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blood advances

Effectiveness and safety of prophylactic anticoagulation among hospitalized patients with inflammatory bowel disease

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Key Points

- Hospitalized patients with IBD are at increased risk of VTE.
- Among patients with IBD, prophylactic use of heparin (vs no use) was associated with a lower rate of VTE without increasing bleeding risk.

Hospitalized patients with inflammatory bowel disease (IBD) are at increased risk of venous thromboembolism (VTE). We aimed to evaluate the effectiveness and safety of prophylactic anticoagulation compared with no anticoagulation in hospitalized patients with IBD. We conducted a retrospective cohort study using a hospital-based database. We included patients with IBD who had a length of hospital stay ≥2 days between 1 January 2016 and 31 December 2019. We excluded patients who had other indications for anticoagulation, users of direct oral anticoagulants, warfarin, therapeutic-intensity heparin, and patients admitted for surgery. We defined exposure to prophylactic anticoagulation using charge codes. The primary effectiveness outcome was VTE. The primary safety outcome was bleeding. We used propensity score matching to reduce potential differences between users and nonusers of anticoagulants and Cox proportional-hazards regression to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The analysis included 56 194 matched patients with IBD (users of anticoagulants, n = 28 097; nonusers, n = 28 097). In the matched sample, prophylactic use of anticoagulants (vs no use) was associated with a lower rate of VTE (HR, 0.62; 95% CI, 0.41-0.94) and with no difference in the rate of bleeding (HR, 1.05; 95% CI, 0.87-1.26). In this study of hospitalized patients with IBD, prophylactic use of heparin was associated with a lower rate of VTE without increasing bleeding risk compared with no anticoagulation. Our results suggest potential benefits of prophylactic anticoagulation to reduce the burden of VTE in hospitalized patients with IBD.

Background

Nearly 1% of Americans have been diagnosed with inflammatory bowel disease (IBD),[1] which includes Crohn's disease (CD) and ulcerative colitis (UC). IBD is a chronic condition with periods of active disease flares. Venous thromboembolism (VTE) affects an estimated 1% to 5%[2,3] of patients with IBD and is a significant source of morbidity and mortality, in both the outpatient and inpatient settings.[4] Approximately 33% of patients with IBD and VTE develop recurrent VTE[5] and up to 22% die within 2 years of the initial VTE event.[6] Patients with IBD have an increased risk of extraintestinal manifestations including platelet aggregation and thrombosis.[7] Clinical risk factors such as hospitalization, older age, and active disease flares may increase the likelihood of VTE.[8,9]

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The data used for this study are not publicly available.

The full-text version of this article contains a data supplement.

Hospitalized patients with IBD have an increased risk of morbidity and mortality due to VTE.[4] This risk can be reduced with prophylactic anticoagulation. Heparins, including subcutaneous low molecular weight heparin (LMWH) and unfractionated heparin (UFH), have been the most commonly used anticoagulants in hospitalized patients with IBD for decades. However, fear of bleeding complications[10] may explain the low rate of VTE prophylaxis, with only one-third of patients with IBD receiving prophylactic anticoagulants in the inpatient setting.[11] Lack of strong evidence of effectiveness in patients with IBD likely also contributes to the low rates of VTE prophylaxis because recommendations for heparin use are based on studies conducted in patients who are acutely ill[12] that included only a small number of patients with IBD. There is also a lack of clinical trials specifically testing VTE prophylaxis among hospitalized patients with IBD. As such, research is needed to determine the effectiveness and safety of prophylactic-intensity heparins among patients with IBD. Herein, we report the results of an observational study of the effectiveness and safety of prophylactic anticoagulation compared with no anticoagulation in hospitalized patients with IBD.

Methods

Database

This was a retrospective cohort study using Premier Healthcare Database, a service-level, all-payer database that provides a comprehensive hospital-based health care experience in the United States. Premier database contains information from >1113 contributing hospitals and health care systems from all payers including Medicaid, Medicare, and commercial insurance. The hospitals come primarily from geographically diverse nonprofit, nongovernmental, community, and teaching hospitals covering health systems in rural and urban areas. Inpatient admissions include >11 million visits per year, accounting for ~25% of annual hospital admissions in the United States. An analysis done by Premier comparing hospital characteristics in the Premier Healthcare Database with those from the American Hospital Association demonstrated that the distribution of hospitals participating in Premiere Healthcare Database (eg, location, type, and bed size) is similar to those at the national level.[13]

The database includes patient-level information such as demographics (eg, age, race, ethnicity, and geographic location), diagnosis codes, procedures performed during hospitalization, in-hospital mortality data, medications (eg, drug names, strength, dose, and quantity), and hospital-level characteristics (eg, hospital location: urban vs rural and hospital type: teaching vs nonteaching hospital).

