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## Venous thromboembolism in inflammatory bowel disease

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### Abstract

Patients with inflammatory bowel disease (IBD) are at an increased risk for venous thromboembolism (VTE). VTE events carry significant morbidity and mortality, and have been associated with worse outcomes in patients with IBD. Studies have suggested that the hypercoagulable nature of the disease stems from a complex interplay of systems that include the coagulation cascade, natural coagulation inhibitors, fibrinolytic system, endothelium, immune system, and platelets. Additionally, clinical factors that increase the likelihood of a VTE event among IBD patients include older age (though some studies suggest younger patients have a higher relative risk of VTE, the incidence in this population is much lower as compared to the older IBD patient population), pregnancy, active disease, more extensive disease, hospitalization, the use of certain medications such as corticosteroids or tofacitinib, and IBD-related surgeries. Despite the increased risk of VTE among IBD patients and the safety of pharmacologic prophylaxis, adherence rates among hospitalized IBD patients appear to be low. Furthermore, recent data suggests that there is a population of high risk IBD patients who may benefit from post-discharge prophylaxis. This review will provide an overview of patient specific factors that affect VTE risk, elucidate reasons for lack of VTE prophylaxis among hospitalized IBD patients, and focus on recent data describing those at highest risk for recurrent VTE post-hospital discharge.

**Key words:** Inflammatory bowel disease; Venous thromboembolism; Prophylaxis; Deep venous thrombosis; Pulmonary embolism; Ulcerative colitis

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**Core tip:** Venous thromboembolism is a known complication in patients with inflammatory bowel disease that is associated with significant cost, morbidity, and mortality. Certain patient specific risk factors, such as age, pregnancy, active disease, colorectal surgery, and the use of corticosteroids and tofacitinib can increase venous

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thromboembolism risk. We herein explore these patient specific risk factors, consider the utility of post-discharge venous thromboembolism prophylaxis, and discuss mechanisms to improve pharmacologic prophylaxis rates among hospitalized inflammatory bowel disease patients.

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## INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated disease that is comprised of ulcerative colitis (UC) and Crohn's disease (CD). The incidence of IBD is increasing with a prevalence of over 1.3% in the US<sup>[1]</sup> and a global prevalence that surpasses 0.3%<sup>[2]</sup>. UC primarily affects the rectum and colon while CD can involve any part of the gastrointestinal tract from the oral cavity to the perianal area. Though they have different clinical characteristics, both CD and UC are associated with an increased risk of venous thromboembolism (VTE).

Several studies have shown that IBD patients are at a 2 to 3-fold higher risk of developing a VTE as compared to the general population<sup>[3]</sup>. This increased risk appears to be unique to patients with IBD, as other chronic inflammatory diseases such as rheumatoid arthritis and celiac disease do not confer this risk<sup>[4]</sup>. Despite the clear link between VTE and IBD, the molecular pathogenesis of VTE in IBD remains complex and incompletely understood. Over the past decade however, there has been an increasing body of literature describing factors that may influence this risk, including disease activity, hospitalization, age, pregnancy, medications, surgery, and genetics.

In this review, we will focus primarily on the patient specific factors that affect VTE risk, and provide a brief overview of the hypercoagulable mechanisms at play. As the cost and mortality of VTE is substantial in IBD patients, we will also focus on current guideline recommendations, with particular attention paid to the utility of VTE prophylaxis while in the hospital and during the post-discharge period.

## MORBIDITY, MORTALITY, AND COST ASSOCIATED WITH VTE

VTE, which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), carries significant morbidity and mortality<sup>[5]</sup>. Within the United States, over 500000 hospitalizations and 100000 deaths have been attributed to VTE annually<sup>[6]</sup>. After an initial VTE event, long-term complications can include post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and recurrence of disease<sup>[7-9]</sup>. In addition to the significant morbidity and mortality, overall medical costs associated with VTE events range from 5-10 billion dollars per year within the United States<sup>[10,11]</sup>. Given the significant health and economic burden of VTE, it is imperative that we continue to focus our healthcare efforts on prevention.

