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Impact of thromboprophylaxis guidelines on clinical outcomes following total hip and total knee replacement

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ABSTRACT

Background: The American College of Chest Physicians (ACCP) guidelines recommends thromboprophylaxis for total hip replacement (THR) and total knee replacement (TKR) patients. We examined alignment with ACCP thromboprophylaxis guidelines among THR/TKR patients, and compared symptomatic venous thromboembolism (VTE), bleeding event rates and risk factors for VTE between patients receiving ACCP-recommended thromboprophylaxis ('ACCP') and those who did not ('non-ACCP').

Methods: This retrospective observational study used a large US health plan claims database that was linked to an inpatient database containing detailed inpatient medication use and a database containing date-of-death information. Patients who had THR/TKR surgery between April 01, 2004 and December 31, 2006 were included. Comparisons of VTE and bleeding events between ACCP and non-ACCP patients were analyzed using chi-squared tests and multivariate logistic regression.

Results: Of 3,497 linked patients, 1,395 (40%) received ACCP recommended thromboprophylaxis. Of the patients who received non-ACCP recommended prophylaxis the majority (81%) received shorter than the recommended minimum 10 day prophylaxis and 118 (5.6%) of patients received no prophylaxis. Overall, non-ACCP patients were almost twice as likely to experience an incident DVT (3.76% versus 2.01%, $p = 0.003$) and more than eight times as likely to experience an incident PE (1.19% versus 0.14%, $p = 0.001$) relative to ACCP patients; there were no statistically significant difference in bleeding rates. Multivariate logistic regression indicated that the odds of a VTE event were significantly lower for ACCP patients (DVT: OR = 0.54; $p = 0.006$; PE: OR = 0.12; $p = 0.004$).

Conclusions: This study offers a unique perspective on 'real-world' thromboprophylaxis patterns and associated outcomes in THR and TKR patients in the US. It suggests that only 40% of THR/TKR patients receive ACCP-recommended thromboprophylaxis and that not receiving ACCP thromboprophylaxis is an independent risk factor for both DVT and PE.

Introduction

Venous thromboembolism (VTE), a serious and sometimes fatal condition that includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE), can occur following major surgery including total hip replacement (THR) and total knee replacement (TKR).[1,2] Both surgeries are associated with increased postoperative VTE risk.[1–3] Symptomatic VTE incidence within 90 days of surgery ranges between 1.5-2.8% for THR and 0.7-2.1% for TKR.[3–5] Thus, the American College of Chest Physicians (ACCP) evidence-based clinical practice thromboprophylaxis guidelines (8th edition) recommend that both THR and TKR patients receive anticoagulant prophylaxis for a minimum of 10 days and up to 28–35 days post-surgery with any of the following drug classes: vitamin K antagonist (VKA), low-molecular-weight heparin (LMWH), or fondaparinux (a factor Xa inhibitor).[2] In five recent studies examining thromboprophylaxis guideline adherence, 20-95% of THR and TKR patients received thromboprophylaxis with anticoagulant and mechanical methods.[3,6–9] However, other important guideline aspects (dose, commencement,

Abbreviations: ACCP, American College of Chest Physicians; CI, confidence interval; CM, clinical modification; DVT, deep vein thrombosis; GLORY, Global Orthopaedic Registry; HIPAA, Health Insurance Portability and Accountability Act; ICD, International Classification of Diseases; LMWH, low-molecular-weight heparin; OR, odds ratio; PE, pulmonary embolism; THR, total hip replacement; TKR, total knee replacement; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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and thromboprophylaxis duration) were evaluated in only 3 studies.[3,8,9] Two studies reported VTE incidence [3,9] with overall 3-month post-surgery VTE rates of 1.7% for THR and 2.3% for TKR.[9] The third study reported a reduction in short-term mortality rates in patients receiving post-discharge thromboprophylaxis (0.6%) compared to no post-discharge thromboprophylaxis (2.0%) within 3 months post-hospital discharge ($p<0.001$).[6] A sixth study reported that 91% of orthopedic surgery patients received anticoagulant therapy while in-hospital, but only 54% filled a prescription within 30 days of discharge.[10] Patient outcomes were not evaluated in this study.[10]

To date, no study has assessed all aspects of guideline adherence and clinical outcomes through the continuum of inpatient and post-discharge care. The purpose of this study was to evaluate a THR/TKR patient population representative of most North American patients undergoing this procedure to determine: 1) alignment with ACCP thromboprophylaxis guidelines, 2) incidence of symptomatic VTE and bleeding events between patients receiving ACCP-recommended thromboprophylaxis and those who did not, and 3) factors influencing VTE risk.

Methods and materials

Study design

The study included commercial enrollees from a large US healthcare plan who underwent THR or TKR surgery (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] procedure codes 81.51 or 81.54 respectively) between April 01, 2004 and December 31, 2006. Revision surgeries were not included. Patients were followed across 3 time periods (Fig. 1). The baseline period included the 90-day period prior to the day of hospital admission (day of hospital admission = *Index Procedure Date*). The *Index hospitalization period* for THR/TKR started on the day of hospital admission (*Index Procedure Date)* until hospital discharge and included both pre-surgery and post-surgery periods. The follow-up period included the 90-day period post-hospital discharge or the time until death (if death occurred < 90 days post-hospital discharge).

