DVT rate	24.30%	2.50%	<0.001

DVT = deep vein thrombosis
*Hypercoagulable Dx: history of factor V Leiden, antiphospholipid antibody, lupus anticoagulant, hypercoagulable state, or previous DVT in database.

DVT prophylaxis drug prescriptions over the study period time.

DVT rates in patients within 6 months after THA or TKA procedures were calculated and are presented in Table 3. DVTs were recorded in 2.20% of patients with claims for prescribed aspirin, 4.74% for warfarin, 3.73% for enoxaparin, 2.69% for fondaparinux, 1.86% for rivaroxaban, 3.83% for dabigatran, and 2.17% for those patients with no postoperative anticoagulation claims. DVT rates within 6 months after THA or TKA for each year during the study period were calculated (Table 4). Figure 3 is a graph demonstrating that no significant change in DVT rates was observed over the study period ($P = 0.07$; $r^2 = 0.41$).

A subanalysis was performed comparing postoperative DVT rates within 6 months after THA or TKA procedures in the hypercoagulable group versus the remainder of the cohort. Patients in the hypercoagulable group had significantly more DVTs within 6 months after THA or TKA procedures compared with the remainder of the cohort (24.30% versus 2.5%; $P < 0.001$) (Table 5). In addition, a significantly greater proportion of patients in the hypercoagulable group were treated with warfarin (64.3% in the hypercoagulable group versus 37.5% in the remainder of the cohort, $P < 0.001$) or lovenox (34.8% in the hypercoagulable group versus 20.6% in the remainder of the cohort, $P < 0.001$).

A multivariate regression analysis was performed, adjusting for age, sex, hypercoagulability, and CCI, comparing each type of anticoagulation to the others (Table 6). The adjusted analysis showed patients on prescribed aspirin (odds ratio: 0.69, 95% confidence interval, 0.49–0.96), fondaparinux (odds ratio: 0.85, 95% confidence interval, 0.76–0.95), and rivaroxaban (odds ratio: 0.57, 95% confidence interval, 0.51–0.63) were markedly less likely to have a DVT within 6 months after THA or TKA procedures when compared individually to patients who were treated with all other types of DVT prophylaxis. Patients on warfarin (odds ratio: 3.60, 95% confidence interval, 3.38–3.84) and enoxaparin (odds ratio: 1.14,

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95% confidence interval, 1.09–1.20) were markedly more likely to have a DVT when compared individually to all other forms of anticoagulation during the 6 months after THA or TKA procedures (Table 6).

Table 6

Odds Ratio of Deep Vein Thrombosis Within 6 Months of Total Hip Arthroplasty or Total Knee Arthroplasty Procedure by Anticoagulant Type Adjusted for Age, Sex, Hypercoagulability Diagnosis, and Charlson Comorbidity Index

Postoperative Medication	Odds Ratio	95% Confidence Interval (Lower, Upper)
Prescription aspirin	0.69	0.49, 0.96
Warfarin	3.60	3.38, 3.84
Enoxaparin	1.14	1.09, 1.20
Fondaparinux	0.85	0.76, 0.95
Rivaroxaban	0.57	0.51, 0.63
Dabigatran	1.09	0.80, 1.47

Conclusion

Patients are in a hypercoagulable state after THA and TKA procedures.[2-4,20] DVT after an elective procedure such as a THA or TKA can have serious ramifications including pulmonary embolism and, in extreme situations, death. Variation exists in the American Academy of Orthopaedic Surgeons and American College of Chest Physicians recommendations on optimal postoperative anticoagulation management of these patients.[6] Consequently, physician preference and clinical decision making are the primary determinants of a patient's postoperative anticoagulant selection.

This investigation demonstrated the changes between year 2004 and year 2013 in surgeon preference for postoperative DVT prophylaxis in patients undergoing THA and TKA procedures. Limiting the study to this period allowed this investigation to obtain a large sample size and observe the changes in practice patterns seen with the introduction of novel postoperative DVT prophylaxis agents. During the study period, a notable decrease was observed in patients prescribed warfarin and an increase seen in patients prescribed rivaroxaban. During the same period, no statistically significant change was noted in the overall DVT rates in the 6 months after THA or TKA. Patients with a hypercoagulable diagnosis had markedly higher rates of DVT within 6 months of a THA or TKA procedure compared with those patients without hypercoagulable diagnosis. No other clinically significant risk factors were identified to distinguish patients at a high risk of DVT. Furthermore, a greater portion of patients with hypercoagulable diagnosis were treated with warfarin and lovenox (Table 5).