## MECHANISM

The pathogenesis of VTE in IBD is multifactorial and incompletely understood. Data suggest that it is not one particular mechanism that leads to hypercoagulability in IBD, but rather a complex interplay of systems<sup>[12]</sup>. On the molecular level, the upregulation of the inflammatory and coagulation systems create a prothrombotic state that involve the coagulation cascade, natural coagulation inhibitors, fibrinolytic system, endothelium, immune system and platelets<sup>[13]</sup>. More specifically, this increased risk of VTE has been attributed to higher levels of inflammatory cytokines, acute phase reactants, procoagulants, and lower levels of anticoagulants<sup>[14]</sup>. Studies have shown that coagulation factors V, VII, VIII, X, XI, XII, von Willebrand factor, and fibrinogen as well as products of fibrin and thrombin formation are all elevated



during an IBD flare<sup>[15,16]</sup>. Additionally, IBD patients have increased platelet counts (thrombocytosis) during active disease states, and have been found to have increased platelet activity<sup>[17]</sup>. In conjunction, studies have suggested that IBD patients have lower levels of protein S and antithrombin during active disease states, which are important drivers of anticoagulation<sup>[18]</sup>.

## VTE RISK FACTORS AMONG PATIENTS WITH IBD

### Age

Beginning in early childhood, patients with IBD have an increased risk of VTE. A nationwide Danish study assessing IBD patients aged 20 years-old and younger noted that these IBD patients had more than a 6-fold higher hazard ratio (HR) of developing a VTE as compared to age and sex-matched patients without IBD<sup>[19]</sup>. Although the relative risk of a VTE event was almost four times higher in younger IBD patients as compared to older IBD patients ( $\geq 60$  years-old), the annual incidence of events was markedly lower in the younger IBD patient population as compared to the older IBD patient population (8.9/10000 person-years *vs* 54.6/10000 person-years, respectively)<sup>[19]</sup>. A retrospective cohort study of hospitalized children and adolescents in the United States noted similar findings, specifically that IBD patients had a 2.4 relative risk of developing a VTE as compared to children and adolescents without IBD<sup>[20]</sup>. Furthermore, Nylund *et al*<sup>[20]</sup> found that the odds of VTE increased as age increased (OR: 2.32; 95%CI: 2.26-2.38).

From these studies we can see that although younger IBD patients may have a high relative risk of VTE, the actual occurrence of such events is infrequent. Thus, guidelines such as the Canadian Association of Gastroenterology recommend against prophylaxis for IBD patients younger than 18 years of age who have never had a VTE, regardless of whether they are experiencing a flare or not<sup>[21]</sup>. As patients age however, the incidence of VTE increases<sup>[6]</sup>. In a retrospective review of Japanese inpatients with IBD, older age was one of the few risk factors noted for the development of VTE<sup>[22]</sup>. Similarly, two recent studies found older age to be associated with the risk of developing a post-hospital discharge VTE<sup>[23,24]</sup> (Table 1). This is of particular importance given the rising prevalence of IBD, and the increasing proportion of patients  $\geq 60$  years-old with IBD<sup>[25]</sup>.

### Pregnancy

VTE is a leading cause of pregnancy-related maternal mortality in developed countries<sup>[26]</sup>, with a 4 to 6-fold increase in relative risk of VTE in pregnant women as compared to non-pregnant women<sup>[27]</sup>. Physiologic changes during pregnancy, including alterations in venous blood flow, mechanical obstruction by the gravid uterus, and vascular injury lead to a higher risk of VTE that can persist for up to 12 wk postpartum<sup>[28]</sup>.

Women with IBD however, are at an even greater risk of VTE during both the pregnancy and postpartum period. Based upon a recent nationwide population-based cohort study that included approximately 2 million deliveries in Denmark from 1980-2013, the relative risk for VTE during pregnancy was almost two-fold higher in women with IBD as compared to those without IBD<sup>[29]</sup>. When considering the postpartum period, patients with IBD were similarly at a 2.1 (95%CI: 2.72-3.04) higher relative risk of developing a VTE as compared to postpartum patients without IBD<sup>[29]</sup>.

