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Comparison of pharmacologic prophylaxis in prevention of venous thromboembolism following total knee arthroplasty

Shawn S. Richardson *, William W. Schairer, Peter K. Sculco, Mathias P. Bostrom

Hospital for Special Surgery, New York, NY, USA

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ABSTRACT

Background: Anticoagulants are used following total knee arthroplasty (TKA) to prevent venous thromboembolism (VTE). These drugs reduce VTE risk but may lead to bleeding-related complications. Recently, surgeons have advocated using antiplatelet agents including aspirin (ASA). However, there is no consensus regarding which medication has the optimal risk/benefit profile. The purpose of this study was to compare rates of VTE using different anticoagulants in anticoagulation-naïve patients being discharged home after TKA.
Methods: A national private insurance database was used to identify patients undergoing unilateral TKA. Patients with a prior history of VTE were excluded. Anticoagulants included ASA, low molecular weight heparin (LMWH), warfarin, factor Xa inhibitors (XaI), and fondaparinux. Postoperative complications, including VTE, blood transfusion, myocardial infarction, and hematoma, were identified using ICD-9 diagnosis codes. Risk of each complication was compared between groups using multivariate logistic regression controlling for demographics, length of stay, and comorbidities.
Results: Of 30,813 patients, 1.82% were diagnosed with VTE. Using ASA as a baseline, there was significantly decreased risk of VTE with LMWH (OR 0.47), XaI (OR 0.50), and fondaparinux (OR 0.32). There was significantly higher risk of transfusion with LMWH (OR 1.56) and fondaparinux (OR 1.84), but no difference in hematoma between medications.
Conclusions: This study shows that there is a decreased risk of VTE with LMWH, XaI, and fondaparinux compared to ASA. However, these medications also had higher rates of bleeding-associated complications. The choice of pharmacologic prophylaxis should be made based on a balance of the risk/benefit profile of each medication.
Level of evidence: III.

1. Introduction

Symptomatic venous thromboembolism (VTE) is one of the more common complications following total knee arthroplasty (TKA). Recent studies have shown that despite advances in perioperative management and VTE prophylaxis, the rate of symptomatic pulmonary embolism (PE) has remained relatively constant over the past two decades while the rate of deep vein thrombosis (DVT) has declined [1,2]. Postoperative VTE complications lead to increased swelling and pain, delayed rehabilitation, longer hospital stays, increased costs, and increased patient mortality [2,3]. For these reasons, among others, there has been significant in-

* Corresponding author at: Hospital for Special Surgery, Academic Training Department, 535 East 70th Street, New York, NY 10021, USA.
E-mail address: richardsons@hss.edu. (S.S. Richardson).

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terest in the orthopedic surgery community in identifying modifiable factors that could lead to a decrease in the rate of symptomatic VTE.

Anticoagulant medications are widely used following TKA in an effort to reduce the rate of postoperative VTE. These drugs may reduce a patient's risk of VTE, but may also lead to bleeding-related complications such as the need for blood transfusion, wound drainage, or hematoma/hemarthrosis [4–8]. An ideal anticoagulant would minimize the rate of VTE without introducing significant risk of additional complications. Various anticoagulant medications have been utilized and studied, including warfarin [4,9,10], low molecular weight heparin (LMWH) [11,12], factor Xa inhibitors [13–16], and fondaparinux [11,17]. These studies, however, typically compare only two medication types rather than the entire array of potential prophylactic options. Recently, a significant amount of research has been dedicated to antiplatelet agents, such as aspirin (ASA) [3,7,18–21]. Many have hypothesized that with advances in other aspects of perioperative care, including early mobilization and increasing discharge home, ASA may provide adequate anticoagulation with the benefit of a more tolerable side effect profile in certain groups of patients. However, despite a large body of data in the literature, there remains no consensus regarding which medication has the optimal risk/benefit profile.

A recent large database study attempted to evaluate the risk of VTE following TKA when patients were treated with ASA, warfarin, LMWH, or factor Xa inhibitors, and concluded that ASA had comparable efficacy as the other medications [22]. However, without controlling for patient characteristics and discharge destination that are known to affect rates of complications [23], the conclusion that ASA is as safe as other agents for VTE prophylaxis must be further evaluated before it can be accepted for routine use.