Using 3 databases, patient information was collected to provide continuous data across the time periods (Fig. 1).

- 'Claims database': The OptumInsight (formerly i3 Innovus)-affiliated (Eden Prairie, MN) US health plan database included claims submitted by physicians, hospitals, and pharmacies for their services. Claims included codes designating patient treatment and post-hospital thromboprophylaxis. However, information on medication use and tests/procedures performed in the hospital, and deaths occurring post-discharge were limited.
- Inpatient database: The Perspective™ Comparative Database (Premier Inc., Charlotte, NC) includes patient-level data from hospital inpatient records. For this analysis, information on diagnosis, treatments, and medication use on each day of inpatient stay (including duration of therapy) for patients with records linked to the claims database was used.
- Date-of-death database: Accurint, a LexisNexis® (Philadelphia, PA) database product, contained death dates for patients who died following index hospitalization.

Patients were ≥ 18 years and were continuously insured with medical and pharmacy benefit during the baseline, index hospitalization, and follow-up periods. Patients with a VTE (DVT or PE) diagnosis code or with a procedure code for orthopedic surgery during the baseline period were excluded (see Appendix Table 1 for codes).

Eligible patients identified in the claims database were linked to the inpatient database using a methodology similar to Hammill et al.[11] Linking was performed at a patient-specific level based on birth year, gender, admission and discharge dates, primary diagnosis on index date and hospital name/location. Patient data were de-identified and accessed with protocols compliant with the Health Insurance Portability and Accountability Act (HIPAA), 1996. An internal HIPAA review was conducted before linking the claims and inpatient databases, while an external privacy board approval was obtained before merging with the date-of-death database.

Baseline demographics and treatment assessments

Patient demographic information (age, gender, and geographic location) was captured from enrollment data in the claims database. Comorbid conditions were identified from claims data using appropriate diagnosis codes. Using the Deyo [12] adaptation of the Charlson Comorbidity Index [13], baseline comorbidity was measured for each patient. Anticoagulant (VKA, LMWH, fondaparinux, or unfractionated heparin) or antiplatelet therapy (aspirin or other antiplatelet agents), dose, and duration were identified during baseline, index hospitalization (pre- and post-surgery), and follow-up periods. In calculating the duration of thromboprophylaxis for any subject, both inpatient and claims databases were used; inpatient database provided the length of thromboprophylaxis during the inpatient stay while the claims database provided the length of thromboprophylaxis following discharge from index hospitalization.

Based on the identification period for the study patients (04/01/2004 to 12/31/2006), the ACCP 7th edition guidelines [1] were used as these were the current guidelines for our observation period. The ACCP and non-ACCP thromboprophylaxis groups were defined as follows:

- ACCP: Patients received an ACCP-recommended prophylactic agent (VKA, LMWH, or fondaparinux) for a minimum of 10 days or until the first occurrence of a bleeding event, VTE, or death. For THR patients, treatment initiation must have occurred within one day of surgery.
- Non-ACCP: Patients did not receive an ACCP-recommended agent or patients received an ACCP-recommended agent but initiation time or treatment duration did not meet ACCP criteria.

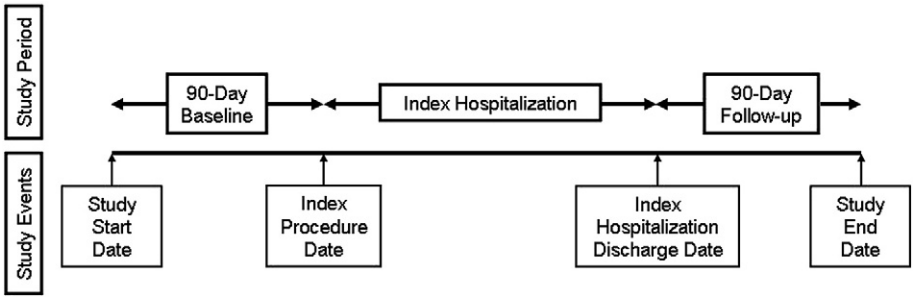

Fig. 1. Observation Period for a Typical THR or TKR Surgery Patient.

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DVT, PE, and major/minor bleeding events were identified from medical claims with an appropriate ICD-9-CM code(s) in either primary or secondary diagnosis position (Appendix Table 1). DVT or PE diagnosis codes that were included in the testing procedure claims for VTE diagnosis determination were not considered VTE event claims.

The definition of major bleeding was based on the International Society on Thrombosis and Haemostasis [14,15] guidelines with the addition of reoperation due to bleeding.[15] Events considered to constitute a major bleed therefore included fatal bleeding, non-fatal bleeding at a critical site, reoperation due to bleeding, or overt bleeding (see Appendix Table 1). Minor bleeding events and respective codes are shown in Appendix Table 1. Major or minor bleeds occurring on the surgical date were excluded to avoid counting excessive bleeding associated with the surgical procedure or blood transfusions given during surgery.

First-time DVT, PE, and bleeding events were counted only if occurrence was during the three defined periods: (i) index hospitalization, (ii) 90-day follow-up period, or (iii) the previous two periods combined (Fig. 1). DVT and PE codes for presumed recurrences were excluded.