A recent meta-analysis, including additional cohort studies from the United States, United Kingdom, and Australia, as well as a population based study in Sweden, showed similar results. The authors concluded that during pregnancy, there was a more than 2-fold higher risk of VTE among patients with IBD, which persisted during the postpartum period<sup>[30]</sup>. On subgroup analysis, VTE risk appeared higher in UC patients as compared to CD patients in both the pregnancy and postpartum period<sup>[30]</sup> (Table 2). Based upon these results, future studies should focus upon identifying pregnant and postpartum IBD patients at highest risk for VTE, as well as assessing the cost-effectiveness of thromboprophylaxis in these patients.

### Genetics

Although the hypercoagulability associated with IBD had previously been thought to be due to inherited genetic mutations, studies have not demonstrated this. When examining the prevalence of genetic mutations such as Factor V Leiden or prothrombin G20210A, similar rates have been seen for both patients with and without IBD, as well as for IBD patients with and without a VTE<sup>[13,31]</sup>. Given that inherited thrombophilia is not more prevalent in the IBD patient population, guidelines such as the Canadian Association of Gastroenterology do not recommend

Table 1 Age and venous thromboembolism risk

Ref.	Findings	Statistics
Kappelman <i>et al</i> <sup>[19]</sup>	IBD patients ≤ 20 are at increased risk of VTE compared to age and sex-matched non-IBD patients	Hazard ratio 6.0 (95%CI: 2.5-14.7) for DVT Hazard ratio 6.4 (95%CI: 2.0-20.3) for PE
	Annual incidence of VTE is higher in older patients than in younger patients with IBD	Age ≤ 20 yr > 60 yr
		Incidence 8.9/10000 persons-years 54.6/10000 persons-years
Nylund <i>et al</i> <sup>[20]</sup>	Hospitalized IBD children/adolescents are at increased risk of developing VTE compared to non-IBD hospitalized children/adolescents	Relative risk 2.36 (95%CI: 2.15-2.58)
	Odds of VTE increased as age increased	Odds ratio 2.32 (95%CI: 2.26-2.38)
Ando <i>et al</i> <sup>[22]</sup>	IBD patients > 50 have an increased odds of developing VTE	Odds ratio 3.52 (95%CI: 1.25-9.94)
Nguyen <i>et al</i> <sup>[5]</sup>	Each incremental decade in age was associated with increased odds of developing VTE	Odds ratio 1.20 (95%CI: 1.15-1.25)
Faye <i>et al</i> <sup>[23]</sup>	Age > 30 had an increased risk of VTE readmission compared with patients younger than 18 years of age	Age (yr) 31-40 41-50 51-65 66-80 > 80
		Relative risk 2.10 (95%CI: 1.29-3.42) 2.08 (95%CI: 1.28-3.37) 3.74 (95%CI: 2.35-5.94) 4.04 (95%CI: 2.54-6.44) 3.06 (95%CI: 1.87-5.02)
McCurdy <i>et al</i> <sup>[24]</sup>	IBD patients > 45 have an increased odds of developing VTE post-discharge	3.76 odds ratio (95%CI: 1.80-7.89)

VTE: Venous thromboembolism; DVT: Deep vein thrombosis; IBD: Inflammatory bowel disease; PE: Pulmonary embolism.

genetic screening, unless the VTE is unprovoked (*ie*, clinical remission, no other risk factors)<sup>[21]</sup>.

### Disease activity, disease location and hospitalization

The presence of active disease has previously been shown to increase the risk of VTE among patients with IBD. In the 2010 retrospective cohort study by Grainge *et al*<sup>[3]</sup>, having an IBD flare was associated with the highest risk of VTE (HR: 8.4; 95%CI: 5.5-12.8) as compared to IBD patients with chronic disease activity or in remission. Analogous results were seen among pregnant IBD patients, as those experiencing a flare had a higher risk of developing a VTE<sup>[29]</sup>. Additionally, in a single-center retrospective study of all IBD patients with VTE events, 71% were found to have had active disease at the time of VTE diagnosis<sup>[32]</sup> (Table 3).

Disease extent is also associated with risk of VTE. In a single-center retrospective review of all IBD patients with a VTE, Solem *et al*<sup>[33]</sup> found that 76% of UC patients had pancolonic involvement while 79% of CD patients had disease involving extensive surfaces (56% with ileocolonic disease, 23% with colonic, and 21% with ileal disease). A recent multinational study of VTE within East Asian IBD patients also found that 71% of UC patients with a VTE had pancolitis, and that all CD patients with a VTE had ileocolonic involvement<sup>[34]</sup>.

