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Thromboprophylaxis Is Associated With Reduced Post-hospitalization Venous Thromboembolic Events in Patients With Inflammatory Bowel Diseases

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BACKGROUND & AIMS: **Patients with inflammatory bowel diseases (IBDs) have increased risk for venous thromboembolism (VTE); those who require hospitalization have particularly high risk. Few hospitalized patients with IBD receive thromboprophylaxis. We analyzed the frequency of VTE after IBD-related hospitalization, risk factors for post-hospitalization VTE, and the efficacy of prophylaxis in preventing post-hospitalization VTE.**

METHODS: **In a retrospective study, we analyzed data from a multi-institutional cohort of patients with Crohn's disease or ulcerative colitis and at least 1 IBD-related hospitalization. Our primary outcome was a VTE event. All patients contributed person-time from the date of the index hospitalization to development of VTE, subsequent hospitalization, or end of follow-up. Our main predictor variable was pharmacologic thromboprophylaxis. Cox proportional hazard models adjusting for potential confounders were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).**

RESULTS: **From a cohort of 2788 patients with at least 1 IBD-related hospitalization, 62 patients developed VTE after discharge (2%). Incidences of VTE at 30, 60, 90, and 180 days after the index hospitalization were 3.7/1000, 4.1/1000, 5.4/1000, and 9.4/1000 person-days, respectively. Pharmacologic thromboprophylaxis during the index hospital stay was associated with a significantly lower risk of post-hospitalization VTE (HR, 0.46; 95% CI, 0.22–0.97). Increased numbers of comorbidities (HR, 1.30; 95% CI, 1.16–1.47) and need for corticosteroids before hospitalization (HR, 1.71; 95% CI, 1.02–2.87) were also independently associated with risk of VTE. Length of hospitalization or surgery during index hospitalization was not associated with post-hospitalization VTE.**

CONCLUSIONS: **Pharmacologic thromboprophylaxis during IBD-related hospitalization is associated with reduced risk of post-hospitalization VTE.**

Keywords: CD; UC; Clot; Vein; Vascular.

Patients with inflammatory bowel diseases (IBDs) (Crohn's disease [CD], ulcerative colitis [UC]) are at increased risk for venous thromboembolism (VTE)[1–7] and associated morbidity and mortality.[2,6] Inflammation is key determinant of VTE risk in IBD, with ambulatory flares and hospitalization being associated with increased risk.[1,2,5,6] Because the absolute VTE risk is greatest during hospitalization, experts recommend routine thromboprophylaxis in such settings.[6,8] However, despite the safety and efficacy of thromboprophylaxis, the rate of adoption remains low.[9,10]

In other settings at high risk for VTE such as after orthopedic surgery, the risk remains elevated for several

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HR, hazard ratio; IBD, inflammatory bowel disease; ICD-9-CM, International Classification of Diseases, 9th Revision-Clinical Modification; IQR, interquartile range; OR, odds ratio; TNF, tumor necrosis factor; UC, ulcerative colitis; VTE, venous thromboembolism.

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weeks because of persistence of risk factors such as limited mobility.[11] Conceivably, patients with IBD who have a severe disease flare requiring hospitalization remain at an elevated risk for VTE until inflammation resolves. Routine extended thromboprophylaxis is widely used after orthopedic surgery[11] but is not beneficial in general medical inpatients.[12] Prophylaxis during all ambulatory IBD flares may not be cost-effective,[13] but identification of subgroups of patients at a higher VTE risk may define those who could potentially experience greater benefit with extended thromboprophylaxis. Furthermore, the impact of thromboprophylaxis during hospitalization on subsequent risk of VTE has not been examined previously.

By using a large multi-institutional cohort of IBD patients, our aims were to (1) examine the frequency of VTE after an IBD-related hospitalization, (2) identify risk factors for post-hospitalization VTE events, and (3) define the use of thromboprophylaxis in an inpatient IBD population and examine its impact on subsequent risk of VTE.

