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**Venous thromboembolism in inflammatory bowel disease**

Cheng K *et al*. Thrombosis in IBD

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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 tofacitinb, 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 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.

**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[1] and a global prevalence that surpasses 0.3%[2]. 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[3]. 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[4]. 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[5]. Within the United States, over 500000 hospitalizations and 100000 deaths have been attributed to VTE annually[6]. After an initial VTE event, long-term complications can include post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and recurrence of disease[7-9]. 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 [10,11]. 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[12]. 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[13]. 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[14]. 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[15,16]. Additionally, IBD patients have increased platelet counts (thrombocytosis) during active disease states, and have been found to have increased platelet activity[17]. In conjunction, studies have suggested that IBD patents have lower levels of protein S and antithrombin during active disease states, which are important drivers of anticoagulation[18].

**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[19]. Although the relative risk of a VTE event was almost four times higher in younger IBD patients as compared to older IBD patients (≥ 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)[19]. 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[20]. Furthermore, Nylund *et al*[20] 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[21]. As patients age however, the incidence of VTE increases[5]. In a retrospective review of Japanese inpatients with IBD, older age was one of the few risk factors noted for the development of VTE[22].Similarly, two recent studies found older age to be associated with the risk of developing a post-hospital discharge VTE[23,24] (Table 1). This is of particular importance given the rising prevalence of IBD, and the increasing proportion of patients ≥ 60 years-old with IBD[25].

***Pregnancy***

VTE is a leading cause of pregnancy-related maternal mortality in developed countries[26], with a 4 to 6-fold increase in relative risk of VTE in pregnant women as compared to non-pregnant women[27]. 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[28].

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[29]. 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[29].

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[30]. On subgroup analysis, VTE risk appeared higher in UC patients as compared to CD patients in both the pregnancy and postpartum period[30] (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[13,31]. Given that inherited thrombophilia is not more prevalent in the IBD patient population, guidelines such as the Canadian Association of Gastroenterology do not recommend genetic screening, unless the VTE is unprovoked (*ie*, clinical remission, no other risk factors)[21].

***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*[3], 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[29]. 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[32] (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*[33] 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[34].

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*[3], 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*[5], 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[35] (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[21].

***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[36]. Immunomodulators such as azathioprine and 6-meraptopurine have also been shown to reduce *in vitro* platelet aggregation[37]. 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*[38], 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[39]. 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[40]. This is of particular concern as older IBD patients, who have the highest incidence of VTE events, are often placed on corticosteroids[41].

In contrast, immunosuppressive medications such as anti-TNFα biologics are thought to decrease the risk of VTE. In 2011, Yoshida *et al*[42] found that within colitis-induced mouse models, TNFα was intimately involved in the hypercoagulable state. This has since led to the theory that inhibiting TNFα may decrease the risk of VTE within the IBD patient population. In one single-center retrospective review, use of anti-TNFα 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[43]. Using a nationwide United States insurance database, Higgins *et al*[44] 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*[45] evaluating post-hospitalization VTE events, suggesting that anti-TNFα therapy is associated with a decreased risk of VTE. Although this has now been shown in several studies examining anti-TNFα medications, future studies 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[46].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[47]. 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[48], with colorectal surgery presenting a particularly elevated risk[49]. In a Canadian randomized double blind trial, more than 9% of colorectal surgery patients had VTE events while receiving adequate thromboprophylaxis[50]. Within the IBD patient population, colorectal surgery confers additional VTE risk. In a nationwide cohort study by Kim *et al*[35], 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[51]. 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[52]. 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[53].

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*[54] 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[52]. 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[55]. 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[56].

**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[57]. 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[58]. In accordance with this, Tinsley *et al*[59] 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*[60] 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[59,61]**.**

Additionally, despite prior data noting the safety of VTE prophylaxis among IBD patients with rectal bleeding[62,63], Faye *et al*[60] 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[60].

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%)[64]. 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)[45]. 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 incidence of VTE from 9.7% to 0.9%[65]. 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[66]. More specifically, Leeds *et al*[66] 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*[24], 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*[60] 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.