In addition to disease activity and location, hospitalization also has been shown to increase the risk of VTE among IBD patients. In the study by Grainge *et al*<sup>[3]</sup>, hospitalized IBD patients, regardless of disease activity, had a higher risk of VTE as compared to patients without IBD. In a nationwide study by Nguyen *et al*<sup>[5]</sup>, patients hospitalized with IBD had higher rates of VTE, as well as VTE-associated mortality, as compared to hospitalized patients without IBD. Additionally, in a recent nationwide study in Korea, IBD patients hospitalized for a non-disease flare had more than a 12-fold increase in VTE risk (aHR: 12.97; 95%CI: 8.68-19.39) as compared to controls<sup>[35]</sup> (Table 4). Given the increased risk of VTE in hospitalized IBD patients, including those hospitalized for reasons other than disease flares, the Canadian Association of Gastroenterology has extended their VTE prophylaxis recommendations to now include IBD patients who are admitted for non-IBD related reasons<sup>[21]</sup>.



Table 2 Pregnancy and venous thromboembolism risk

Ref.	Findings	Statistics	
Hansen <i>et al</i> <sup>[29]</sup>	Pregnant IBD patients are at increased risk of developing VTE as compared to pregnant non-IBD patients	Relative risk 1.67 (95%CI: 1.15-2.41)	
	Postpartum IBD patients are at a higher risk of developing VTE than postpartum non-IBD patients	Relative risk 2.10 (95%CI: 1.33-3.30)	
	Incidence of VTE is greatest in postpartum IBD women	Group	Incidence rate
		Pregnant non-IBD	2.41 (95%CI: 2.33-2.50)
		Pregnant IBD	4.20 (95%CI: 2.83-5.58)
		Postpartum non-IBD	2.88 (95%CI: 2.72-3.04)
Kim <i>et al</i> <sup>[30]</sup>	Pregnant IBD patients are at increased risk of developing VTE as compared to non-IBD pregnant patients	Relative risk 2.13 (95%CI: 1.66-2.73)	
	Postpartum IBD patients are at increased risk of developing VTE as compared to postpartum non-IBD patients	Relative risk 2.61 (95%CI: 1.84-3.69)	
	UC patients are at an increased risk of developing VTE as compared to CD patients both during pregnancy and in postpartum period	Group	Relative risk
		Pregnant UC <i>vs</i> CD patients	2.24 (95%CI: 1.60-3.11)
		Postpartum UC <i>vs</i> CD patients	2.85 (95%CI: 1.79-4.52)

VTE: Venous thromboembolism; IBD: Inflammatory bowel disease; CD: Crohn's Disease; UC: Ulcerative colitis.

### Medications

Data regarding the risk of VTE from concomitant use of aminosalicylates is limited. Often used in mild UC, aminosalicylates such as mesalamine and sulfasalazine have been shown to inhibit spontaneous and thrombin-induced platelet activation<sup>[36]</sup>. Immunomodulators such as azathioprine and 6-mercaptopurine have also been shown to reduce *in vitro* platelet aggregation<sup>[37]</sup>. Although these medications may reduce the risk of VTE, future studies specifically evaluating this association within the IBD patient population are needed.

Corticosteroids however, which are often used to help induce remission in IBD patients with active disease, often have a myriad of adverse side-effects including an increased risk of VTE. In a 2018 meta-analysis by Sarlos *et al*<sup>[38]</sup>, corticosteroid use was associated with a higher risk of VTE events among IBD patients (OR: 2.2; 95%CI: 1.7-2.9). While it has been speculated that the increased VTE risk may be secondary to disease activity rather than corticosteroid use alone, studies examining VTE risk within the general patient population have shown similar risks<sup>[39]</sup>. The mechanism is thought to be related to excess cortisol, as patients with Cushing's syndrome have an increased risk of VTE from an elevated production of procoagulation factors and an impaired fibrinolytic capacity<sup>[40]</sup>. This is of particular concern as older IBD patients, who have the highest incidence of VTE events, are often placed on corticosteroids<sup>[41]</sup>.