Thus, the purpose of the present study was to perform a population-level analysis of the rates of venous thromboembolism and bleeding complications with different prophylactic medications after total knee arthroplasty. To allow the results to be most generalizable, we aimed to improve on prior evidence by selecting a homogenous patient population being discharged home within a standard-length hospital stay and performing an analysis controlling for patient comorbidities.

2. Materials and methods

2.1. Patient selection

Subjects were selected from the Pearl Diver Patient Records Database (www.pearldiverinc.com, Fort Wayne, IN), a nationwide private health insurance derived database. The Humana full claims database was queried, representing over 20.9 million patients. Patients who underwent unilateral TKA between 2007 and 2016 and were active in the insurance plan for 90 days prior to and after their TKA were selected using the appropriate International Classification of Diseases (ICD) 9 procedure code (81.54). As the database does not contain records of in-hospital medications, we excluded patients with hospital stays beyond five days or with a perioperative diagnosis of DVT in order to create a more homogenous group of non-complicated patient stays. Additionally, patients with a history of VTE or records indicating preoperative anticoagulant use within 90 days of surgery were excluded. However, patients were not excluded if their only prior anticoagulant was ASA, as this is not typically prescribed to treat existing VTE.

2.2. Anticoagulants

Postoperative anticoagulation was identified by filled postoperative outpatient prescriptions for one of the following medications: ASA, LMWH, warfarin, direct Xa inhibitors (XaI; rivaroxaban, apixaban), and fondaparinux. Fondaparinux was considered separately from the direct Xa inhibitors as it functions through an indirect mechanism by inhibiting antithrombin III rather than directly inhibiting factor Xa [24]. Prescriptions were required to be filled during the patient's hospitalization or within two days of discharge to minimize inclusion of non-compliant patients.

If a patient was diagnosed with a DVT or PE during the two days after discharge, only medications filled prior to the diagnosis were considered so as to avoid inadvertently attributing a DVT or PE to the treatment drug rather than the preceding prophylaxis medication. Patients who received no prescription or multiple types of anticoagulant prescriptions were excluded, with the exception of ASA plus an additional anticoagulant. In this setting, the patient was included in the appropriate non-ASA anticoagulant group only.

2.3. Outcomes

Age, demographic information, and length of stay were recorded for all patients. Comorbidities were identified using corresponding ICD codes as previously described by Elixhauser et al. [25]. The primary outcome was diagnosis of DVT or PE. Secondary outcomes were additional complications, including transfusion, hematoma, myocardial infarction, and all-cause readmission. All outcomes were identified using appropriate ICD codes within 90 days following TKA.

2.4. Statistical analysis

Patients included in the study were subdivided into groups based on their postoperative anticoagulant. Demographic and comorbidity data as well were compared between the groups using multiple chi-squared tests. The raw complication rates were compared among medication cohorts using multiple chi-squared tests. Multivariate logistic regression was then performed to

determine the odds of each postoperative complication based on the anticoagulant used. All multivariate logistic regressions controlled for patient age, gender, comorbidities, and length of stay. Female patients between ages 60 and 69 with a length of stay of three days were used as the baseline for comparisons as these were the most common patients included in the study. ASA was used as the baseline comparison agent. Analyses were performed using the Pearl Diver software and STATA (version 14.2, Statacorp, College Station, TX). p values of less than 0.05 were considered statistically significant.

2.5. Source of funding

Internal institutional funding supports ongoing access to the Pearl Diver database. No other funding was required to complete this study.

Table 1
Demographics.
A comparison of the age, gender, length of stay and comorbidities for all patients and subdivided by thromboprophylactic medication used following TKA. Comparisons between medication groups were performed utilizing multiple chi-squared analyses. Statistically significant differences are noted with a p value of less than 0.05.