**REFERENCES**

1 **Dahlhamer JM**, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of Inflammatory Bowel Disease Among Adults Aged ≥18 Years - United States, 2015. *MMWR Morb Mortal Wkly Rep* 2016; **65**: 1166-1169 [PMID: 27787492 DOI: 10.15585/mmwr.mm6542a3]

2 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]

3 **Grainge MJ**, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010; **375**: 657-663 [PMID: 20149425 DOI: 10.1016/S0140-6736(09)61963-2]

4 **Miehsler W**, Reinisch W, Valic E, Osterode W, Tillinger W, Feichtenschlager T, Grisar J, Machold K, Scholz S, Vogelsang H, Novacek G. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 2004; **53**: 542-548 [PMID: 15016749 DOI: 10.1136/gut.2003.025411]

5 **Nguyen GC**, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008; **103**: 2272-2280 [PMID: 18684186 DOI: 10.1111/j.1572-0241.2008.02052.x]

6 **Centers for Disease Control and Prevention (CDC).** Venous thromboembolism in adult hospitalizations - United States, 2007-2009. *MMWR Morb Mortal Wkly Rep* 2012; **61**: 401-404 [PMID: 22672974]

7 **Piran S**, Schulman S. Management of venous thromboembolism: an update. *Thromb J* 2016; **14**: 23 [PMID: 27766049 DOI: 10.1186/s12959-016-0107-z]

8 **Fernandez MM**, Hogue S, Preblick R, Kwong WJ. Review of the cost of venous thromboembolism. *Clinicoecon Outcomes Res* 2015; **7**: 451-462 [PMID: 26355805 DOI: 10.2147/CEOR.S85635]

9 **Kyrle PA**, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. *Lancet* 2010; **376**: 2032-2039 [PMID: 21131039 DOI: 10.1016/S0140-6736(10)60962-2]

10 **Grosse SD**. Incidence-based cost estimates require population-based incidence data. A critique of Mahan et al. *Thromb Haemost* 2012; **107**: 192-3; author reply 194-5 [PMID: 22159589 DOI: 10.1160/TH11-09-0666]

11 **Stone J**, Hangge P, Albadawi H, Wallace A, Shamoun F, Knuttien MG, Naidu S, Oklu R. Deep vein thrombosis: pathogenesis, diagnosis, and medical management. *Cardiovasc Diagn Ther* 2017; **7**: S276-S284 [PMID: 29399531 DOI: 10.21037/cdt.2017.09.01]

12 **Danese S**, Sans M, Fiocchi C. Inflammatory bowel disease: the role of environmental factors. *Autoimmun Rev* 2004; **3**: 394-400 [PMID: 15288007 DOI: 10.1016/j.autrev.2004.03.002]

13 **Giannotta M**, Tapete G, Emmi G, Silvestri E, Milla M. Thrombosis in inflammatory bowel diseases: what's the link? *Thromb J* 2015; **13**: 14 [PMID: 25866483 DOI: 10.1186/s12959-015-0044-2]

14 **Papa A**, Gerardi V, Marzo M, Felice C, Rapaccini GL, Gasbarrini A. Venous thromboembolism in patients with inflammatory bowel disease: focus on prevention and treatment. *World J Gastroenterol* 2014; **20**: 3173-3179 [PMID: 24695669 DOI: 10.3748/wjg.v20.i12.3173]

15 **Kume K**, Yamasaki M, Tashiro M, Yoshikawa I, Otsuki M. Activations of coagulation and fibrinolysis secondary to bowel inflammation in patients with ulcerative colitis. *Intern Med* 2007; **46**: 1323-1329 [PMID: 17827828 DOI: 10.2169/internalmedicine.46.0237]

16 **Alkim H**, Ayaz S, Alkim C, Ulker A, Sahin B. Continuous active state of coagulation system in patients with nonthrombotic inflammatory bowel disease. *Clin Appl Thromb Hemost* 2011; **17**: 600-604 [PMID: 21593018 DOI: 10.1177/1076029611405034]