Methods

Study Population

The data source for our study was an electronic medical record cohort of patients with CD and UC that has been described in our previous publications.[14–17] From a multihospital healthcare system in the Greater Boston area serving a population of more than 3 million patients, we identified all potential IBD patients by the presence of at least 1 International Classification of Diseases, 9th Revision-Clinical Modification (ICD-9-CM) code for CD (555.x) or UC (556.x). We extracted a range of codified data encompassing manifestations indicating severity or disease-related complications. From our electronic prescription system, we also extracted information on whether the patients had ever been prescribed medications used in the treatment of IBD including corticosteroids, mesalamine, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), or anti–tumor necrosis factor (TNF) biologic agents (infliximab, adalimumab, certolizumab pegol). We then extracted narrative free-text concepts identified by using natural language processing with the clinical Text Analysis and Knowledge Extraction System[18] as outlined in our previous publications. These could include terms such as "Crohn's disease," "ulcerative colitis," phrases used in endoscopic reports ("aphthous ulcers"), radiology ("ileal wall thickening"), or pathology reports ("ileitis"). We then developed an algorithm that used logistic regression with adaptive lasso to identify variables that predicted a diagnosis of CD or UC. This assigned each patient a probability between 0 and 1 of truly having CD or UC. We selected a cutoff for classifying disease that corresponded to a positive predictive value of 97%. The final algorithm was validated in an independent subset of patients and yielded our final IBD cohort of 5522 UC and 5506 CD patients when applied to the entire population of potential patients.

Cases of VTE were identified by the presence of validated ICD-9 codes for deep venous thrombosis, pulmonary embolism, intra-abdominal or portal thrombosis, and other thrombotic events such as cerebral thrombosis (ICD-9-CM 415.1, V125.1, 451.1–451.8, 453.0–453.9, 671.5, 325.0, 437.6, 671.9).[2,4,19,20] All VTE events were classified as occurring while inpatient or outpatient, and where this distinction was not possible, the events were labeled unclassified.

Variables

We extracted the patients' age including age at first diagnosis code for either CD or UC, gender, race (white or nonwhite), and defined comorbidity by using the validated Charlson comorbidity index.[21] We determined the occurrence of IBD-related hospitalizations or surgeries by using the primary reason for discharge among hospitalized patients. Medication use was defined as ever or never use before the event of interest. We also ascertained whether a patient had received a diagnosis of solid organ or metastatic tumor before the index hospitalization.

Primary Analysis: Predictors and Outcomes

Our primary analysis focused on occurrence of post-hospitalization VTE in adult IBD patients who had an IBD-related hospitalization or surgery. After excluding 22 patients who were on Coumadin at the time of the index hospitalization, we arrived at a final cohort of 2788 patients with CD or UC. Our main outcome variable was time to an outpatient VTE event. Patients who developed thrombosis during the initial hospitalization or during a subsequent hospitalization were excluded. Our main predictor of interest was receipt of venous thromboprophylaxis, namely the use of unfractionated heparin, enoxaparin, or dalteparin. We classified use of IBD-related medications as those occurring before the index hospitalization and extracted information on the duration of hospitalization and if it was related to a surgical procedure. In a subset of patients where this was available, we obtained information on the most recent laboratory markers of disease severity at the time of the index hospitalization including hemoglobin, albumin, serum creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, and white blood cell count.

Statistical Analysis

Analysis was performed by using Stata 12.0 (StataCorp, College Station, TX). Continuous variables were summarized by using medians and interquartile ranges (IQRs); categorical variables were expressed as

proportions and compared by using the χ^2 test. All patients contributed person-time from the date of the index hospitalization (either medical or surgical) to development of VTE, subsequent hospitalization or surgery, or end of follow-up within our electronic medical record. We used a Cox proportional hazards model and entered variables meeting statistical significance at a threshold of $P < .10$ into our final multivariate model. Independent predictors were considered significant if the two-sided P value was $\leq .05$. All models satisfied the proportionality of hazards assumption. Our study was approved by the institutional review board of Partners Healthcare.

Results

From our initial IBD cohort of 5506 patients with CD and 5522 with UC, 760 (7%) had at least 1 VTE event (Figure 1). Of these, 431 were inpatient and 276 outpatient, and for 53 VTE events, we were unable to determine admission status at the time of the event. IBD patients who had a VTE event were older, had a greater Charlson comorbidity index, and were more likely to have had an IBD-related hospitalization or surgery than those who did not develop VTE ($P < .001$) (Table 1). Patients who developed inpatient VTE were similar to those with outpatient VTE. During a median follow-up of 10 years, 7% of patients without VTE died, compared with 18% of those with outpatient VTE and 27% of those with an inpatient VTE event ($P < .001$).

Three variables were independent predictors of a VTE event (Table 2). An IBD-related hospitalization was the strongest risk factor for VTE (odds ratio [OR], 1.72; 95% confidence interval [CI], 1.39–2.12). Each additional comorbidity included in the Charlson score was associated with an independent increase in risk of VTE (OR, 1.43; 95% CI, 1.36–1.50), and each year increase in age was associated with 2% increase in risk (OR, 1.02; 95% CI, 1.02–1.03).