Number	All patients	Aspirin	LMWH	Warfarin	Xa inhibitors	Fondaparinux	p-Value
	30,813	548	10,444	11,757	6524	1540	
	%	%	%	%	%	%	
Age 49 and under	2.76	5.66	2.92	2.50	2.36	4.22	<0.001*
Age 50–59	13.78	25.00	13.82	12.90	13.67	16.75	
Age 60–69	39.66	42.34	39.43	39.70	39.50	40.58	
Age 70–79	37.49	22.99	37.48	38.07	38.83	32.60	
Age 80–89	5.64	3.65	5.64	5.86	5.55	5.00	
Age 90 and over	0.68	<2.01	0.72	0.97	<0.17	0.84	
Gender (F)	60.67	61.13	60.47	61.01	60.67	59.29	0.731
Gender (M)	39.33	38.87	39.53	38.99	39.33	40.71	–
LOS 0	0.58	<2.01	0.39	0.62	0.77	<0.71	<0.001*
LOS 1	2.73	14.96	2.43	2.03	3.54	2.21	
LOS 2	24.04	40.69	21.58	22.15	31.02	19.61	
LOS 3	53.70	37.04	54.51	54.54	51.52	57.08	
LOS 4	14.79	5.11	16.42	16.15	10.04	16.82	
LOS 5	4.16	<2.01	4.66	4.51	3.11	3.70	
Congestive heart failure	1.65	<2.01	1.46	1.75	1.85	1.49	0.188
Cardiac arrhythmias	5.33	2.55	5.43	5.63	5.09	4.42	0.007*
Heart valvular disease	2.41	<2.01	2.30	2.52	2.42	2.60	0.706
Pulmonary circulation disorders	0.34	<2.01	0.30	0.42	0.26	<0.71	0.306
Peripheral vascular disorders	1.49	2.01	1.46	1.45	1.46	2.01	0.393
Hypertension	68.08	61.68	69.10	67.09	69.37	65.45	<0.001*
Paralysis	0.05	<2.01	<0.11	<0.09	<0.17	<0.71	0.346
Other neurologic disorders	1.31	<2.01	1.36	1.15	1.56	1.23	0.161
Chronic pulmonary disease	13.57	9.67	13.64	13.41	14.38	12.14	0.008*
Diabetes	22.16	16.97	22.61	21.54	23.39	20.52	<0.001*
Hypothyroidism	15.59	16.42	15.41	15.59	16.16	14.16	0.336
Renal failure	0.12	<2.01	<0.11	0.16	<0.17	<0.71	0.436
Liver disease	0.75	<2.01	0.84	0.81	0.63	<0.71	0.148
Peptic ulcer disease	1.13	<2.01	1.16	1.19	1.03	0.97	0.841
AIDS	<0.04	<2.01	<0.11	<0.09	<0.17	<0.71	0.898
Lymphoma	0.30	<2.01	0.31	0.30	0.31	<0.71	0.722
Metastatic cancer	<0.04	<2.01	<0.11	<0.09	<0.17	<0.71	0.766
Solid tumors without metastasis	7.75	8.94	7.44	8.28	7.25	7.47	0.05*
Rheumatoid arthritis/collagen vascular diseases	4.43	4.38	4.48	4.28	4.92	3.12	0.03*
Coagulopathy	1.51	<2.01	1.52	1.61	1.29	1.88	0.099
Obesity	17.90	21.72	17.26	18.07	18.44	17.14	0.034*
Weight loss	0.12	<2.01	0.17	<0.09	<0.17	<0.71	0.175
Fluid and electrolyte disorders	7.54	4.74	7.98	7.37	7.28	7.92	0.033*
Blood loss anemia	1.34	<2.01	1.55	1.29	1.12	1.36	0.142
Deficiency anemias	11.66	8.21	12.48	10.90	11.24	14.94	<0.001*
Alcohol abuse	0.72	<2.01	0.71	0.69	0.75	0.71	0.35
Drug abuse	0.32	<2.01	0.43	0.19	0.41	<0.71	0.012*
Psychoses	1.62	2.19	1.60	1.51	1.87	1.23	0.2
Depression	11.53	11.50	11.15	11.21	12.55	12.27	0.038*
Smoking	7.36	6.75	7.67	7.07	7.40	7.53	0.506

* Denotes $p < 0.05$.