Statistical analyses

Study variables were compared between ACCP and non-ACCP using Chi-squared tests for categorical variables and t-tests for continuous variables. Logistic regression was used to assess factors affecting probability of DVT, PE, and major and minor bleeding events while controlling for observed baseline characteristics (age, gender, geographic region, Charlson-Deyo Comorbidity score, physician specialties, and/or ACCP thromboprophylaxis group).

Role of funding source

Bayer Inc (Toronto, Canada) provided external funding to OptumInsight (formerly i3 Innovus) for this study.

Results

Patient characteristics

The claims database consisted of 19,149,233 enrollees of which 37,705 underwent THR/TKR surgery and 30,644 met the eligibility criteria (Fig. 2). Of these eligible patients, 3,497 or 11% (1,229 THR patients and 2,268 TKR patients) had corresponding linkable in-hospital data from the inpatient database; this represents a large patient dataset with continuous care information available from 90 days prior to surgery through 90 days post-hospitalization. Patients who could not be linked to the inpatient database had surgeries at hospitals not affiliated with Premier Inc network. Included and excluded patients showed similar baseline, time dependent characteristics, and comorbidities with the exception of geographic variables (Table 1).

Initial medication used as prophylaxis post-surgery (Table 2)

Initial prophylaxis used by the entire cohort of patients is shown in Table 2. The majority of patients received VKA (41%), 34% received LMWH and 13% received combination therapy. In addition, a small proportion of patients received fondaparinux (7%), unfractionated heparin (0.14%), or an antiplatelet agent (0.31%). Finally, 3.4% of patients received no prophylaxis.

Stratification by ACCP status

Of the 3,497 linked patients, 1,395 (40%) received ACCP-aligned thromboprophylaxis. There were 2,102 who received non-ACCP thromboprophylaxis. Reasons for classification as 'non-ACCP' included: receiving less than 10 days with an ACCP-recommended agent ($n=1712$, 81%), receiving non-recommended agents ($n=211$, 10%), receiving no thromboprophylaxis ($n=118$, 5.6%), and initiation of thromboprophylaxis outside of the recommended time window ($n=61$, 3%; THR only) (Fig. 2). For ACCP-aligned patients, the mean prophylaxis duration was 27 ± 16 days (median: 25 days) whereas for non-ACCP the mean prophylaxis duration was 3 ± 3 days (median: 2 days; p-value <0.001).

Compared to non-ACCP patients, the ACCP patient group had a significantly higher proportion of males (48% vs. 41%; $p<0.001$) and were younger (58 vs. 61 years; $p<0.001$; Table 3). Of note, baseline comorbidities were not significantly different between ACCP and non-ACCP patients. Although ACCP patients had significantly lower Charlson-Deyo comorbidity scores (0.39 vs. 0.48; $p<0.0006$), all patients in this study were less than 1 (scale: 0 to 28) and the difference between groups (0.09) was considered clinically insignificant.

Incidence of clinical outcomes

Incidence of DVT, PE, bleeding events, and mortality are reported in Table 4. There were a total of 30 events in the ACCP patients (28 DVT and 2 PE). These 30 events occurred in 28 unique patients (i.e. 2 patients had both a DVT and a PE). A total of 104 events occurred in the non-ACCP patients (79 DVT and 25 PE). These events occurred in 79 unique patients (i.e. 25 patients had both a DVT and a PE).

Non-ACCP patients experienced incident DVTs approximately 4 times more frequently (1.71% versus 0.43%; $p=0.001$) during the index hospitalization (post index surgery) period and almost 1.5 times more frequently (2.08% versus 1.58%; $p=0.291$) during the follow-up period compared to ACCP patients. Overall (across both time periods), non-ACCP patients were almost twice as likely as ACCP patients (3.76% versus 2.01%; $p=0.003$) to have a DVT.

Non-ACCP patients experienced incident PEs more frequently (0.67% versus 0.00%; $p=0.002$) during index hospitalization (post index surgery) period and almost four times as frequently (0.53% versus 0.14%; $p=0.069$) during follow-up compared to ACCP patients. Overall (across both time periods), non-ACCP patients were more than eight times as likely as ACCP patients (1.19% versus 0.14%; $p=0.001$) to experience an incident PE. There were no significant differences for major bleeding rates or mortality rates between non-ACCP and ACCP patients during the 3 time periods (Table 4).

Overall, in the 118 patients who received no prophylaxis, the incidence of DVT was 27% (32 events) and the incidence of PE was 8.5% (10 events). These 42 events occurred in 32 unique patients (i.e. 10 patients experienced both a DVT and PE). 8.5% of patients receiving no prophylaxis experienced a major bleed and 5.9% experienced a minor bleed.

The association between VTE/bleeding events and thromboprophylaxis use as assessed with multivariate logistic regression modeling is shown in Table 5. Following index surgery, ACCP patients had significantly lower probability of experiencing DVT ($OR=0.54$; $p=0.006$) or PE ($OR=0.12$, $p=0.004$). Other factors were not associated with DVT or PE. Importantly, ACCP thromboprophylaxis did not significantly affect the probability of having a major or minor bleeding event.