In contrast, immunosuppressive medications such as anti-TNF $\alpha$  biologics are thought to decrease the risk of VTE. In 2011, Yoshida *et al*<sup>[42]</sup> found that within colitis-induced mouse models, TNF $\alpha$  was intimately involved in the hypercoagulable state. This has since led to the theory that inhibiting TNF $\alpha$  may decrease the risk of VTE within the IBD patient population. In one single-center retrospective review, use of anti-TNF $\alpha$  medications had a reduced risk of VTE (OR: 0.2; 95%CI: 0.04-0.99), whereas corticosteroid use was associated with a 4-fold increase in the risk of VTE<sup>[43]</sup>. Using a nationwide United States insurance database, Higgins *et al*<sup>[44]</sup> found that patients receiving biologics were approximately five times less likely to have VTE event as compared to those receiving corticosteroids. Similar results were seen in a study by Ananthakrishnan *et al*<sup>[45]</sup> evaluating post-hospitalization VTE events, suggesting that anti-TNF $\alpha$  therapy is associated with a decreased risk of VTE. Although this has now been shown in several studies examining anti-TNF $\alpha$  medications, future studies

**Table 3** Disease activity and venous thromboembolism risk

Ref.	Findings	Statistics
Grainge <i>et al</i> <sup>[3]</sup>	IBD flares are associated with increased risk of developing VTE as compared to non-IBD matched controls	Hazard ratio 8.40 (95%CI: 5.50-12.80)
Hansen <i>et al</i> <sup>[29]</sup>	IBD flare during pregnancy is associated with increased risk of developing VTE as compared to non-IBD pregnant patients (also compared to IBD pregnant patients without a flare)	Unadjusted relative risk 2.64 (95%CI: 1.69-4.14)
Bollen <i>et al</i> <sup>[32]</sup>	A significant proportion of patients had active disease at the time of VTE diagnosis	60/84 (71%) patients with VTE had active disease

VTE: Venous thromboembolism; IBD: Inflammatory bowel disease.

evaluating newer biologics such as vedolizumab (anti-integrin) and ustekinumab (anti-interleukin) are needed.

In the last several years, a new class of medication, small molecule inhibitors, has been added to the IBD therapy armamentarium. Tofacitinib, a JAK 1&3 inhibitor, is a recently approved small molecule therapy that is being used for the treatment of moderate to severe UC. Recent safety data from the United States Food and Drug Administration (FDA) has suggested that doses of 10 mg twice daily may increase the risk of VTE<sup>[46]</sup>. This signal however, was seen in a study of rheumatoid arthritis patients over the age of 50 years-old with at least one additional cardiovascular risk factor. In a recent post-hoc analysis of UC patients treated with tofacitinib, 5 patients had a VTE as compared to 2 patients on placebo therapy<sup>[47]</sup>. When looking at incidence rates, a DVT was observed in 0.04 patients/100 patient-years whereas a PE was observed in 0.16 patients/100 patient-years. Of note, all patients who had a VTE on tofacitinib were also receiving 10mg twice daily, and had additional risk factors for VTE. Although safety data is currently limited at this time, all patients on tofacitinib should ideally be lowered to 5mg twice daily as able, and particular caution should be paid if using this medication in older patients with additional risk factors for VTE (Table 5).

### Surgery

VTE is a well-established postoperative complication in the general population<sup>[48]</sup>, with colorectal surgery presenting a particularly elevated risk<sup>[49]</sup>. In a Canadian randomized double blind trial, more than 9% of colorectal surgery patients had VTE events while receiving adequate thromboprophylaxis<sup>[50]</sup>. Within the IBD patient population, colorectal surgery confers additional VTE risk. In a nationwide cohort study by Kim *et al*<sup>[35]</sup>, IBD patients who required any surgery were at an increased risk of VTE, though patients who required IBD-related surgery had the highest risk of VTE (aHR: 40.81; 95%CI: 10.16-163.92). A study looking at surgical admissions within the United States also found that IBD patients undergoing disease-related surgery were at an increased risk for both in-hospital and post-discharge VTE events, even when compared to non-IBD patients undergoing surgery for active malignancy<sup>[51]</sup>. This was also demonstrated in a recent meta-analysis of 38 studies, which showed that IBD patients undergoing colorectal surgery were at a higher risk for postoperative VTE as compared to non-IBD patients undergoing surgery for colorectal cancer<sup>[52]</sup>. Although models incorporating IBD as a risk factor for post-operative VTE exist, recent studies have shown that these models still underestimate the risk in this patient population<sup>[53]</sup>.