3. Results

3.1. Demographics

There were a total of 137,076 primary TKAs performed during the study period. Twenty-six thousand nine hundred ninety patients were excluded either due to a history of VTE, a history of preoperative anticoagulant use, or a diagnosis of VTE during the hospitalization following TKR. An additional 70,967 patients were excluded due to insufficient follow-up, length of stay greater than five days, a discharge destination to a location other than home, or failure to fill a prescription for anticoagulation within two days of discharge from the hospital. This left a total of 30,813 patients to be analyzed in the study. This cohort represents the specific group of patients we attempted to analyze in our study (anticoagulation-naïve patients with no history of VTE discharged home after a typical length hospital stay that were compliant with postoperative anticoagulation). Of these, 548 were treated with ASA (1.8%), 10,444 with LMWH (33.9%), 11,757 with warfarin (38.2%), 6524 with factor Xa inhibitors (21.2%), and 1540 with fondaparinux (5.0%). The majority of patients had a length of stay of three days postoperatively. The most common age at the time of surgery was between 60 and 79. Overall 60.1% of patients were female. A complete breakdown of patient characteristics and comorbidities may be found in Table 1. Overall the ASA cohort tended to be of younger age with fewer comorbidities than the other anticoagulation groups.

3.2. Rates and risk of VTE

Of 30,813 patients, 1.42% were diagnosed with DVT and 0.59% with PE. The overall rate of VTE was 1.82%. Rates of complications, including VTE, are displaced in Table 2. Controlling for demographic and comorbidity variables and using ASA as a baseline, there was a significantly decreased risk of VTE with LMWH (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.29–0.83), XaI (OR 0.50, 95% CI 0.30–0.89), and fondaparinux (OR 0.32, 95% CI 0.16–0.64), and warfarin showed a trend towards a decreased risk (OR 0.59, 95% CI 0.36–0.104, $p = 0.050$) compared to ASA. Results of this regression are shown in Table 3.

Separate models evaluating risk of DVT and PE showed that ASA had a significantly higher risk of DVT compared to the other medications except for warfarin, and ASA had significantly higher risk of PE compared to all other medications (Table 4).

3.3. Other complications

Blood transfusion was performed in 10.5% of patients. Compared to ASA, there was increased risk of transfusion associated with LMWH (OR 1.56, 95% CI 1.07–2.39) and fondaparinux (OR 1.84, 95% CI 1.23–2.87). Postoperative hematoma occurred in 0.88% of patients while myocardial infarction occurred in 0.33%, and the 90 day all cause readmission rate was 7.41%. There was no statistically significant difference in odds of hematoma, myocardial infarction, or readmission between ASA and the other anticoagulant medications (Table 4).

4. Discussion

Despite improvements in perioperative management and surgical technique, VTE remains a concern for surgeons performing TKA. Our data show a post-discharge rate of DVT at 1.42% in anticoagulation-naïve patients undergoing primary TKA discharged home, although this would not include any patients diagnosed with a DVT during their index hospitalization. Furthermore, 0.59% of patients were diagnosed with a PE, a potentially life-threatening complication. For this reason, significant research in the orthopedic literature has centered on the optimal pharmacologic prophylaxis to prevent these complications. The most important findings of this population-level and comorbidity controlled study show that anticoagulation-naïve patients discharged home with ASA as VTE prophylaxis had increased risk of PE compared to all medications, and an increased risk of DVT compared to all medications except for warfarin.

Table 2
Rates of complications by medication type.
The rates of various complications are displayed depending on the medication used as postoperative VTE prophylaxis. The complication rates were compared among medication cohorts using multiple chi-squared tests. Statistically significant differences are noted with a p value of less than 0.05.

Number	All patients	Aspirin	LMWH	Warfarin	Xa inhibitors	Fondaparinux	p-Value
	30,813	548	10,444	11,757	6524	1540	
	%	%	%	%	%	%	
DVT	1.42	2.37	1.33	1.69	1.21	<0.71	<0.001*
PE	0.59	<2.01	0.54	0.60	0.58	<0.71	0.026*
VTE	1.82	2.92	1.67	2.08	1.69	1.10	0.006*
Transfusion	10.53	5.11	12.09	10.71	7.37	13.96	<0.001*
Hematoma	0.88	<2.01	1.03	0.79	0.87	<0.71	0.231
Myocardial infarction	0.33	<2.01	0.38	0.31	0.34	<0.71	0.707
90 day readmission	7.41	8.58	8.02	7.10	7.07	6.69	0.030*

* Denotes $p < 0.05$.