Study population

The study population included adults aged ≥18 years who were hospitalized and had a diagnosis of IBD between 1 January 2016 and 31 December 2019. We identified patients with IBD based on a previously validated definition.[14] We selected all admissions with a principal or first-listed position (indicative of the reason for admission) code for IBD, including CD and UC (international classification of disease [ICD], 10th revision, clinical modification [ICD-10-CM] codes: K50.XX for CD and K51.XX for UC). These codes were previously validated vs medical chart records and were found to have high sensitivity (92% for CD and 84% for UC) and specificity (99% for both CD and UC).[14] The cohort was limited to patients whose length of hospital stay was ≥2 days. The following served as exclusion criteria for the study if present on admission or day 1: (1) diagnosis of VTE including deep vein thrombosis (DVT) or pulmonary embolism (PE), because we are interested in evaluating VTE prophylaxis and not treatment; (2) diagnosis of atrial fibrillation; or (3) mechanical heart valve because they have an alternative indication for anticoagulation[15]; and (4) users of direct oral anticoagulants, warfarin, and therapeutic-intensity heparin; and (5) patients admitted for surgical procedures (supplemental Table 1). The study was conducted in accordance with the Declaration of Helsinki.

Exposure ascertainment

We defined exposure to prophylactic anticoagulation using charge codes for heparin including LMWH and UFH. We classified patients as users of prophylactic anticoagulation if they had charge codes for heparin within the first 2 days of admission, whereas we classified patients as nonusers if they did not receive any anticoagulant. Prophylactic use of anticoagulants was defined based on the presence of at least 1 prescription of LMWH (enoxaparin ≤40 mg/day; dalteparin ≤5000 IU/day), UFH (≤5000 IU 2 or 3 times daily), and fondaparinux (2.5 mg).

Outcomes ascertainment

The primary effectiveness outcome was VTE defined using ICD-10-CM codes listed in supplemental Table 1 with prescriptions for therapeutic-dose anticoagulants initiated after day 2 or presence of VTE-diagnostic procedures (eg, computed tomography scan). Diagnosis codes of VTE were previously found to have a positive predictive value of 95% (95% confidence interval [CI], 93%-97%).[16] For the safety analysis, the primary outcome of interest was bleeding events requiring blood transfusion defined as a composite of gastrointestinal or intracranial bleeding. The diagnosis codes for bleeding were found to have a positive predictive value of 89% (95% CI, 83%-92%).[17] Secondary study outcomes included all-cause in-hospital mortality, 30-day VTE-related readmission, and nonmajor bleeding events.

Covariates

We used information present on admission or day 1 for the ascertainment of patients' comorbidities and risk factors related to VTE or bleeding. We included the following covariates: (1) demographics including age on admission, sex, ethnicity, race (ie, Asian, Black, White, and Other), and geographic location; (2) comorbidities such as heart failure, peripheral vascular disease, hypertension, malnutrition, renal impairment, liver disease, and drug abuse; (3) inpatient use of medications such as insulin, angiotensin-converting enzyme inhibitors, beta-blockers, nonsteroidal anti-inflammatory drugs, antiplatelet agents, steroids, and selective serotonin reuptake inhibitors; (4) hospital-level characteristics such as hospital type (teaching vs nonteaching hospitals) and hospital location (urban vs rural hospitals); and (5) IBD type (CD vs UC). We conducted a secondary analysis of patients likely presenting with IBD flares on admission. We included patients in this analysis if they had any of the following by day 2: (1) biological therapy; (2) systemic steroids; (3) colonoscopy or sigmoidoscopy; (4) magnetic resonance imaging or computed tomography of the abdomen and pelvis or pelvis alone; or (5) testing for Clostridium difficile.