Within IBD, patients with UC may be at higher risk for post-operative VTE as compared to those with CD. Examining the Swiss IBD patient population, Alatri *et al*<sup>[54]</sup> found that IBD-related surgery was an independent predictor of VTE within the UC patient population but not within CD patients. Several other studies have had analogous results, with a recent meta-analysis concluding that UC patients appear to be at higher post-operative VTE risk than CD patients<sup>[52]</sup>. When considering timing of post-operative VTE, a retrospective study looking at IBD patients undergoing elective abdominal surgery found that greatest risk was observed within the first two weeks of hospital discharge, with 61% of post-operative VTE events occurring within that time period<sup>[55]</sup>. Although data is sparse as to the benefit of post-discharge VTE prophylaxis, it is imperative that all IBD patients undergoing colorectal surgery be placed on prophylaxis throughout their hospital stay, particularly UC patients, who appear to be at highest risk of VTE<sup>[56]</sup>.

Table 4 Hospitalization and venous thromboembolism risk

Ref.	Findings	Statistics	
Grainge <i>et al</i> <sup>[3]</sup>	Hospitalized IBD patients (regardless of disease activity) have an increased risk of VTE	Hazard ratio 2.10 (95%CI: 1.40-3.20)	
	Absolute risk of VTE in IBD patients is higher during hospitalized periods than during ambulatory periods	Group	Absolute risk
		Hospitalized	25.2/1000 person-years
Nguyen <i>et al</i> <sup>[5]</sup>	Hospitalized IBD patients with VTE had greater mortality compared to those without VTE	Ambulatory	1.8/1000 person-years
		Odds ratio 2.50 (95%CI: 1.83-3.43)	
	Incidence of VTE in hospitalized IBD patients is increasing	Group	Percent rise in odds
		Hospitalized IBD	17% rise over 7 yr
Kim <i>et al</i> <sup>[35]</sup>	Hospitalized IBD patients without a disease flare had higher risk of VTE as compared to age- and sex-matched non-IBD patients	Hospitalized non-IBD	14% rise over 7 yr
		Hazard ratio 12.97 (95%CI: 8.68-19.39)	

VTE: Venous thromboembolism; IBD: Inflammatory bowel disease.

## VTE PREVENTION

Despite the increased risk of VTE among IBD patients, thromboprophylaxis rates among hospitalized IBD patients appear to be low. In a single-center study assessing all IBD-related VTE events, researchers found that only half of these patients received adequate prophylaxis<sup>[57]</sup>. Furthermore, based upon a survey of gastroenterologists, although 81% reported knowledge of a higher risk of VTE in IBD patients, only 35% selected that they would give pharmacologic VTE prophylaxis to a patient hospitalized with severe UC<sup>[58]</sup>. In accordance with this, Tinsley *et al*<sup>[59]</sup> found that in 2013 only 68% of patients hospitalized with active UC were prescribed VTE prophylaxis.

In order to elucidate risk factors associated with lack of VTE prophylaxis among hospitalized IBD patients, Faye *et al*<sup>[60]</sup> conducted a recent retrospective study examining this. Among 474 patients with IBD, those admitted to a medical service were significantly less likely to receive VTE prophylaxis as compared to those admitted to a surgical service. Similar results have been noted in prior studies, which may be attributable to differences in order sets between the services<sup>[59,61]</sup>.

Additionally, despite prior data noting the safety of VTE prophylaxis among IBD patients with rectal bleeding<sup>[62,63]</sup>, Faye *et al*<sup>[60]</sup> found that IBD patients with minor hematochezia (OR: 0.27; 95%CI: 0.16-0.46) were significantly less likely to receive VTE prophylaxis. This finding is of particular importance, as 95% of patients with hematochezia were experiencing a disease flare, and as discussed above, are at a significantly increased risk of VTE during this time. Additionally, when comparing transfusion differences and changes in hemoglobin among IBD patients with hematochezia who received VTE prophylaxis to those who did not receive VTE prophylaxis, no significant differences were seen<sup>[60]</sup>.