Discussion

In order to fully evaluate alignment with ACCP-recommended thromboprophylaxis guidelines and associated outcomes, we merged three databases and followed patients from surgery up to 90 days post-hospital discharge. By doing so, our study offers a unique perspective of real world thromboprophylaxis practice patterns and associated outcomes in US patients undergoing THR/TKR. In the approximately 3,500 patients evaluated in our analysis VKA and

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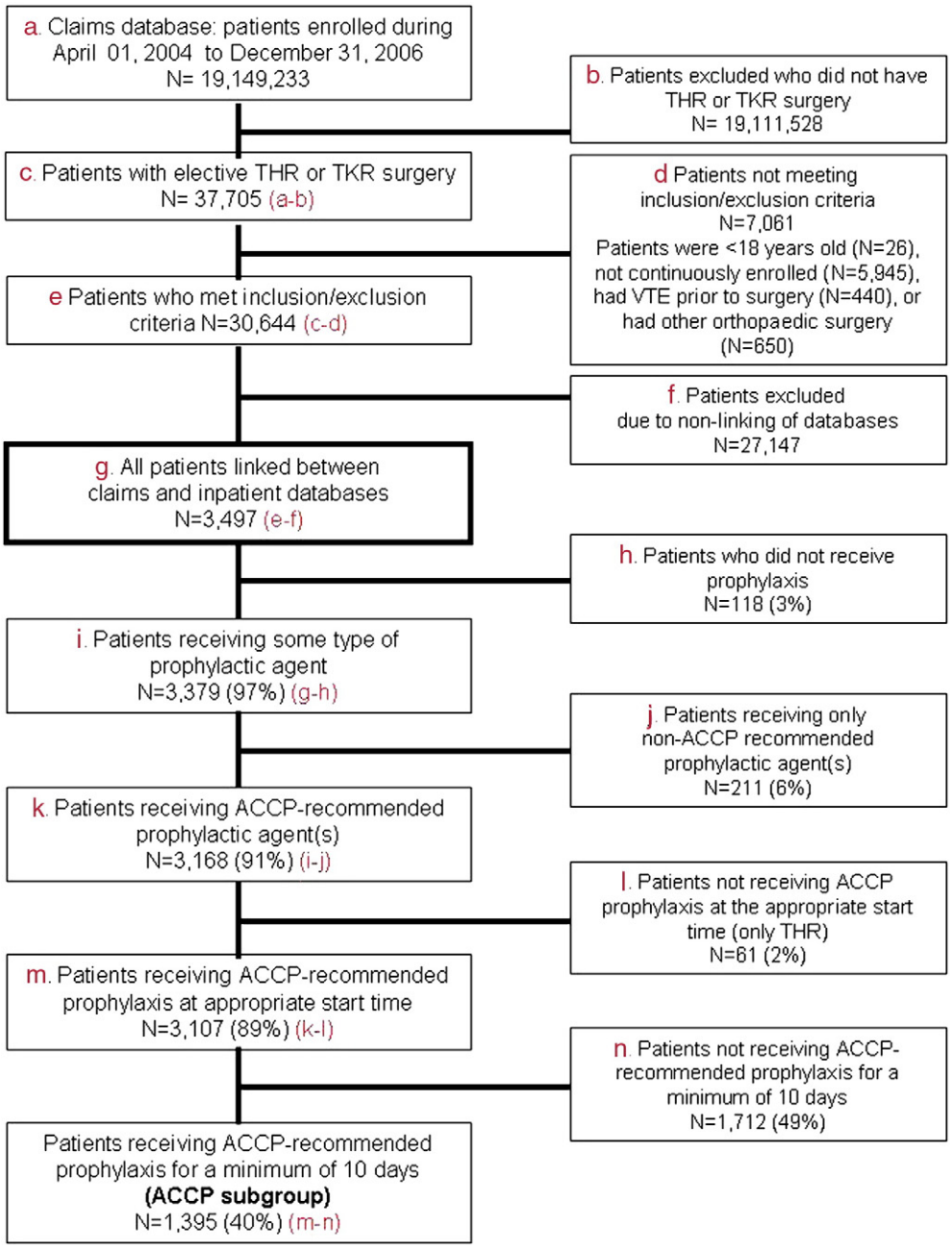

Fig. 2. Patient Enrollment and Attrition.