Table 3
VTE odds by medication type.
The results of a multivariate logistic regression comparing the odds of VTE for patients depending on their treatment medication. The ASA cohort with female gender, age 60 to 69, length of stay of 3 days, and no comorbidities was used as the baseline. Statistically significant differences are noted with a p value of less than 0.05. Comorbidities with too few patients to perform a comparison are noted with 'NA.'

Logistic regression VTE (DVT/PE)	OR	95% CI	p-Value
LMWH	0.47	(0.29, 0.83)	0.005*
Warfarin	0.59	(0.36, 1.04)	0.050
Xa inhibitors	0.50	(0.30, 0.89)	0.012*
Fondaparinux	0.32	(0.16, 0.64)	0.001*
LOS 0	0.70	(0.04, 3.18)	0.726
LOS 1	0.84	(0.44, 1.45)	0.559
LOS 2	0.94	(0.75, 1.18)	0.613
LOS 4	1.44	(1.14, 1.81)	0.002*
LOS 5	2.69	(1.98, 3.59)	0.000*
Age 49 and under	1.56	(0.93, 2.47)	0.075
Age 50–59	1.44	(1.11, 1.86)	0.006*
Age 70–79	1.19	(0.98, 1.46)	0.084
Age 80–89	1.50	(1.05, 2.09)	0.021*
Age 90 and over	0.73	(0.18, 1.95)	0.591
Male	1.21	(1.01, 1.44)	0.038*
Congestive heart failure	0.70	(0.31, 1.33)	0.325
Cardiac arrhythmias	1.81	(1.34, 2.39)	0.000*
Heart valvular disease	0.97	(0.55, 1.59)	0.905
Pulmonary circulation disorders	1.71	(0.51, 4.24)	0.303
Peripheral vascular disorders	0.64	(0.25, 1.31)	0.278
Hypertension	1.20	(0.99, 1.45)	0.066
Paralysis	5.78	(0.87, 22.07)	0.025*
Other neurologic disorders	1.07	(0.48, 2.04)	0.842
Chronic pulmonary disease	1.47	(1.17, 1.83)	0.001*
Diabetes	0.87	(0.70, 1.07)	0.201
Hypothyroidism	0.95	(0.74, 1.21)	0.686
Renal failure	1.35	(0.08, 6.33)	0.771
Liver disease	0.92	(0.28, 2.21)	0.872
Peptic ulcer disease	1.47	(0.69, 2.70)	0.265
AIDS	5.79	(0.30, 34.41)	0.108
Lymphoma	2.53	(0.76, 6.16)	0.074
Metastatic cancer	NA	NA	0.964
Solid tumors without metastasis	1.09	(0.79, 1.47)	0.568
Rheumatoid arthritis/collagen vascular diseases	0.83	(0.52, 1.26)	0.409
Coagulopathy	1.29	(0.68, 2.23)	0.391
Obesity	1.18	(0.95, 1.46)	0.129
Weight loss	1.28	(0.07, 6.06)	0.806
Fluid and electrolyte disorders	1.27	(0.95, 1.66)	0.098
Blood loss anemia	1.23	(0.61, 2.19)	0.532
Deficiency anemias	1.15	(0.89, 1.46)	0.277
Alcohol abuse	0.68	(0.17, 1.81)	0.514
Drug abuse	1.03	(0.16, 3.43)	0.965
Psychoses	0.90	(0.43, 1.67)	0.767
Depression	0.79	(0.58, 1.05)	0.111
Smoking	0.74	(0.50, 1.05)	0.111

* Denotes $p < 0.05$.

Many recent studies have attempted to demonstrate the safety of ASA as appropriate pharmacologic prophylaxis following total joint arthroplasty. Huang et al. analyzed 30,270 patients undergoing total joint arthroplasty treated with either ASA or warfarin for VTE prophylaxis. Their data showed that rates of VTE and other complications were significantly lower with ASA compared to warfarin, especially in high risk patients [18]. This study included patients undergoing a variety of procedures, including both primary and revision TKA and total hip arthroplasty (THA). This data is not in concordance with our results. Our data show that the risk of PE was lower with warfarin compared to ASA in our cohort. This could be due to the fact that our cohort includes specifically patients undergoing primary TKA. It is possible that ASA is more effective in THA than in TKA, and thus combining the procedures may have biased their result. Furthermore, Huang et al. did not include any other classes of anticoagulant. Our data show ASA and warfarin were the medications with the highest rate of VTE.