Statistical analysis

We used propensity score matching to minimize potential differences between users and nonusers of prophylactic anticoagulants. We calculated propensity score using a logistic regression model (PROC LOGISTIC in SAS) that predicted the probability of prescribing prophylactic anticoagulation vs no anticoagulation as a function of the variables listed in Table 1. We matched without replacement using 1:1 matching based on a maximum caliper width of 0.1 of standard deviation of the logit of propensity score. Propensity score matching involves selecting matched sets of users and nonusers of anticoagulants who have a similar value of propensity score. We graphically compared the distribution of propensity score values between users and nonusers of anticoaglants. Given the large sample size, we used absolute standardized differences to compare the balance in baseline covariates before and after propensity score matching between users and nonusers of anticoagulants.[18] We calculated the incidence rates of VTE and bleeding per 10 000 person-years. We used Cox proportional hazards regression (PROC PHREG in SAS) using a robust variance estimator to estimate adjusted marginal hazard ratios (HRs) and corresponding 95% CIs. Cox proportional hazards regression model included study outcome as the dependent variable and exposure as the independent variable, adjusting for steroid use and malnutrition.

Sensitivity and subgroup analyses

We conducted several sensitivity analyses. First, we changed the follow-up period for VTE-related readmission from 30 days to 60 days and 90 days. Second, we separately examined the bleeding outcomes including gastrointestinal and intracranial bleeding. Third, we compared the risk of VTE, bleeding, all-cause in-hospital mortality, and 30-day VTE-related readmission between LMWH and UFH. We rematched to maintain the balance in baseline characteristics between users of LMWH and UFH. Because propensity score matching balances observed covariates, we calculated the E-value to assess the impact of residual confounding by unmeasured variables. The E-value reflects the minimum needed strength of association between an unmeasured confounder, exposure, and study outcomes to move the observed effect estimates and CIs to the null value of 1, conditional on measured covariates (www.evalue-calculator.com).

We conducted post hoc analyses to examine whether the primary results were consistent across relevant subgroups of interest including: age, sex, cancer, IBD type, heart failure, and IBD flares. We assessed the potential for effect modification within selected subgroups for the effectiveness and safety outcomes by including an interaction term in the primary models. We performed matching again within each of the selected subgroups and reported the HRs and corresponding 95% CIs. We used Bonferroni adjustment to account for multiple testing. We considered results statistically significant if P value for interaction was $\leq \alpha$ (ie, .05) / n (in which, n = total number of subgroup analyses).[19] We conducted all analyses using SAS v9.4 (SAS Institute Inc., Cary, NC).

Results

The study included 78 764 patients with IBD. Of those, 38 552 (49%) were users of prophylactic anticoagulation and 40 212 (51%) were nonusers (supplemental Figure 1). Compared with nonusers, users of prophylactic anticoagulants had a higher prevalence of chronic kidney disease (28% vs 23%), chronic lung disease (24% vs 19%), and heart failure (11% vs 7%); were more likely to use aspirin (8% vs 4%), beta-blockers (13% vs 9%), and insulin (12% vs 7%); and were more likely to be admitted to a teaching hospital (57% vs 47%) (Table 1). The distribution of propensity scores before and after matching is described in supplemental Figure 2. The matched cohort included 28 097 users and 28 097 nonusers, of whom 42% had UC. After propensity score matching, all characteristics were well balanced between the 2 groups (standardized mean differences <0.1) (supplemental Figure 3). We did not include history of bleeding or IBD flares in the propensity score matching model because both variables were well balanced in the nonmatched cohort. In the matched cohort, the standardized differences were also well balanced for history of bleeding (n = 2844 [10.1%] among users vs n = 2945 [10.5%] among nonusers; *standardized difference* = 0.01) and IBD flares (n = 1218 [4.3%] among users vs n = 1326 [4.7%] among nonusers; *standardized difference* = 0.01).

Primary outcomes

In the propensity score–matched sample of patients with IBD, the incidence rate of VTE per 10 000 person-days of follow-up was 1.8 among users and 2.8 among nonusers. After matching, use of prophylactic anticoagulants (vs no use) was associated with a lower rate of VTE (HR, 0.62; 95% CI, 0.41-0.94) (Table 2). In the matched cohort, the incidence rate of bleeding per 10 000 person-days of follow-up was 11.4 among users and 10.5 among nonusers. After matching, there was no difference in the rate of bleeding between users of prophylactic anticoagulants vs nonusers (HR, 1.05; 95% CI, 0.87-1.26).