LMWH appear to be the most frequently-prescribed prophylaxis agents following THR/TKR: over 40% of patients received VKA following surgery while over 34% of patients received LMWH. Our data suggest that only 40% of patients received thromboprophylaxis in alignment with ACCP guidelines. Furthermore, failure to follow ACCP guidelines resulted in almost twice the probability of incident symptomatic DVT (3.76% versus 2.01%, $p = 0.003$) and more than eight times the probability of incident symptomatic PE (1.19% versus 0.14%, $p = 0.001$). Multivariate analyses indicated that the only factor lowering the incidence of VTE was use of appropriate thromboprophylaxis (OR = 0.54, $p = 0.006$ for DVT and OR = 0.12, $p = 0.004$ for PE). Importantly, there were no significant differences between ACCP and non-ACCP patients in the probability of major or minor bleeding or mortality. Although only 40% of the patients received ACCP-aligned thromboprophylaxis, approximately 94% of all patients received an anticoagulant or antiplatelet and the majority received an ACCP-recommended agent. The most common reason for ACCP non-alignment was not receiving thromboprophylaxis for the minimum ACCP-recommended duration of 10 days (81% of non-ACCP patients). In the 118 patients who did not receive any prophylaxis, the incidence of DVT was 27% (32 events) while the incidence of PE was 8.5% (10 events). The primary reason for analyzing the no-prophylaxis subgroup separately was to assess if event rates in this subgroup were the highest and driving the difference in event rates seen between the ACCP and non-ACCP patient groups. When the no prophylaxis group is subtracted from the non-ACCP group, the rates of DVT and PE in the non-ACCP group are 3.37% (vs. 2.01% for the ACCP group) and 0.7% (vs. 0.14% in the ACCP group), respectively. In our study, ACCP and non-ACCP subgroup definitions were based on the ACCP 7th edition thromboprophylaxis guidelines [1] which were the relevant guidelines for the period of analysis and included drug type, dose, start time, and minimum duration of 10 days. Since then, the ACCP 8th edition guidelines have been published. [2] However, the recommendations for the parameters listed above remain

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Table 1
Characteristics of Patients Included and Excluded in the Sample after Linking.

Patient Characteristics	Patients Included (N = 27,147)		Patients Excluded (N = 3,497)		p-value
	n	%	n	%	
Gender					
Male	11,774	43.37	1,520	43.47	0.9278
Female	15,373	56.63	1,977	56.53	0.9278
Geographic Regions					
Northeast	2,400	8.84	186	5.32	**<.0001**
Midwest	10,486	38.63	1,203	34.40	**<.0001**
South	9,826	36.20	1,691	48.36	**<.0001**
West	4,435	16.34	417	11.92	**<.0001**
Age Groups					
18-34	271	1.00	30	0.86	0.4671
35-54	7,283	26.83	970	27.74	0.2568
55-64	12,117	44.63	1,493	42.69	**0.0300**
65-74	4,844	17.84	673	19.25	**0.0443**
75+	2,632	9.70	331	9.47	0.6927
Baseline Comorbid Conditions					
	Mean	SD	Mean	SD	
Age	59.98	10.26	60.01	10.12	0.8751
Charlson-Deyo Comorbidity Score	0.45	0.85	0.44	0.84	0.6772
	n	%	n	%	
Hypertension	12,703	46.79	1,662	47.53	0.4179
Long-term use of Anticoagulants	615	2.27	80	2.29	0.9040
Long-term use of Antiplatelets / Antithrombotics	9	0.03	1	0.03	1.0000
Personal History of PE	72	0.27	6	0.17	0.3740
Personal History of Thrombophlebitis	5	0.02	1	0.03	0.5167
Hepatic Disease	295	1.09	42	1.20	0.5461
Renal Disease	2,404	8.86	322	9.21	0.4876
Cancer (excluding MDS)	1,080	3.98	131	3.75	0.5488
Hemophilia	12	0.04	1	0.03	1.0000
Coagulation Defects other than Hemophilia	193	0.71	33	0.94	0.1405
Abnormal Coagulation Profile	56	0.21	8	0.23	0.6962

Note: Significant p-values are bold.
Abbreviations: ACCP = American College of Chest Physicians, AIDS = Acquired immune deficiency syndrome, HIV = Human immunodeficiency virus, MDS = Myelodysplastic syndromes

Table 3
Patient Baseline Characteristics.

Therapy Used	Total N = 3,497		ACCP (N = 1,395)		Non-ACCP (N = 2,102)		p-value
	n	%	n	%	n	%	
Gender: Male	1,520	43.47	664	47.60	856	40.72	**<.0001**
Age Groups							
18-34	30	0.86	12	0.86	18	0.86	**<.0001**
35-54	970	27.74	432	30.97	538	25.59	
55-64	1,493	42.69	664	47.60	829	39.44	
65-75	673	19.25	232	16.63	441	20.98	
75+	331	9.47	55	3.94	276	13.13	
Geographic Regions							
Northeast	186	5.32	64	4.59	122	5.80	0.0977
Midwest	1,203	34.40	505	36.20	698	33.21	
South	1,691	48.36	673	48.24	1,018	48.43	
West	417	11.92	153	10.97	264	12.56	
	mean	**std**	**mean**	**std**	**mean**	**std**	
Age, in years (continuous)	60.01	10.12	58.21	8.66	61.20	10.82	**<.0001**
Charlson-Deyo Comorbidity Score	0.44	0.84	0.39	0.74	0.48	0.90	**0.0006**
Baseline Comorbidity Score							
	n	**%**	**n**	**%**	**n**	**%**	
Hypertension	1,662	47.53	636	45.59	1,026	48.81	0.0619
Anticoagulants	80	2.29	20	1.43	60	2.85	**0.0059**
Long-term Use Antiplatelets/ Antithrombotics Long-term Use	1	0.03	1	0.07	0	0.00	0.2196
Personal History of PE	6	0.17	1	0.07	5	0.24	0.2449
Personal History of Thrombophlebitis	1	0.03	0	0.00	1	0.05	0.4152
Hepatic Disease	42	1.20	12	0.86	30	1.43	0.1317
Renal Disease	322	9.21	125	8.96	197	9.37	0.6803
Cancer (excluding MDS)	131	3.75	43	3.08	88	4.19	0.0923
Hemophilia	1	0.03	0	0.00	1	0.05	0.4152
Coagulation Defects other than Hemophilia	33	0.94	18	1.29	15	0.71	0.0841
Abnormal Coagulation Profile	8	0.23	5	0.36	3	0.14	0.1911
HIV Infection/AIDS	4	0.11	0	0.00	4	0.19	0.1031