The goal of VTE prevention must also be balanced with the risk of bleeding complications, such as blood transfusion and hematoma/hemarthrosis. Our data show that LMWH and fondaparinux, two of the medications most effective at preventing VTE, also conferred higher odds of postoperative transfusion. Similar results were found by Radzak et al. when comparing the rates of transfusion after TKA when patients were treated postoperatively with LMWH versus ASA [6]. Our data, however, did not show any significant increase in the risk of postoperative hematoma with any other anticoagulant when compared with ASA. Multiple prior studies, including a large systematic review and meta-analysis, have shown an increase in the risk of surgical site

Table 4
Odds of complications by medication type.
The results of a multivariate logistic regression comparing the odds of multiple complications for patients depending on their treatment medication. The ASA cohort with female gender, age 60 to 69, length of stay of three days, and no comorbidities was used as the baseline. Statistically significant differences are noted with a p value of less than 0.05. Comorbidities with too few patients to perform a comparison are noted with 'NA.'

	LMWH			Warfarin		
	OR	95% CI	p-Value	OR	95% CI	p-Value
DVT	0.47	(0.27, 0.89)	0.012*	0.60	(0.35, 1.13)	0.089
PE	0.26	(0.13, 0.57)	0.000*	0.29	(0.15, 0.64)	0.001*
VTE	0.47	(0.29, 0.83)	0.005*	0.59	(0.36, 1.04)	0.050
Transfusion	1.56	(1.07, 2.39)	0.028*	1.38	(0.94, 2.10)	0.116
Hematoma	1.27	(0.53, 4.20)	0.639	0.99	(0.41, 3.29)	0.991
Myocardial infarction	1.44	(0.30, 25.81)	0.720	1.20	(0.25, 21.47)	0.860
90 day readmission	0.93	(0.68, 1.29)	0.638	0.81	(0.60, 1.13)	0.199
	XaI			Fondaparinux		
	OR	95% CI	p-Value	OR	95% CI	p-Value
DVT	0.44	(0.25, 0.85)	0.008*	0.21	(0.08, 0.49)	0.000*
PE	0.30	(0.15, 0.68)	0.002*	0.26	(0.10, 0.70)	0.007*
VTE	0.50	(0.30, 0.89)	0.012*	0.32	(0.16, 0.64)	0.001*
Transfusion	1.05	(0.71, 1.62)	0.805	1.84	(1.23, 2.87)	0.005*
Hematoma	1.17	(0.47, 3.88)	0.770	0.71	(0.23, 2.66)	0.577
Myocardial infarction	1.26	(0.26, 22.79)	0.822	0.75	(0.09, 15.21)	0.801
90 day readmission	0.81	(0.60, 1.13)	0.201	0.76	(0.53, 1.11)	0.145

* Denotes $p < 0.05$.

bleeding following total joint arthroplasty (TJA) with LMWH compared to controls; this result was similar to other more potent anticoagulants including factor Xa inhibitors [5]. Furthermore, Jones et al. showed that wound drainage following TJA was increased with both ASA and LMWH when compared to patients who did not receive pharmacologic thromboprophylaxis [8]. A recent study found that certain anticoagulants, including warfarin, direct factor Xa inhibitors, and fondaparinux, increased the risk of manipulation under anesthesia following TKR compared to aspirin or LMWH [26]. Clearly these risks must be balanced with the benefits of treatment.