Secondary outcomes

In the propensity score matched sample of patients with IBD, 813 patients died (users, n = 393; nonusers, n = 420). There was no difference in all-cause in-hospital mortality between users of prophylactic anticoagulants (vs nonusers) (HR, 1.05; 95% CI, 0.91-1.20). The incidence rate of 30-day VTE-related readmission per 10 000 person-days of follow-up was 5.1 among users and 5.7 among nonusers. After matching, there was no significant difference between users of prophylactic anticoagulants vs nonusers in the rate of 30-day readmission (HR, 0.89; 95% CI, 0.78-1.01) and nonmajor bleeding events (HR, 1.04; 95% CI, 0.86-1.04).

Results from sensitivity and subgroup analyses

Findings from sensitivity analyses showed a lower rate of VTE-related readmission at 60 days (HR, 0.88; 95% CI, 0.78-0.99) and 90 days (HR, 0.88; 95% CI, 0.79 to 0.99) in users than in nonusers (supplemental Table 2). We found no difference in VTE, all-cause in-hospital mortality, and 30-day VTE-related readmission when comparing LMWH with UFH. However, the rate of bleeding was lower with LMWH vs UFH (HR, 0.65; 95% CI, 0.50-0.84) (supplemental Table 3). There was no evidence of effect modification across patient subgroups including age, sex, heart failure, use of nonsteroidal anti-inflammatory drugs, antiplatelet agents, or IBD type (Table 3). Lastly, we identified 14 806 patients with IBD flares (users, n = 6261; nonusers, n = 8545). Patients with IBD flares who were users (vs nonusers) were slightly older (56 years vs 51 years) and had a higher prevalence of comorbidities including

Table 1. Demographic and clinical characteristics of patients with IBD comparing users of anticoagulants with nonusers before and after matching