Note: Significant p-values are bold.
Abbreviations: ACCP = American College of Chest Physicians, AIDS = Acquired immune deficiency syndrome, HIV = Human immunodeficiency virus, MDS = Myelodysplastic syndromes.

unchanged between the two guidelines. Therefore, our results are applicable to both editions.[1,2] Two previous studies also used the 7th edition guidelines; however alignment (19-88%) was defined by thromboprophylaxis agent and did not include commencement or duration.[6,7] Two other studies used ACCP 6th edition guidelines [8,16] to determine alignment; however, thromboprophylaxis included pharmacological interventions with or without mechanical thromboprophylaxis.[17] Additionally, one study reported alignment by surgery type (47% THR and 61% TKR).[8] The three databases combined provided a large comprehensive source of information (including medication use) from hospitalization prior to surgery through 90-days post-discharge, allowing us to describe the continuum of care following THR/TKR surgery for both inpatient and outpatient periods. Most other studies have either used a shorter timeframe by evaluating thromboprophylaxis cross-sectionally, inpatient only, community-based only, [6,7] or physician-reported participation.[3,8,9] Three studies have used Premier's Perspective™ database to evaluate VTE.[10,16,18] Two were limited to in-hospital thromboprophylaxis use.[16,18] One of these evaluated specific drug use [18] (not ACCP alignment) in orthopedic patients and the other evaluated ACCP 6th edition alignment in hospitalized non-THR/TKR patients (33.9%).[16] The third study evaluated anticoagulant utilization among orthopedic surgery patients in both in-patient and outpatient settings, and found that although almost all patients receive anticoagulant therapy while in-hospital, approximately half did not fill a prescription within 30 days of discharge.[10] Our overall VTE rates (3.83%) were comparable to overall VTE rates reported by White and colleagues in California patients who underwent unilateral THR/TKR and had linked hospital discharge data (1998), where the VTE rate was 4.9%.[3] In a retrospective cohort analysis using the Perspective™ database, overall VTE rates were 2.5% for patients receiving injectable antithrombotic agents following THR, TKR, and hip fracture surgeries in participating US hospitals.[16] Thus, our results complement previous findings.[3,6–9,18,19]

Table 2
Initial Anticoagulant/Antiplatelet Used As Prophylaxis Post-Surgery.

Therapy	Total N = 3497	
	n	**%**
Vitamin K antagonist or warfarin only	1,445	41.32%
Low-molecular weight heparin only	1,193	34.11%
Fondaparinux only	259	7.41%
Unfractionated heparin only	5	0.14%
Platelet aggregation inhibitor only	11	0.31%
Combination Therapy	466	13.33%
No Prophylaxis	118	3.37%

This study has some limitations, which are typical of retrospective database review studies. First, filled-prescription claims do not indicate that medication was taken as prescribed and may result in over estimation of the effect of prophylaxis. As well, medications filled over-the-counter (aspirin) or physician-provided samples are not

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Table 4
Incidence of first DVT, PE, Major and Minor Bleeding Events by Time Period.

	Total N = 3497		ACCP (N = 1,395)		Non-ACCP (N = 2,102)		p-value
	n	%	n	%	n	%	
Incident Events Occurring During Index Hospitalization							
DVT	42	1.20	6	0.43	36	1.71	**0.001**
PE	14	0.40	0	0.00	14	0.67	**0.002**
Major Bleeding*	12	0.34	4	0.29	8	0.38	0.642
Minor Bleeding*	9	0.26	0	0.00	9	0.43	**0.014**
Mortality‡	5	0.14	3	0.22	2	0.10	0.3581
Incident Events Occurring Up to 90 Days Following Discharge from Index Hospitalization							
DVT	65	1.88	22	1.58	43	2.08	0.291
PE	13	0.37	2	0.14	11	0.53	0.069
Major Bleeding*	30	0.86	8	0.57	22	1.05	0.137
Minor Bleeding	117	3.35	44	3.15	73	3.49	0.592
Mortality ‡	2	0.06	0	0.00	2	0.10	0.2491
Overall Incident Events Occurring Following Index Surgery until End of Study							
DVT	107	3.06	28	2.01	79	3.76	**0.003**
PE	27	0.77	2	0.14	25	1.19	**0.001**
Major Bleeding*	42	1.20	12	0.86	30	1.43	0.132
Minor Bleeding*	126	3.60	44	3.15	82	3.90	0.246
Mortality	7	0.20	3	0.22	4	0.19	0.8730

Note: Significant p-values are bold.
Abbreviations: ACCP = American College of Chest Physicians, DVT = deep vein thrombosis, PE = pulmonary embolism.
*Major and minor bleeding rates do not include events occurring on index date. Major bleeding events were not recurrent.
**Patients that experienced an event for the first time were classified as "New".
†Patients that had experienced a similar event during the index hospitalization period and then another event during the 90 days following discharge from index hospitalization were classified as "Recurrent". In order for a DVT or PE event to be defined as "recurrent", such an event must result in a new hospitalization or an emergency room admission.

