Thromboprophylaxis is associated with reduced post-hospitalization venous thromboembolic events in patients with inflammatory bowel diseases

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Abstract

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Background & Aims—Patients with inflammatory bowel diseases (IBD) 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 following 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 (HR) and 95% confidence intervals (CI).

Results—From a cohort of 2788 patients with at least 1 IBD-related hospitalization, 62 patients developed VTE following 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 co-morbidities (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

INTRODUCTION

Patients with inflammatory bowel diseases (IBD; 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]. As 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 following orthopedic surgery, the risk remains elevated for several weeks due to 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 till inflammation resolves. Routine extended thromboprophylaxis is widely used following 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.

Using a large multi-institutional cohort of IBD patients, our aims were to (i) examine the frequency of VTE following an IBD-related hospitalization; (ii) identify risk factors for post-hospitalization VTE events; and (iii) 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 which has described in our previous publications[14–17]. From a multi-hospital healthcare system in the Greater Boston area serving a population of over 3 million patients, we identified all potential IBD patients by the presence of at least one international classification of diseases, 9th edition, 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, 5-aminosalicylates, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), or anti-tumor necrosis factor biologic agents (anti-TNF) (infliximab, adalimumab, certolizumab pegol). We then extracted narrative free-text concepts identified using natural language processing (NLP) with the clinical Text Analysis and Knowledge Extraction System (cTAKES)[18] as outlined in our previous publications. These could include terms such as "Crohn's disease" "ulcerative colitis", phrases used in endoscopic reports such as ("aphthous ulcers"), radiology ("ileal wall thickening"), or pathology reports ("ileitis"). We then developed an algorithm using 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 when applied to the entire population of potential patients, yielded our final IBD cohort of 5,522 UC and 5,506 CD patients.

Cases of venous thromboembolism 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 non-white), and defined co-morbidity using the validated Charlson

co-morbidity index[21]. We determined the occurrence of IBD-related hospitalizations or surgeries using the primary reason for discharge among hospitalized patients. Medication use was defined as ever or never use prior to the event of interest. We also ascertained whether a patient had received a diagnosis of solid organ or metastatic tumor prior to 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 2,788 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 prior to 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 using Stata 12.0 (StataCorp, College Station, TX). Continuous variables were summarized using medians and interquartile ranges (IQR); categorical variables were expressed as proportions and compared using the chi-square 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 EMR. We used a Cox proportional hazards model and entered variables meeting statistical significance at a threshold of $p < 0.10$ into our final multivariate model. Independent predictors were considered significant if the two-sided p-value was 0.05. 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 5,506 patients with CD and 5,522 with UC, 760 (7%) had at least one VTE event (Figure 1). Of these, 431 were inpatient, 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 co-morbidity index, and were more likely to have had an IBD-related hospitalization or surgery than those who did not develop VTE ($p < 0.001$) (Table 1). Patients who developed inpatient VTE were similar to those with outpatient VTE. Over a median follow-up of 10 years, 7% of patients without VTE died compared to 18% of those with outpatient VTE and 27% of those with an inpatient VTE event ($p < 0.001$).

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 co-morbidity 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 a 2% increase in risk (Odds ratio (OR) 1.02, 95% confidence interval (CI) 1.02 – 1.03).

For our primary analysis, we utilized a cohort of 2,788 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, and 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 co-morbidity (Hazard ratio (HR) 1.30, 95% CI 1.16 – 1.47) was an independent predictor of post-hospitalization VTE. Use of corticosteroids prior to 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).

Since 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 1g/dL increase in serum albumin was associated with a reduced risk of VTE (HR 0.66, 95% CI 0.42 – 1.05) while 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 to those with normal serum albumin who had a risk of 5/1000 person-days (p < 0.05). C-reactive protein, ESR, platelet count or WBC 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. While only 19% of patients with hemoglobin below 10g/dL received thromboprophylaxis compared to 32% of patients with a value 10g/dL (p < 0.05), hemoglobin level, anemia, or blood transfusion were not in themselves predictive of post-discharge VTE and did not alter the association between thromboprophylaxis and VTE.

DISCUSSION

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 co-morbidity burden or who required steroids prior to 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 co-morbidity were both associated with increased risk of VTE, consistent with our results[2]. Disease activity has also been consistently associated with increased VTE risk[5]. In the study by Grainge *et al*., the absolute risk was lower among non-hospitalized patients (6.4 per 1000 person-years) compared to hospitalized patients (37.5 per 1000 person-years)[5]. 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. While 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 glucocorticoids use was associated with a two-fold increase in risk for VTE[24] and oral glucocorticoids were associated with an increased risk of PE particularly within the first 30 days of use though 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 anti-thrombotic 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 to 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 become 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 ulcerative colitis and Crohn's disease[30, 31]. Since 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 few studies have examined the effect of extended thromboprophylaxis. In a series following patients undergoing major surgery, between 2–5% of patients experienced a VTE within 30 days of discharge suggesting there may be benefit to extended prophylaxis[32, 33]. In contrast, Fanikos *et al*. found no difference in the 90 day VTE rate between general medical inpatients who received extended prophylaxis after discharge compared to in-hospital prophylaxis only[12]. In a systematic review, extended thromboprophylaxis with LMWH heparin was effective in reducing risk of major VTE events in high-risk patients[34].