Characteristics	Before matching					After matching				
	Users of anticoagulants, n = 38 552*		Nonusers, n = 40 212		Standardized difference	Users of anticoagulants, n = 28 097*		Nonusers, n = 28 097		Standardized difference
Age, mean (SD), y	57.0	(17.9)	52.0	(19.1)	0.27	54.2	(17.9)	54.1	(18.8)	0.00
Sex, male, n (%)	16 477	(42.7)	17 103	(42.5)	0.00	11 793	(42.0)	11 836	(42.1)	0.00
Hispanic, n (%)	1925	(5.0)	2712	(6.7)	0.08	1580	(5.6)	1601	(5.7)	0.00
Race, n (%)										
Asian	364	(0.9)	518	(1.3)	0.04	297	(1.1)	298	(1.1)	0.00
Black	4210	(10.9)	4724	(11.8)	0.03	3186	(11.3)	3142	(11.2)	0.00
Other	2702	(7.0)	2602	(6.5)	0.02	1829	(6.5)	1865	(6.6)	0.01
Unknown	706	(1.8)	906	(2.3)	0.03	550	(2.0)	544	(1.9)	0.00
White	30 570	(79.3)	31 462	(78.2)	0.03	22 235	(79.1)	22 248	(79.2)	0.00
Division, n (%)										
East North Central	6851	(17.8)	5481	(13.6)	0.11	4221	(15.0)	4323	(15.4)	0.01
East South Central	2297	(6.0)	3002	(7.5)	0.06	1944	(6.9)	1890	(6.7)	0.01
Middle Atlantic	8255	(21.4)	5875	(14.6)	0.17	4831	(17.2)	4863	(17.3)	0.00
Mountain	1883	(4.9)	2616	(6.5)	0.08	1651	(5.9)	1638	(5.8)	0.00
New England	1183	(3.1)	952	(2.4)	0.04	748	(2.7)	756	(2.7)	0.00
South Atlantic	10 355	(26.9)	12 077	(30.0)	0.07	8216	(29.2)	8190	(29.2)	0.00
West North Central	1898	(4.9)	2225	(5.5)	0.03	1524	(5.4)	1506	(5.4)	0.00
West South Central	3443	(8.9)	4743	(11.8)	0.10	2953	(10.5)	2933	(10.4)	0.00
Pacific	2387	(6.2)	3241	(8.1)	0.08	2009	(7.2)	1998	(7.1)	0.00
Comorbidities, n (%)										
Alcohol abuse	1541	(4.0)	1909	(4.8)	0.04	1227	(4.4)	1199	(4.3)	0.00
Anemia	3790	(9.8)	5800	(14.4)	0.15	3069	(10.9)	3166	(11.3)	0.01
Cancer	2984	(7.7)	2660	(6.6)	0.04	2050	(7.3)	2078	(7.4)	0.00
Chronic kidney disease	10873	(28.2)	9209	(22.9)	0.12	7093	(25.2)	7128	(25.4)	0.00
Chronic lung disease	9123	(23.7)	7481	(18.6)	0.12	5837	(20.8)	5868	(20.9)	0.00
Drug abuse	2413	(6.3)	2950	(7.3)	0.04	2009	(7.2)	2004	(7.1)	0.00
End stage renal disease	792	(2.1)	581	(1.4)	0.04	459	(1.6)	444	(1.6)	0.00
Heart failure	4043	(10.5)	2633	(6.6)	0.13	2152	(7.7)	2176	(7.7)	0.00
Hyperlipidemia	9339	(24.2)	7442	(18.5)	0.13	5771	(20.5)	5815	(20.7)	0.00
Hypertension	19 428	(50.4)	16 700	(41.5)	0.18	12 816	(45.6)	12 797	(45.6)	0.00
Liver disease	2770	(7.2)	3668	(9.1)	0.07	2254	(8.0)	2218	(7.9)	0.00
Malnutrition†	3191	(8.3)	3401	(8.5)	0.00	2289	(8.1)	2426	(8.6)	0.01
Peripheral vascular disease	1963	(5.1)	1778	(4.4)	0.03	1271	(4.5)	1276	(4.5)	0.00
Renal impairment	5554	(14.4)	4422	(11.0)	0.10	3477	(12.4)	3450	(12.3)	0.00
Tobacco use	7191	(18.7)	7169	(17.8)	0.02	5266	(18.7)	5252	(18.7)	0.00
Ulcer	678	(1.8)	1414	(3.5)	0.13	597	(2.1)	539	(1.9)	0.01
Medications, n (%)										
ACE	22	(0.1)	25	(0.1)	0.00	16	(0.1)	13	(0.1)	0.00
Antiplatelets	753	(2.0)	294	(0.7)	0.09	298	(1.1)	276	(1.0)	0.01
Aspirin	3190	(8.3)	1421	(3.5)	0.17	1429	(5.1)	1327	(4.7)	0.02
Azathioprine	358	(0.9)	356	(0.9)	0.00	253	(0.9)	240	(0.9)	0.00
Beta blockers	5153	(13.4)	3431	(8.5)	0.14	2942	(10.5)	2895	(10.3)	0.01

ACEs, angiotensin converting enzyme inhibitors; CCBs, calcium channel blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

*Defined based on the presence of at least 1 prescription of prophylactic-dose heparin including LMWH (enoxaparin ≤40 mg/day, dalteparin ≤5000 IU/day) and UFH (≤5000 IU/ twice daily or 3 times a day).

†Malnutrition and steroids were not included in the propensity score model.

Table 1 (continued)

Characteristics	Before matching					After matching				
	Users of anticoagulants, n = 38 552*		Nonusers, n = 40 212		Standardized difference	Users of anticoagulants, n = 28 097*		Nonusers, n = 28 097		Standardized difference
CCBs	2235	(5.8)	1513	(3.8)	0.09	1273	(4.5)	1238	(4.4)	0.01
Direct vasodilators	1353	(3.5)	877	(2.2)	0.07	762	(2.7)	738	(2.6)	0.01
Insulin	4639	(12.0)	2723	(6.8)	0.16	2297	(8.2)	2325	(8.3)	0.00
Loop diuretics	1706	(4.4)	978	(2.4)	0.10	812	(2.9)	805	(2.9)	0.00
Mesalamine	1982	(5.1)	2359	(5.9)	0.03	1454	(5.2)	1419	(5.1)	0.01
NSAIDs	1600	(4.2)	939	(2.3)	0.09	884	(3.2)	859	(3.1)	0.01
Potassium diuretics	229	(0.6)	238	(0.6)	0.00	161	(0.6)	168	(0.6)	0.00
SSRIs	2145	(5.6)	1848	(4.6)	0.04	1385	(4.9)	1362	(4.9)	0.00
Steroids†	2712	(7.0)	2366	(5.9)	0.04	1908	(6.8)	1620	(5.8)	0.04
Sulfasalazine	560	(1.5)	486	(1.2)	0.02	347	(1.2)	370	(1.3)	0.01
Thiazide diuretics	363	(0.9)	242	(0.6)	0.04	211	(0.8)	195	(0.7)	0.01
Hospital characteristics, n (%)										
Type, teaching	21 995	(57.1)	18 978	(47.2)	0.20	14 459	(51.5)	14 652	(52.2)	0.01
Location, urban	34 841	(90.4)	36 174	(90.0)	0.01	25 283	(90.0)	25 304	(90.1)	0.00
IBD type, UC	15 781	(40.9)	18 787	(46.7)	0.18	11 758	(41.9)	11797	(42.0)	0.00