measurable with claims data and may result in under estimating therapy duration. Second, the databases we used were not formally validated for coding accuracy. Therefore, a diagnosis code on a claim may not indicate positive disease presence and may have been either incorrectly coded or included as rule-out criteria rather than actual disease. The issue of accurately identifying VTE based on ICD-9 codes is not settled in the literature. For example, one study by White et al. [20] found the positive predictive value (PPV) for VTE ICD-9 codes in the primary diagnosis position to be 79%, while another study by the same authors [21] found it to be around 95%. Similarly, the PPV for lower extremity deep vein thrombosis was between 44-48% in the first study while the same was 91% in the second. As the above studies suggest, PPV for ICD-9 codes appears to be a function of the database. Even if the PPV for the ICD-9 codes in our database was low the coding rule was applied equally to both ACCP and non-ACCP groups and so no systematic bias would have been introduced in determining the outcomes. To minimize false positives due to suspected DVT / PE cases that were not subsequently confirmed we excluded DVT / PE codes that appeared only in the claims for various diagnostic or other test procedures but for whom no follow-up diagnosis for the same was recorded.

Third, the impact of race/ethnicity, [22] body mass index, [23] number of days to first ambulation, [23] type and duration of anesthesia, [23,24] adequacy of anticoagulation and other risk factors [22,23,25] on VTE and bleeding events was not evaluable in these databases. We also could not capture the use of mechanical prophylaxis as a sole or combined modality that may have been a confounder in the ACCP patients. Lastly, in our study patient geographic distribution differed between included and non-included patients reflecting geographic differences between patient health plan coverage (claims data) and hospital Premier network (inpatient data) participation. Although this may induce differences in practice patterns across geographic regions, baseline characteristics between patients included and excluded from the final sample were similar.

In conclusion, by following patients from surgery through to community-based care, this study offers a unique perspective on 'real-world' thromboprophylaxis patterns and clinical outcomes in THR/TKR patients. Our study suggests that only 40% of THR/TKR patients received ACCP-aligned thromboprophylaxis. The most common reason for ACCP non-alignment was the failure to receive thromboprophylaxis for a minimum of 10 days (81% of non-ACCP patients). Compared to ACCP-aligned patients, non-ACCP patients were almost twice as likely

Table 5
Logistic Regression Results.

	Whether had a DVT following index surgery	Whether had a PE following index surgery	Whether had a minor bleeding* following index surgery	Whether had a major bleeding* following index surgery
	OR [95% CI] (p-value)	OR [95% CI] (p-value)	OR [95% CI] (p-value)	OR [95% CI] (p-value)
Age as of the index date	1.01 [0.99, 1.03] (0.191)	0.98 [0.94, 1.02] (0.251)	1.01[0.99,1.02] (0.578)	1.00 [0.97,1.04] (0.934)
Male; Reference: Female	1.19 [0.81,1.77] (0.380)	0.56 [0.24,1.30] (0.176)	**1.85 [1.27,2.70] (0.001)**	0.86 [0.44,1.68] (0.656)
Baseline Charlson-Deyo Comorbidity Score	0.87 [0.67,1.13] (0.285)	0.78 [0.44,1.36] (0.376)	1.15 [0.94,1.39] (0.165)	1.21 [0.90,1.62] (0.206)
Whether had ACCP-compliant thromboprophylaxis	**0.54 [0.35,0.84] (0.006)**	**0.12 [0.03,0.50 (0.004)**	0.83 [0.69,1.51] (0.360)	0.69 [0.34,1.39] (0.299)
Observations	3497	3497	3434	3220
Pseudo R^2	0.018	0.070	0.022	0.068
Hosmer-Lemeshow Lack-of-Fit Test's p-value	0.568	0.118	0.295	0.721

Note: Significant p-values are bold.
Abbreviations: CI = confidence interval, DVT = deep vein thrombosis, PE = pulmonary embolism.
*Minor or major bleeding events on the index date are not considered.

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to have an incident symptomatic DVT and more than eight times as likely to experience an incident symptomatic PE while there were no overall differences in major/minor bleeding rates. Furthermore, multivariate logistic regression showed that ACCP-aligned patients had significantly lower probability of experiencing DVT (OR = 0.54; p = 0.006) or PE (OR = 0.12; p = 0.004); thus, alignment to ACCP thromboprophylaxis guidelines was an independent predictor of VTE incidence. Our study supports the finding of many prior studies that despite overwhelming evidence supporting thromboprophylaxis, its use remains far from optimal. [26] Successful implementation strategies that will bridge this knowledge: care gap remain the most important current challenge in this area. These strategies must be multifaceted, utilizing local, systems-based approaches as well as legislation and incentives that reinforce best practices. [26]

Reproducible research statement

Study protocol: Available from Dr. Bijan Borah (E-mail: borah.bijan@mayo.edu)

Statistical code and data set: Not available

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Conflict of interest statement

The research was performed at OptumInsight (formerly i3 Innovus), Eden Prairie, MN. Editorial and financial support for this publication was provided by Bayer, Inc (Canada) to OptumInsight. The authors, however, were fully responsible for content, analyses, and editorial decisions for this manuscript. Any and all potential competing interests (conflicts of interest) are identified as follows: Drs Selby, Crowther, and Wells have received research honorariums from Bayer Inc. Dr. Borah was an employee of i3 Innovus when this manuscript was prepared. Dr. Henk is an employee of OptumInsight and H. McDonald is an employee of Bayer, Inc.