17 **Collins CE**, Cahill MR, Newland AC, Rampton DS. Platelets circulate in an activated state in inflammatory bowel disease. *Gastroenterology* 1994; **106**: 840-845 [PMID: 8143990 DOI: 10.1016/0016-5085(94)90741-2]

18 **Zezos P**, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. *World J Gastroenterol* 2014; **20**: 13863-13878 [PMID: 25320522 DOI: 10.3748/wjg.v20.i38.13863]

19 **Kappelman MD**, Horvath-Puho E, Sandler RS, Rubin DT, Ullman TA, Pedersen L, Baron JA, Sørensen HT. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. *Gut* 2011; **60**: 937-943 [PMID: 21339206 DOI: 10.1136/gut.2010.228585]

20 **Nylund CM**, Goudie A, Garza JM, Crouch G, Denson LA. Venous thrombotic events in hospitalized children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2013; **56**: 485-491 [PMID: 23232326 DOI: 10.1097/MPG.0b013e3182801e43]

21 **Nguyen GC**, Bernstein CN, Bitton A, Chan AK, Griffiths AM, Leontiadis GI, Geerts W, Bressler B, Butzner JD, Carrier M, Chande N, Marshall JK, Williams C, Kearon C. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology* 2014; **146**: 835-848.e6 [PMID: 24462530 DOI: 10.1053/j.gastro.2014.01.042]

22 **Ando K**, Fujiya M, Nomura Y, Inaba Y, Sugiyama Y, Iwama T, Ijiri M, Takahashi K, Tanaka K, Sakatani A, Ueno N, Kashima S, Moriichi K, Mizukami Y, Okumura T. The incidence and risk factors of venous thromboembolism in Japanese inpatients with inflammatory bowel disease: a retrospective cohort study. *Intest Res* 2018; **16**: 416-425 [PMID: 30090041 DOI: 10.5217/ir.2018.16.3.416]

23 **Faye AS**, Wen T, Ananthakrishnan AN, Lichtiger S, Kaplan GG, Friedman AM, Lawlor G, Wright JD, Attenello FJ, Mack WJ, Lebwohl B. Acute Venous Thromboembolism Risk Highest Within 60 Days After Discharge From the Hospital in Patients With Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol* 2019 [PMID: 31336196 DOI: 10.1016/j.cgh.2019.07.028]

24 **McCurdy JD**, Israel A, Hasan M, Weng R, Mallick R, Ramsay T, Carrier M. A clinical predictive model for post-hospitalisation venous thromboembolism in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2019; **49**: 1493-1501 [PMID: 31066471 DOI: 10.1111/apt.15286]

25 **Jeuring SF**, van den Heuvel TR, Zeegers MP, Hameeteman WH, Romberg-Camps MJ, Oostenbrug LE, Masclee AA, Jonkers DM, Pierik MJ. Epidemiology and Long-term Outcome of Inflammatory Bowel Disease Diagnosed at Elderly Age-An Increasing Distinct Entity? *Inflamm Bowel Dis* 2016; **22**: 1425-1434 [PMID: 26933752 DOI: 10.1097/MIB.0000000000000738]

26 **Creanga AA**, Syverson C, Seed K, Callaghan WM. Pregnancy-Related Mortality in the United States, 2011-2013. *Obstet Gynecol* 2017; **130**: 366-373 [PMID: 28697109 DOI: 10.1097/AOG.0000000000002114]

27 **Heit JA**, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005; **143**: 697-706 [PMID: 16287790 DOI: 10.7326/0003-4819-143-10-200511150-00006]

28 **Jackson E**, Curtis KM, Gaffield ME. Risk of venous thromboembolism during the postpartum period: a systematic review. *Obstet Gynecol* 2011; **117**: 691-703 [PMID: 21343773 DOI: 10.1097/AOG.0b013e31820ce2db]