For our primary analysis we used a cohort of 2788 patients with an IBD-related hospitalization. Among them, 62 patients (2%) developed VTE, 3 of which were pulmonary emboli, 2 were intra-abdominal thromboses, and the remaining were deep venous thrombosis events. The incidence of VTE at 30, 60, 90, and 180 days after the index hospitalization was 3.7/1000, 4.1/1000, 5.4/1000, and 9.4/1000, respectively. Table 3 presents the results of the univariate and adjusted models examining predictors of post-hospitalization VTE. Increasing comorbidity (hazard ratio [HR], 1.30; 95% CI, 1.16–1.47) was an independent predictor of post-hospitalization VTE. Use of corticosteroids before the hospitalization was independently associated with risk of VTE (HR, 1.71; 95% CI, 1.02–2.87). Length of hospitalization or whether index hospitalization was related to surgery was not predictive of subsequent VTE. In the hospitalized cohort, 788 patients (28.3%) were administered pharmacologic thromboprophylaxis. Interestingly, receiving thromboprophylaxis during the hospitalization was associated with a significantly lower risk of post-hospitalization VTE (HR, 0.46; 95% CI, 0.22–0.97) (Figure 2). This effect was greater for VTE that occurred within 90 days (HR, 0.19; 95% CI, 0.02–1.48) than those occurring 90 days or more after the hospitalization (HR, 0.52; 95% CI, 0.23–1.17).

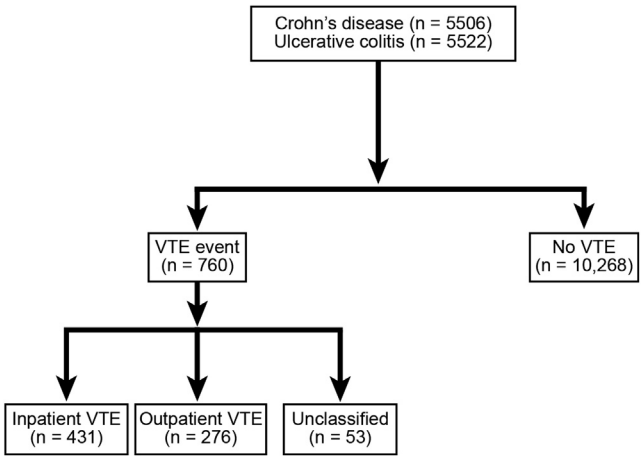

Figure 1. Flowchart showing ascertainment of cases and outcomes.

Table 1. Characteristics of Patients Included, Stratified by VTE

Characteristic	No VTE (n = 10,268)	Inpatient VTE (n = 431)	Outpatient VTE (n = 276)	*P* value
Age (*y*), median (IQR)	38 (25–53)	53 (37–65)	51 (38–62)	<.001
Modified Charlson score, median (IQR)	0 (0–1)	2 (0–3)	2 (0–3)	<.001
Female	54	55	54	.90
White	85	89	90	.006
IBD type				.95
CD	49	48	48	
UC	51	52	52	
IBD hospitalization before VTE event	28	50[a]	27	<.001
IBD surgery before VTE event	14	23	15	<.001
Cancer diagnosis	7	9	10	.08
Died	7	27	18	<.001

[a]Does not include hospitalization associated with the index VTE event.

Table 2. Multivariate Analysis of Predictors of VTE

Characteristic	OR	95% CI
Age (*y*)	1.02	1.02–1.03
Female	1.08	0.91–1.28
Nonwhite race	0.84	0.71–1.01
Modified Charlson score	1.43	1.36–1.50
Cancer diagnosis	1.24	0.93–1.66
IBD hospitalization	1.72	1.39–2.12
IBD surgery	1.22	0.95–1.58

Table 3. Predictors of Post-hospitalization VTE Events

Predictor	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Age	1.02	1.00–1.03	1.01	0.99–1.02
Female	0.90	0.55–1.59		
Nonwhite	1.08	0.53–2.20		
Modified Charlson score	1.34	1.20–1.48	1.30	1.16–1.47
Cancer	1.18	0.54–2.61		
Index surgical hospitalization	1.18	0.68–2.04		
Hospitalization >7 days	1.44	0.82–2.54		
IBD type, UC	0.94	0.56–1.58		
Steroid use	1.55	0.93–2.60	1.71	1.02–2.87
Anti-TNF use	0.79	0.11–5.73		
Immunomodulator use	2.05	0.64–6.55		
VTE prophylaxis	0.44	0.21–0.91	0.46	0.22–0.97