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References

[1] Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126:338S–400S.
[2] Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. American College of Chest Physicians. Prevention of Venous Thromboembolism: American College of Chest Physicians evidence-based clinical practice guidlines (8th edition). Chest 2008;133:381S–453S.
[3] White RH, Ramano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Arch Intern Med 1998;158:1525–31.
[4] Mantilla CB, Horlacker TT, Schroeder DR, Berry DJ, Brown DL. Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. Anesthesiology 2002;96:1140–6.
[5] Howie C, Hughes H, Watts AC. Venous thromboembolism associated with hip and knee replacement over a ten-year period: a population-based study. J Bone Joint Surg 2005;87-B:1675–80.
[6] Rahme E, Dasgupta K, Burman M, Yin H, Bernatsky S, Berry G, Nedjar H, Kahn SR. Post-discharge thromboprophylaxis and mortality risk after hip- or knee-replacement surgery. CMAJ 2008;178:1545–54.
[7] Cohen AT, Tapson VF, Bergmann J-F, Goldhaber SZ, Kakkar AK, Deslandes B, Huang W, Zayaruzny M, Emery L, Anderson Jr FA. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008;371:387–94.
[8] Friedman RJ, Gallus AS, Cushner FD, Fitzgerald G, Anderson Jr FA. Global Orthopaedic Registry Investigators. Physician compliance with guidelines for deep-vein thrombosis prevention in total hip and knee anthroplasty. Curr Med Res Opin 2008;24:87–97.
[9] Warwick D, Friedman RJ, Agnelli G, Gil-Garay E, Johnson K, FitzGerald G, Turibio FM. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. J Bone Joint Surg 2007;89:799–807.
[10] Amin A, Lin J, Ryan A. Need to improve thromboprophylaxis across the continuum of care for surgical patients. Adv Ther 2010;27:81–93.
[11] Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to Medicare claims data using indirect identifiers. Am Heart J 2009:995–1000.
[12] Deyo RA, Cherkin DC, Ciol MA. Adapting a Clinical Comorbidity Index for Use with ICD-9-CM Administrative Databases. J Clin Epidemiol 1992;45:613–9.
[13] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. J Chronic Dis 1987;40:373–83.
[14] Schulman S, Kearon C, on behalf of the Subcommittee on control of anticoagulation of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.
[15] Vera-Llonch M, Gagiwara M, Oster G. Clinical and Economic Consequences of Bleeding following Major Orthopedic Surgery. Thromb Res 2006;117:569–77.
[16] Amin A, Stemkowski SA, Lin J, Yang G. Thromboprophylaxis rates in US medical centers: success or failure? J Thromb Haemost 2007;5:1610–6.
[17] Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson Jr FA, Wheeler HB. Prevention of venous thromboembolism. Chest 2001;119(1 Suppl.):132S–75S.
[18] Shorr AF, Kwong LM, Sarnes M, Happe L, Farrelly E, Mody-Patel N. Venous thromboembolism after orthopedic surgery: implications of the choice for prophylaxis. Thromb Res 2007;121:17–24.
[19] Samama CM, Ravaud P, Parent F, Barre J, Mertl P, Mismetti P. Epidemiology of venous thromboembolism after lower limb arthroplasty: the FOTO study. J Thromb Haemost 2007;5:2360–7.
[20] White RH, Sadeghi B, Tancredi DJ, Zrelak P, Cuny J, Sama P, Utter GH, Geppert JJ, Romano PS. How valid is the ICD-9-CM based AHRQ patient safety indicator for postoperative venous Thromboembolism? Med Care Dec 2009;47(12):1237–43.
[21] White RH, Garcia M, Sadeghi B, Tancredi DJ, Zrelak P, Cuny J, Sama P, Gammon H, Schmaltz S, Romano PS. Evaluation of the predictive value of ICD-9-CM coded administrative data for venous Thromboembolism in the United States. Thromb Res Jul 2010;126(1):61–7.
[22] Keenan CR, White RH. The effects of race/ethnicity and sex on the risk of venous thromboembolism. Curr Opin Pul Med 2007;13:377–83.
[23] White RH, Gettner S, Newman JM, Trauner KB, Romano PS. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty; 2000. p. 1758–64.
[24] Jaffer AK, Barsoum WK, Krebs V, Hurbanek JG, Morra N, Brotman DJ. Duration of anesthesia and venous thromboembolism after hip and knee arthroplasty. Mayo Clin Proc 2005;80:732–8.
[25] White RH, Henderson MC. Risk factors for venous thromboembolism after total hip and knee replacement surgery. Curr Opin Pul Med 2002;8:365–71.
[26] Selby R, Geerts W. Prevention of venous thromboembolism: consensus, controversies and challenges. Hematol Am Soc Hematol Educ Program 2009:286–92.

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