29 **Hansen AT**, Erichsen R, Horváth-Puhó E, Sørensen HT. Inflammatory bowel disease and venous thromboembolism during pregnancy and the postpartum period. *J Thromb Haemost* 2017; **15**: 702-708 [PMID: 28135041 DOI: 10.1111/jth.13638]

30 **Kim YH**, Pfaller B, Marson A, Yim HW, Huang V, Ito S. The risk of venous thromboembolism in women with inflammatory bowel disease during pregnancy and the postpartum period: A systematic review and meta-analysis. *Medicine (Baltimore)* 2019; **98**: e17309 [PMID: 31568016 DOI: 10.1097/MD.0000000000017309]

31 **Papa A**, Danese S, Grillo A, Gasbarrini G, Gasbarrini A. Review article: inherited thrombophilia in inflammatory bowel disease. *Am J Gastroenterol* 2003; **98**: 1247-1251 [PMID: 12818264 DOI: 10.1111/j.1572-0241.2003.07491.x]

32 **Bollen L**, Vande Casteele N, Ballet V, van Assche G, Ferrante M, Vermeire S, Gils A. Thromboembolism as an important complication of inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2016; **28**: 1-7 [PMID: 26513610 DOI: 10.1097/MEG.0000000000000495]

33 **Solem CA**, Loftus EV, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. *Am J Gastroenterol* 2004; **99**: 97-101 [PMID: 14687149 DOI: 10.1046/j.1572-0241.2003.04026.x]

34 **Weng MT**, Park SH, Matsuoka K, Tung CC, Lee JY, Chang CH, Yang SK, Watanabe M, Wong JM, Wei SC. Incidence and Risk Factor Analysis of Thromboembolic Events in East Asian Patients With Inflammatory Bowel Disease, a Multinational Collaborative Study. *Inflamm Bowel Dis* 2018; **24**: 1791-1800 [PMID: 29726897 DOI: 10.1093/ibd/izy058]

35 **Kim TJ,** Kong SM, Shin JB, Kim ER, Hong SN, Chang DK, Kim YH. Risk of venous thromboembolism according to disease activity, hospitalization, or surgery in inflammatory bowel disease: a nationwide cohort study. Journal of Crohn's and Colitis. 2019; 12: S189-S190 [DOI: 10.1093/ecco-jcc/jjy222.320]

36 **Carty E**, MacEy M, Rampton DS. Inhibition of platelet activation by 5-aminosalicylic acid in inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; **14**: 1169-1179 [PMID: 10971234 DOI: 10.1046/j.1365-2036.2000.00824.x]

37 **Thomas G**, Skrinska VA, Lucas FV. The influence of glutathione and other thiols on human platelet aggregation. *Thromb Res* 1986; **44**: 859-866 [PMID: 3099423 DOI: 10.1016/0049-3848(86)90031-9]

38 **Sarlos P**, Szemes K, Hegyi P, Garami A, Szabo I, Illes A, Solymar M, Petervari E, Vincze A, Par G, Bajor J, Czimmer J, Huszar O, Varju P, Farkas N. Steroid but not Biological Therapy Elevates the risk of Venous Thromboembolic Events in Inflammatory Bowel Disease: A Meta-Analysis. *J Crohns Colitis* 2018; **12**: 489-498 [PMID: 29220427 DOI: 10.1093/ecco-jcc/jjx162]

39 **Johannesdottir SA**, Horváth-Puhó E, Dekkers OM, Cannegieter SC, Jørgensen JO, Ehrenstein V, Vandenbroucke JP, Pedersen L, Sørensen HT. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA Intern Med* 2013; **173**: 743-752 [PMID: 23546607 DOI: 10.1001/jamainternmed.2013.122]

40 **van der Pas R**, Leebeek FW, Hofland LJ, de Herder WW, Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. *Clin Endocrinol (Oxf)* 2013; **78**: 481-488 [PMID: 23134530 DOI: 10.1111/cen.12094]