Bala et al. recently published a study attempting to analyze the risk of VTE following TKA when patients were treated with ASA, warfarin, LMWH, or factor Xa inhibitors [22]. Their results showed the lowest rates of VTE with ASA and factor Xa inhibitors, with a lower rate of bleeding complications with ASA. This study, while using the same database as our current study, has significant methodological flaws. First, the authors defined their medication groups by merely searching for any filled prescriptions in the first two weeks following TKA. They did not mention controlling for whether a patient was diagnosed with VTE before they filled a prescription, which would erroneously elevate the VTE rate for medications commonly used to treat VTE, such as LMWH, warfarin, and factor Xa inhibitors. Furthermore, allowing prescriptions to be filled such a long time after TKA potentially includes patients who were non-compliant with their prescribed thromboprophylaxis. The authors also demonstrated numerous differences in the comorbidity profiles of their various groups, but failed to control for these differences in their analysis. They also did not control for length of stay and discharge destination, both of which are known to have a significant impact on the rate of VTE [23].

Our study has many strengths. Few other studies have compared the full spectrum of typically administered thromboprophylactic medications. Employing strict criteria regarding medication prescriptions, such as requiring filling to occur within two days of discharge and prior to any diagnosis of VTE, maximizes the likelihood of patient compliance and minimizes the chance of misattributing a complication to a drug used to treat, rather than prevent, VTE. The statistical analysis controlled for a wide variety of influential confounding factors, including many that had not been controlled in prior studies, such as length of stay and discharge destination. Restricting to patients discharged home improves the accuracy with which we were able to identify the thromboprophylactic agent use, and also focuses the result on a more homogenous population of patients. Utilizing a nationwide database allowed for the inclusion of a large number of patients in varying practice settings. Furthermore, use of a health-insurance based database maximizes the ability to track patients across geographic and health care settings, a limitation of state or individual hospital databases. Patients were only included if they were active in the database for 90 days before and after TKA, and thus no patients were lost to follow-up during the period of interest.

This study does, however, suffer from common limitations of large database studies. The quality of data relies on accurate and complete biller coding, and any errors in coding could introduce error into the study. Complications were defined using ICD diagnosis codes, which are unable to signify the severity or symptomatic nature of complications; this is particularly relevant for VTE as symptomatic cases are likely inherently different from asymptomatic cases. Additionally, the data only show prescriptions filled, and thus cannot confirm patient compliance. Our study population is also limited to privately insured patients, and thus may not be reflective of the entire general population.

The size and characteristics of the ASA group in our study differ from the other anticoagulation cohorts. The etiology of smaller size of the ASA cohort is likely multifactorial. ASA has begun to gain popularity only in recent years and may have not been used significantly during the earlier time points included in the study. Furthermore, many patients may buy ASA over the counter rather than by filling a prescription, and these patients would not be captured in our study. The ASA cohort also tended to be younger with fewer comorbid conditions. This would tend to lead to a lower rate of VTE in that group, but despite this patients treated with ASA had one of the highest rates of VTE. Furthermore, our demographic and comorbidity controlled regressions showed that the ASA group was at higher risk of VTE despite these differences.

Ultimately the decision whether to proceed with any medical intervention is based on a balance of expected risks and benefits. Our data show that the odds of VTE following TKA in patients discharged home are at least 50% lower with multiple medications when compared to ASA, including LMWH, factor Xa inhibitors, and fondaparinux. This benefit must be balanced with the risk of complications; the odds of transfusion in our patient population were significantly higher with LMWH or fondaparinux compared with ASA. There was no notable difference in myocardial infarction or 90 day all cause readmission between medications.

There is likely no single medication that strikes the optimal balance for all patients; patients at low risk of VTE may be better served with ASA, trading a slightly higher odds of VTE for a lower complication profile. In our cohort, Factor Xa inhibitors provided an excellent combination of low VTE risk and minimal bleeding-related complications; however, there may be complications unaccounted for in this study. Although our study provides useful data, a future prospective, randomized study would likely provide the best evidence for an optimal medication for various subsets of patients.

5. Conclusions

In this nationwide health insurance based database study, controlling for patient age, gender, comorbidities, and length of stay, the odds of VTE in anticoagulation-naïve patients undergoing TKA discharged home were at least 50% lower with multiple medications, including LMWH, factor Xa inhibitors, and fondaparinux, when compared to ASA. This benefit must be balanced with the risk of bleeding-related complications, such as transfusion, which may be higher with these medications. The optimal balance of expected risks and benefits should be assessed for each patient and used to guide the choice of thromboprophylaxis.

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