ACEs, angiotensin converting enzyme inhibitors; CCBs, calcium channel blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

*Defined based on the presence of at least 1 prescription of prophylactic-dose heparin including LMWH (enoxaparin ≤40 mg/day, dalteparin ≤5000 IU/day) and UFH (≤5000 IU/ twice daily or 3 times a day).

†Malnutrition and steroids were not included in the propensity score model.

chronic kidney disease (31% vs 23%), chronic lung disease (25% vs 18%), heart failure (10% vs 6%), and hypertension (51% vs 39%) (supplemental Table 4). In the matched sample (users, n = 5093; nonusers, n = 5093), patients characteristics were well balanced. We found no evidence of effect modification by the presence of IBD flares for VTE ($P = .94$) or bleeding ($P = .02$) when comparing users (vs nonusers) of anticoagulants (Table 3).

We calculated E-values (supplemental Figure 4) corresponding to the upper bound of the 95% CI that were 1.36 for the effectiveness outcome (E-value for the point estimate, 2.61), conditional on measured covariates.

Discussion

In this nationwide sample of IBD-related admissions in the United States, we found that prophylactic use of heparin was associated with a lower rate of VTE without increasing bleeding risk than no anticoagulation. There was no difference in all-cause in-hospital mortality and 30-day VTE-related readmission when comparing users and nonusers of prophylactic anticoagulants. However, results from sensitivity analyses showed a reduction in 60-day and 90-day VTE-related readmissions with prophylactic use of heparin (vs no use). These findings have important clinical implications for hospitalized patients with IBD who are at increased risk of VTE and VTE-related complications.

IBD is characterized by chronic inflammation of the gastrointestinal tract. Patients with IBD have an increased risk of extraintestinal manifestations including platelet aggregation and thrombosis.[7] VTE is a common and potentially fatal complication of IBD.[20] A meta-analysis of observational studies reported that patients with IBD (vs those without IBD) have a twofold increased risk of VTE (relative risk [RR], 2.20; 95% CI, 1.83-2.65).[21] Another meta-analysis of 33 studies that included 207 814 patients with IBD and 577 898 controls found an increased risk of DVT and PE among patients with IBD compared with the general population (RR, 2.42; 95% CI, 1.78-3.30 vs RR, 2.53; 95% CI, 1.95-3.28).[22] The same study reported a higher risk of VTE in UC than CD, when considering the inpatient setting only.[22]

International guidelines for the management of hospitalized patients with IBD recommend thromboprophylaxis regardless of reason for admission.[23,24] These recommendations were implemented based on American College of Clinical Pharmacy guidelines for prevention of VTE in patients who are acutely ill.[25] Evidence for the effectiveness of heparins comes from large randomized clinical trials of patients who were acutely ill drawn from the general population of hospitalized patients. For example, the PREVENT trial, Placebo-Controlled Trial of Dalteparin for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients, assessed the efficacy and safety of dalteparin in the prevention of VTE in patients who were acutely ill. The trial included patients who were aged ≥40 years, had an acute medical condition (including IBD), and had a projected length of hospitalization of ≥4 days. The trial found that the use of dalteparin 5000 IU once daily (vs placebo) halved the rate of VTE without increasing bleeding risk. However, this trial included only 18 patients with IBD (n = 10 for treatment; and n = 8 for placebo). A few observational studies evaluated the effectiveness of thromboprophylaxis among hospitalized patients with IBD. Ananthakrishnan et al examined the effectiveness of heparin prophylaxis in reducing the risk of post-hospitalization VTE.[26] The analysis found that 760 (7%) of 11 028 hospitalized patients with IBD developed VTE. The same study