In order to limit the number of VTE events among hospitalized IBD patients, it is imperative that all providers be educated on the increased risk of VTE as well as the safety of pharmacologic prophylaxis. In a retrospective study examining all hospitalized patients at risk for VTE, prophylaxis use significantly reduced the likelihood of a VTE event (3.4% to 0.6%)<sup>[64]</sup>. Additionally, in a multicenter study of patients hospitalized with at least one IBD-related admission, the use of VTE prophylaxis was shown to lower the risk of post-hospitalization VTE (HR: 0.46; 95%CI: 0.22-0.97)<sup>[45]</sup>. The question remains though, in hospitalized IBD patients at high risk for VTE, is there a benefit in continuing VTE prophylaxis post-discharge?

## EXTENDED-DURATION VTE PROPHYLAXIS

From the oncology literature, there is evidence that extending VTE prophylaxis may reduce the future risk of VTE. In a study examining post-operative colorectal cancer patients, 4 wk of VTE prophylaxis as compared to 1 week reduced the 3-month

**Table 5 Medications and venous thromboembolism risk**

Medications	Risk of VTE
5-ASA	Possible ↓
Corticosteroids	↑↑↑
Azathioprine and 6-Mercaptopurine	Possible ↓
TNFα inhibitors	↓↓
Tofacitinib (10 mg twice a day)	↑

VTE: Venous thromboembolism.

incidence of VTE from 9.7% to 0.9%<sup>[65]</sup>. A recent decision analysis assessing the cost-benefit of outpatient VTE prophylaxis among all post-operative CD patients found uniform implementation not to be cost-effective<sup>[66]</sup>. More specifically, Leeds *et al*<sup>[66]</sup> found extended VTE prophylaxis to be cost-effective when post-discharge VTE rates exceeded 4.9%.

As a result, prediction models aimed at identifying IBD patients at highest risk for post-discharge VTE events are needed. In the recent study by McCurdy *et al*<sup>[24]</sup>, a risk score for IBD patients which includes characteristics such as age (> 45 years-of-age) and length of admission (> 7 d), was able to discriminate the subset of IBD patients who may benefit from post-discharge VTE prophylaxis. In this model, post-discharge VTE prophylaxis would only be given to those at highest risk, and from their results, would help avoid post-discharge VTE prophylaxis in 92% of hospitalized IBD patients. In another recent study examining predictors of post-discharge VTE among IBD patients, Faye *et al*<sup>[60]</sup> found that factors such as older age, discharge to a skilled nursing facility, and a history of *C. difficile* on initial admission increased this risk. Furthermore, they found that over 90% of VTE readmissions occurred within 60-d post-discharge, with the majority occurring in the first 20-d. In order to further assess the benefit of post-discharge prophylaxis, studies examining the cost-effectiveness of post-discharge prophylaxis among high risk IBD patients are needed. In addition to cost, benefits of continued prophylaxis need to be weighed against risk of bleeding and polypharmacy.

## CONCLUSION

VTE carries substantial morbidity and mortality, with even higher mortality rates reported in the IBD patient population. Although there is no genetic predisposition increasing the risk of VTE in IBD patients, studies have shown that the hypercoagulable nature of the disease likely stems from a complex interplay of the endothelium, platelets, and coagulation cascade.

Clinical factors that increase the likelihood of a VTE event among IBD patients include active and more extensive disease, surgery (particularly colorectal), hospitalization, pregnancy, and the use of corticosteroids or tofacitinib. Additionally, although younger age may be associated with a higher relative risk of VTE among IBD patients, older patients have a much higher incidence of VTE, and therefore more often present with a VTE. Although guidelines differ in their recommendations for patients hospitalized for non-IBD related reasons, all guidelines recommend VTE prophylaxis for IBD patients admitted with a disease-flare who do not have hemodynamically significant bleeding. Despite this, adherence to such guidelines remains low, as many IBD patients with minor hematochezia do not receive adequate VTE prophylaxis. In addition to in-hospital VTE prophylaxis, the risk-benefit of extending prophylaxis post-discharge in those at highest risk for VTE remains unknown. Future studies focusing upon IBD-specific risk assessment models are therefore needed to evaluate this. As the prevalence of IBD continues to rise, it is imperative that we continue to focus our efforts on VTE prevention in this vulnerable population.

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