Because recent laboratory markers were available on only a subset of patients, we performed an exploratory analysis of their utility in predicting post-hospitalization VTE. Each 1 g/dL increase in serum albumin was associated with a reduced risk of VTE (HR, 0.66; 95% CI, 0.42–1.05), whereas greater serum creatinine was associated with an increased risk (HR, 1.34; 95% CI, 1.14–1.58). The risk of VTE at 30 days in patients with a low albumin on hospitalization was 10/1000 person-days, compared with those with normal serum albumin who had a risk of 5/1000 person-days ($P < .05$). CRP, ESR, platelet count, or white blood cell count at hospitalization were not predictive of subsequent VTE risk. Recognizing that patients with severe disease and rectal bleeding may be considered to be at higher bleeding risk from thromboprophylaxis despite their higher VTE risk, we adjusted for hemoglobin at the time of hospitalization. Although only 19% of patients with hemoglobin below 10 g/dL received thromboprophylaxis compared with 32% of patients with a value ≥10 g/dL ($P < .05$), hemoglobin level, anemia, and blood transfusion were not in themselves predictive of post-discharge VTE and did not alter the association between thromboprophylaxis and VTE.

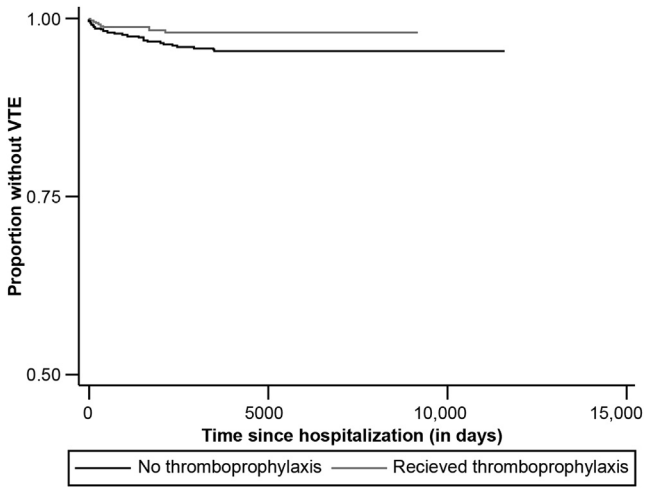

Figure 2. Effect of venous thromboprophylaxis on post-hospitalization venous thromboembolic events.

Discussion

By using a large IBD cohort, we demonstrate that a substantial fraction of VTE events in IBD patients occurs in the outpatient setting. Among patients with an IBD-related hospitalization, the risk of VTE within 180 days after hospitalization was significantly higher in those with older age, greater comorbidity burden, or who required steroids before hospitalization. Receiving thromboprophylaxis during the hospitalization was associated with a reduced risk of post-discharge VTE.

Prior studies have examined risk factors for VTE in IBD patients. Inherited thrombophilias have not been consistently associated with the initial or recurrent VTE.[3,6,22,23] In a prior study, age and comorbidity were both associated with increased risk of VTE, which was consistent with our results.[2] Disease activity has also been consistently associated with increased VTE risk.[5] In the study by Grainge et al,[5] the absolute risk was lower among non-hospitalized patients (6.4 per 1000 person-years) when compared with hospitalized patients (37.5 per 1000 person-years). The risk of VTE in the post-hospitalization period was similar to ambulatory disease flares and higher than that for IBD overall reported from previous cohort studies.[1,4]

We found systemic steroids to be associated with increased risk of post-hospitalization VTE. Although this, in part, likely reflects the association between inflammation and VTE, other studies have suggested that use of steroids in itself could be a risk factor for VTE. In a large cohort study, systemic glucocorticoid use was associated with a 2-fold increase in risk for VTE,[24] and oral glucocorticoids were associated with an increased risk of pulmonary embolism particularly within the first 30 days of use, although the elevation in risk persisted for 1 year.[25] Low serum albumin is a well-recognized risk factor for VTE in nephrotic syndrome[26] and chronic liver disease.[27] Even in the general population, low serum albumin may be associated with a modest increase in risk of VTE.[28] Prior studies on VTE risk in IBD have been limited by lack of laboratory data to examine this association. Low albumin levels may reflect excess loss of protein and, in particular, circulating antithrombotic proteins. It may be a marker of underlying inflammation as a negative acute phase reactant. Finally, low albumin may be associated with chronic illness and associated prothrombotic risk factors such as reduced mobility.