Table 2. Risk of VTE, bleeding events, all-cause mortality, and 30-day VTE-related readmission in patients with IBD who were users of prophylactic anticoagulants compared with nonusers

Outcome	Users of anticoagulants, n	Events, n	Person-days of follow-up	Incidence rate per 10 000 person-days	Nonusers, n	Events, n	Person-days of follow-up	Incidence rate per 10 000 person-days	Adjusted marginal HR* (95% CI)
Primary outcomes									
VTE	28 097	36	204 766	1.8	28 097	57	201 844	2.8	0.62 (0.41-0.94)
Bleeding		234	204 968	11.4		212	202 139	10.5	1.05 (0.87-1.26)
Secondary outcomes									
All-cause in-hospital mortality		420	205 035	20.5		393	202 178	19.4	1.05 (0.91-1.20)
30 day VTE-related readmission		438	863 207	5.1		491	862 193	5.7	0.89 (0.78-1.01)
Non major bleeding events		226	207 915	10.9		204	201 921	10.1	1.04 (0.86-1.04)

*Adjusted for steroid use and malnutrition.

reported that patients who received thromboprophylaxis during hospitalization (vs nonusers) had a lower risk of VTE after discharge (HR, 0.46; 95% CI, 0.22-0.97). However, the study focused on events occurring after hospitalization, whereas we focused in our primary analysis on VTE events occurring during the inpatient stay. Nonetheless, in our secondary analysis, we observed a similar reduction in readmission for VTE with in-hospital heparin-based VTE prophylaxis. Thus, it appears that the benefits of VTE prophylaxis are evident both during the index hospitalization and during the next several months after discharge.

Our results confirm those reported in prior analyses regarding the underutilization of thromboprophylaxis in hospitalized patients with IBD. For instance, we found that 49% of patients with IBD received thromboprophylaxis compared with 40% in a prior analysis.[27] The low rate of VTE prophylaxis likely results from fear of bleeding complications and lack of knowledge of the increased risk of VTE among patients with IBD. Although we were unable to study the knowledge component in this research, we did confirm that heparin-based VTE prophylaxis did not increase the risk of bleeding complications.

The incidence rate of VTE in this study was relatively small (1.8 among users vs 2.8 among nonusers per 10 000 person-days). A prior analysis by Bernstein et al conducted using data from Statistics Canada's Health Person Oriented Information found that PE and DVT occurred in 0.5% and 1.18% of the patients with IBD, respectively.[28] However, the study included VTE events occurring during hospitalization along with those reported on admission. Another analysis using a multihospital health care system in the Greater Boston area reported an incidence of VTE among patients with IBD after hospital discharge of 3.7 per 1000 days at 30 days and 4.1 per 1000 days at 60 days.[26] Unlike these analyses, we defined VTE cases based on a combination of ICD-10-CM codes, therapeutic-dose anticoagulants, and presence of diagnostic procedures and excluded patients with VTE on admission.

Our test for heterogeneity of treatment effect did not identify any interactions that reached statistical significance after adjusting for multiple comparisons. This suggests that use of VTE prophylaxis with heparin is appropriate for most patients with IBD. However, the tests for interaction for IBD type and IBD flares both had nominal P values $< .05$ for associations with bleeding. Because these subgroup analyses are likely underpowered, we also compared the stratum-specific hazard ratios (and 95% CI), which showed no clinically meaningful difference. Furthermore, we found that prophylactic use of LMWH was associated with a lower rate of bleeding than that of UFH (HR, 0.65; 95% CI, 0.50-0.84). LMWHs have more predictable bioavailability than UFH. A recent observational study of patients who are acutely ill found that enoxaparin was associated with reduced rates of VTE, death, and major bleeding compared with UFH.[29] Although our results were not statistically significant for the VTE and in-hospital mortality outcomes, our point estimates were very similar to that of the prior study (HR, 0.84; 95% CI, 0.46-1.53 vs odds ratio, 0.85; 95% CI, 0.78-0.94) for VTE and (HR, 0.91; 95% CI, 0.75-1.20 vs odds ratio, 0.91; 95% CI, 0.88-0.94) for all-cause in-hospital mortality.[29] Thus, in addition to the lower risk of heparin-induced thrombocytopenia, there may be an advantage to the use of LMWH over UFH for patients with IBD.