Vitamin K antagonists such as warfarin pose a variety of challenges, which have likely contributed to its decreasing popularity. Patients must be closely monitored to ensure that their international normalized ratio (INR) is within the therapeutic range. If the INR is above or below the therapeutic range, patients will have to adjust their doses accordingly. In addition, dietary changes can influence the metabolism of the drug subsequently affecting the overall effectiveness and influence on the INR.[14,21] Warfarin has been classically considered to be relatively low cost; however, after taking into account the cost of laboratory monitoring, the overall cost of warfarin prophylaxis has been shown to actually be greater than prophylaxis with low-molecular-weight heparin.[22] However, warfarin provides the greatest advantage over other types of anticoagulant because it can be readily reversed if bleeding or anticoagulation-related complications arise. Newer medications, such as factor Xa inhibitors and direct thrombin inhibitors are attractive solutions because they can be administered orally, do not require laboratory monitoring, and have predictable pharmacokinetics irrespective of body mass or diet.[23,24] Downsides of these medications include cost and the only option to reverse the drug with fresh frozen plasma if bleeding complications arise; however, studies have shown no increase in wound complication and thromboembolic rates in factor Xa inhibitors compared with other forms of anticoagulation.[25]

Aspirin is appealing because of its low cost, oral administration, predictable pharmacokinetics, and easy access over the counter. A recent meta-analysis showed that patients undergoing THA or TKA did not have any difference in proximal DVT risk when comparing aspirin versus other anticoagulants.[26] However, this analysis included studies, which performed screening for DVT on all patients; this practice is neither practical nor recommended.[5,6,11] In this investigation, information was collected on prescribed aspirin claims. The number of patients taking aspirin as the primary prophylaxis after TKA and THA may be higher than reported in this investigation because this drug is also available without a prescription. In a subanalysis, we included data on 129,505 patients who did not have any prescription anticoagulant. This cohort did not have markedly higher DVT rates within 6 months of THA or TKA procedures compared with prescription anticoagulants. It

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is possible that these patients were taking over-the-counter anticoagulants; however, this cannot be confirmed with the available data.

The study found markedly increased DVT rates in the 6 months after THA and TKA procedures in patients treated with warfarin (odds ratio: 3.60, 95% confidence interval, 3.38–3.84) and enoxaparin (odds ratio: 1.14, 95% confidence interval, 1.09–1.20). The exact reason for the increased DVT rate in this subgroup cannot be determined from this study and beyond the scope of this investigation. This study focused on claims information and did not have any information on INR levels or patient compliance. Studies have demonstrated that patients are within the therapeutic range only 45.9% of the time postoperatively.[27] Enoxaparin is administered subcutaneously and provides challenges inherent to people hesitant to administer the drug on themselves; however, this has not been shown to prevent compliance.[28] It is unclear whether the increased rate of DVT observed is due to failure of patient compliance or another confounding variable unaccounted for in the regression model. Importantly, the results in this study represent the actual observed population-level rates over a decade of time with the use of various prophylactic regimens. Consequently, these findings are informative to both surgeons and patients as to the expected population rates of DVT.

This study has limitations inherent to any retrospective review. The database is likely to represent a representative sample of the overall population but does not include patients without insurance or on Medicaid. The information in the database is limited to the specified time; however, this provides the benefit of a large sample size. Patients who did not have medication claims data were also excluded from this analysis. Medications that were obtained over the counter were also not captured by the database. Patient compliance with medications could not be determined from our data because the usual course of anticoagulants prescribed after a THA or TKA is too brief to calculate medication possession ratios.

Overall, this investigation demonstrates, at a population level, recent trends in DVT prophylaxis after THA and TKA procedures. Although warfarin is still the most commonly prescribed prophylaxis after THA and TKA procedures, use of this agent is decreasing. Patients with a history of DVT or hypercoagulability are at a higher risk of postoperative DVT, regardless of the type of prophylaxis prescribed. After adjusting for age, sex, and hypercoagulability diagnosis, the likelihood of DVT within 6 months of THA and TKA procedures was markedly increased in patients treated with warfarin and lovenox and markedly decreased in those treated with aspirin, fondaparinux, and rivaroxaban. Given the sample size of the data over a prolonged period in the actual observed clinical setting, this information is useful for surgeons when counseling their patients on the different types of anticoagulants available before undergoing THA or TKA procedures.

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