The most important finding of our study was that in-hospital thromboprophylaxis was associated with a reduced risk of post-discharge VTE. Despite widespread acknowledgement of the increased risk for venous

thrombosis in IBD, rates of thromboprophylaxis remain low.[10,29] In a large practice survey, only 35% of gastroenterologists indicated routine use of VTE prophylaxis in hospitalized patients with severe UC.[29] The rates of VTE prophylaxis are higher among surgical compared with medical inpatients.[9,10] There are a few mechanisms through which thromboprophylaxis in-hospital may reduce risk of post-discharge VTE. First, some of the thrombosis events identified in the group not receiving thromboprophylaxis may have been present at the time of hospitalization but became apparent only after discharge, explaining the protective effect of in-hospital prophylaxis. Second, prior clinical trials have demonstrated that unfractionated heparin itself may be beneficial in the treatment of some patients with active UC and CD.[30,31] Because one key mechanism underlying VTE risk in patients with IBD is the inflammatory burden, it is plausible that some of the anti-inflammatory effects of heparin may aid in earlier or more substantial resolution of the circulating inflammatory burden in the cohort receiving thromboprophylaxis. The fact that the protective effect is strongest within 1–3 months after discharge is consistent with such short-term mechanisms of effect.

Whether the occurrence of post-hospitalization VTE translates to need for extended thromboprophylaxis in hospitalized IBD patients is unclear. Only a few studies have examined the effect of extended thromboprophylaxis. In a series following patients undergoing major surgery, between 2% and 5% of patients experienced VTE within 30 days of discharge, suggesting there may be benefit to extended prophylaxis.[32,33] In contrast, Fanikos et al[12] found no difference in the 90-day VTE rate between general medical inpatients who received extended prophylaxis after discharge compared with in-hospital prophylaxis only. In a systematic review, extended thromboprophylaxis with low-molecular-weight heparin was effective in reducing risk of major VTE events in high-risk patients.[34]

There are several implications to our findings. Because the absolute risk of VTE after hospitalization was lower in our cohort than in the postsurgical literature, it is unlikely that extending thromboprophylaxis in IBD patients will be cost-effective. In a recent decision analysis, although pharmacologic VTE reduced lifetime risk of VTE, it was not associated with a significant improvement in quality-adjusted life-years.[13] However, identification of high-risk subgroups may allow targeting studies of extended prophylaxis in IBD to those at highest risk of post-discharge VTE. In the meantime, in-hospital prophylaxis appears to protect not only during VTE events associated with the hospitalization but also early post-hospitalization VTE. Consequently, continued attempt to improve rates of prophylaxis is important. There are infrequent risks associated with thromboprophylaxis including bleeding risk and heparin-induced thrombocytopenia. Although such risks should be incorporated into personalized decision-making, they are of lower magnitude than the risk of VTE.

We acknowledge several limitations to our study. First, the 2 main hospitals contributing to our patient cohort are both referral hospitals, biasing our cohort toward severe disease. However, because this is the group at the highest risk of VTE, it represents an important patient population for study. Second, identification of VTE was triggered by symptoms. However, recent studies have demonstrated that asymptomatic deep venous thrombosis is uncommon in hospitalized patients with IBD.[35] Third, we examined thromboprophylaxis use as a dichotomous variable. Further studies with greater detail may be better suited to examine the effect of dose or duration of VTE prophylaxis on risk of subsequent VTE. Finally, we analyzed only the first VTE event to retain homogeneity and to ensure that all patients were potentially eligible to receive pharmacologic thromboprophylaxis. Future studies should examine the impact of prior VTE on the risk of recurrence after hospitalization.

In conclusion, we demonstrate that a substantial fraction of VTE events in IBD patients occur in the outpatient setting. Subgroups of patients including those with older age, greater comorbidity, and need for systemic steroids are at greater risk for VTE after discharge. Pharmacologic thromboprophylaxis during hospitalization is associated with reduced risk of post-hospitalization VTE. Consequently, it is important to increase adoption of thromboprophylaxis routinely in the hospitalized IBD patient, and exploratory studies of extended thromboprophylaxis should be targeted to those with additional risk factors.

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The authors disclose no conflicts.

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