There are several implications to our findings. As the absolute risk of VTE following hospitalization was lower in our cohort than in the post-surgical literature, it is unlikely that extending thromboprophylaxis in IBD patients will be cost-effective. In a recent decision analysis, though 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 not only protect 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. While 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 two main hospitals contributing to our patient cohort are both referral hospitals, biasing our cohort towards severe disease. However, as 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 DVT 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 post-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 co-morbidity, and need for systemic steroids are at greater risk for VTE post-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 while exploratory studies of extended thromboprophylaxis should be targeted to those with additional risk factors.

Acknowledgments

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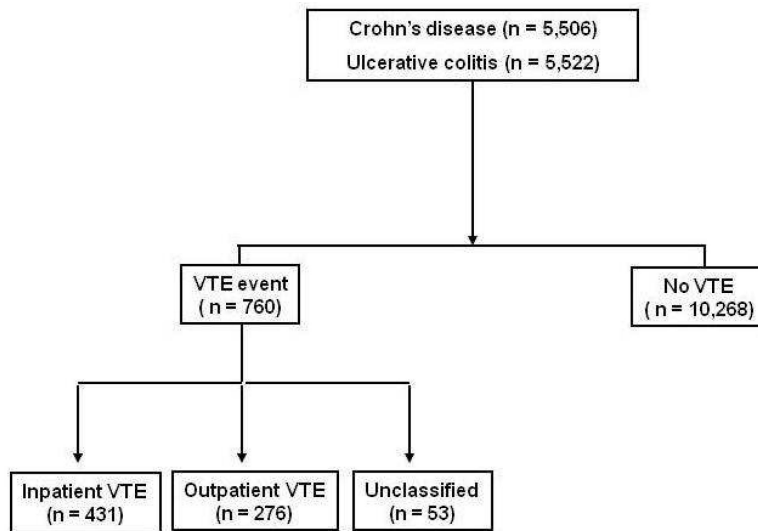
Figure 1.
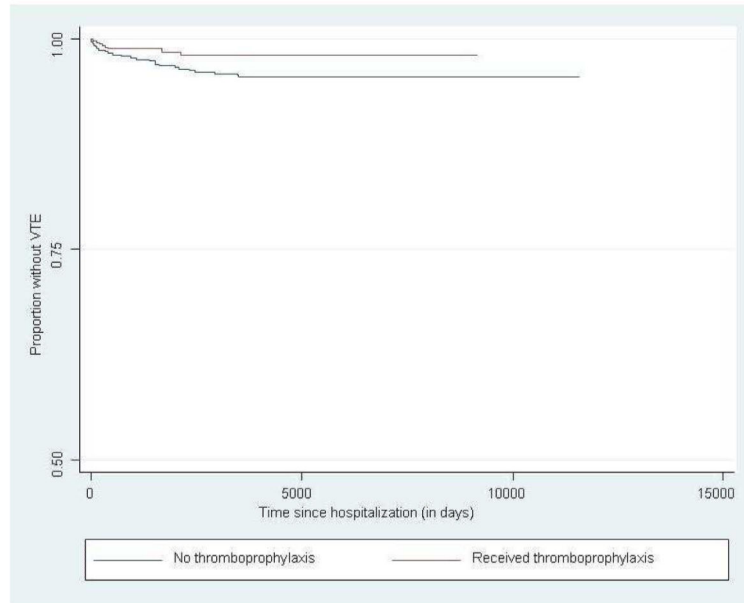Flowchart demonstrating ascertainment of cases and outcomes

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

Table 1

Characteristics of patients included, stratified by venous thromboembolism

Characteristic	No VTE (n = 9,268)	Inpatient VTE (n=388)	Outpatient VTE (n=224)	p-value
Age (in years) (Median (IQR))	38 (25 – 53)	53 (37 – 65)	51 (38 – 62)	< 0.001
Modified Charlson score (Median (IQR))	0 (0 – 1)	2 (0 – 3)	2 (0 – 3)	< 0.001
Female	54	55	54	0.90
White	85	89	90	0.006
IBD type				0.95
Crohn's disease	49	48	48	
Ulcerative colitis	51	52	52	
IBD hospitalization prior to VTE event	28	50[†]	27	< 0.001
IBD surgery prior to VTE event	14	23	15	< 0.001
Cancer diagnosis	7	9	10	0.08
Died	7	27	18	< 0.001

[†] Does not included hospitalization associated with the index VTE event

Table 2

Multivariate analysis of predictors of venous thromboembolism

Characteristic	Odds Ratio	95% confidence interval
Age (in years)	1.02	1.02 – 1.03
Female	1.08	0.91 – 1.28
Non-white 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 venous thromboembolic events

Predictor	Univariate		Multivariate	
	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
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	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 – ulcerative colitis	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