Table 3. Results from subgroup analyses

Examination of effect modification within clinically relevant subgroups*	Users	Nonusers	HR (95% CI) for VTE	*P* for interaction for VTE*	HR (95% CI) for bleeding	*P* for interaction for bleeding*
Age, y						
<65	19 205	19 205	0.69 (0.40-1.19)	.63	1.06 (0.84-1.34)	.09
≥65	8442	8442	1.38 (1.02-1.87)		1.38 (1.03-1.90)	
Sex				.21		.51
Male	11 528	11 528	1.06 (0.63-1.79)		1.13 (0.86-1.49)	
Female	16 322	16 322	0.54 (0.29-0.99)		1.18 (0.92-1.53)	
Cancer				.11		.68
Yes	1861	1861	1.14 (0.40-3.26)		1.18 (0.66-2.11)	
No	25 947	25 947	0.76 (0.50-1.16)		1.03 (0.84-1.25)	
IBD type				.06		.02
UC	11 361	11 361	0.65 (0.37-1.15)		0.99 (0.76-1.29)	
CD	17 377	17 377	0.46 (0.22-0.94)		1.12 (0.89-1.45)	
Heart failure				.97		.84
Yes	1885	1885	0.53 (0.13-2.12)		1.58 (0.93-2.71)	
No	25 966	25 966	0.61 (0.39-0.95)		1.03 (0.84-1.26)	
IBD flares						
Yes	5093	5093	0.70 (0.26-1.88)	.94	1.02 (0.70-1.47)	.02
No	22 985	22 985	0.55 (0.33-0.92)		1.13 (0.91-1.41)	

*We used Bonferroni adjustment to account for multiple testing. Results were considered statistically significant if the corresponding *P* value was ≤ α (ie, .05) / n, in which n = total number of subgroup analyses.

Strengths of this study include the large sample size from a geographically diverse population that is representative of the general population of patients hospitalized in the United States.[13] The Premier database includes in-hospital medication use, which is absent from most sources of claims data used for epidemiologic research in the United States. This allowed for us to directly test the effectiveness and safety of VTE prophylaxis and have more specific outcome definitions. Despite these advantages, there is the potential for outcome misclassification if VTE or bleeding events were incorrectly coded. We addressed this in our analysis by requiring therapy with anticoagulation for the VTE outcome and requiring receipt of a blood transfusion for the bleeding outcome. There is the potential for residual confounding due to variables not captured in the current data, such as smoking status, immobility, disease severity, mechanical thromboprophylaxis, and body mass index, that may contribute to the risk of VTE. We addressed this concern in our sensitivity analyses. We may have underestimated VTE-related readmissions because patients readmitted to hospitals who are not part of Premier Healthcare Database will not be included. Our secondary analysis of VTE-related readmission is susceptible to exposure misclassification because anticoagulants prescribed after hospital discharge are not captured. However, VTE prophylaxis after discharge is even less common than VTE prophylaxis while in hospital. Moreover, it would be very unlikely for someone to receive postdischarge VTE prophylaxis if they did not receive VTE prophylaxis as an inpatient. As such, any misclassification bias resulting from lack of outpatient prescriptions was likely small. We may have misclassified patients admitted with IBD flares because we relied on testing and treatment as a surrogate marker for flare. Future research is needed to develop and validate indicators to identify disease flare among patients with IBD. Our analysis may be underpowered to detect heterogeneity of treatment effect in selected subgroups due to the small sample size and small number of events.

Conclusions

In this study of hospitalized patients with IBD, prophylactic use of heparin was associated with a lower rate of VTE without increasing bleeding risk than no anticoagulation. Given the strong evidence supporting VTE prophylaxis with heparins in patients who are acutely ill, these new data strengthen the recommendations for VTE prophylaxis in hospitalized patients with IBD. Implementation research is needed to find ways to improve care through greater use of VTE prophylaxis.

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Authorship

Contribution: G.K.D. contributed to conception and design, statistical expertise, analysis of the data, and drafted the manuscript; A.C., D.E.S., and J.D.L. contributed to study design, interpretation of the data, and critical revision of the manuscript for important intellectual content.

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