41 **Ananthakrishnan AN**, Donaldson T, Lasch K, Yajnik V. Management of Inflammatory Bowel Disease in the Elderly Patient: Challenges and Opportunities. *Inflamm Bowel Dis* 2017; **23**: 882-893 [PMID: 28375885 DOI: 10.1097/MIB.0000000000001099]

42 **Yoshida H**, Yilmaz CE, Granger DN. Role of tumor necrosis factor-α in the extraintestinal thrombosis associated with colonic inflammation. *Inflamm Bowel Dis* 2011; **17**: 2217-2223 [PMID: 21987296 DOI: 10.1002/ibd.21593]

43 **deFonseka AM**, Tuskey A, Conaway MR, Behm BW. Antitumor Necrosis Factor-α Therapy Is Associated With Reduced Risk of Thromboembolic Events in Hospitalized Patients With Inflammatory Bowel Disease. *J Clin Gastroenterol* 2016; **50**: 578-583 [PMID: 26368297 DOI: 10.1097/MCG.0000000000000408]

44 **Higgins PD**, Skup M, Mulani PM, Lin J, Chao J. Increased risk of venous thromboembolic events with corticosteroid vs biologic therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2015; **13**: 316-321 [PMID: 25038374 DOI: 10.1016/j.cgh.2014.07.017]

45 **Ananthakrishnan AN**, Cagan A, Gainer VS, Cheng SC, Cai T, Scoville E, Konijeti GG, Szolovits P, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP. Thromboprophylaxis is associated with reduced post-hospitalization venous thromboembolic events in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2014; **12**: 1905-1910 [PMID: 24632349 DOI: 10.1016/j.cgh.2014.02.034]

46 **Communication,** F.D.S., FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR); FDA Drug Safety Communication; 2019. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-app

47 **Sandborn WJ**, Panés J, Sands BE, Reinisch W, Su C, Lawendy N, Koram N, Fan H, Jones TV, Modesto I, Quirk D, Danese S. Venous thromboembolic events in the tofacitinib ulcerative colitis clinical development programme. *Aliment Pharmacol Ther* 2019; **50**: 1068-1076 [PMID: 31599001 DOI: 10.1111/apt.15514]

48 **Heit JA**. Venous thromboembolism: disease burden, outcomes and risk factors. *J Thromb Haemost* 2005; **3**: 1611-1617 [PMID: 16102026 DOI: 10.1111/j.1538-7836.2005.01415.x]

49 **Fleming F**, Gaertner W, Ternent CA, Finlayson E, Herzig D, Paquette IM, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guideline for the Prevention of Venous Thromboembolic Disease in Colorectal Surgery. *Dis Colon Rectum* 2018; **61**: 14-20 [PMID: 29219916 DOI: 10.1097/DCR.0000000000000982]

50 **McLeod RS**, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, Silverman RE, Atkinson KG, Burnstein M, Marshall JC, Burul CJ, Anderson DR, Ross T, Wilson SR, Barton P; Canadian Colorectal Surgery DVT Prophylaxis Trial investigators. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. *Ann Surg* 2001; **233**: 438-444 [PMID: 11224634 DOI: 10.1097/00000658-200103000-00020]

51 **Alhassan N**, Trepanier M, Sabapathy C, Chaudhury P, Liberman AS, Charlebois P, Stein BL, Lee L. Risk factors for post-discharge venous thromboembolism in patients undergoing colorectal resection: a NSQIP analysis. *Tech Coloproctol* 2018; **22**: 955-964 [PMID: 30569263 DOI: 10.1007/s10151-018-1909-8]

52 **McKechnie T**, Wang J, Springer JE, Gross PL, Forbes S, Eskicioglu C. Extended thromboprophylaxis following colorectal surgery in patients with inflammatory bowel disease: a comprehensive systematic clinical review. *Colorectal Dis* 2019 [PMID: 31490000 DOI: 10.1111/codi.14853]

53 **Ohta Y**, Arai M, Nakagawa T, Akizue N, Ishikawa K, Hamanaka S, Koseki H, Taida T, Okimoto K, Saito K, Yoshihama S, Maruoka D, Matsumura T, Katsuno T, Kato N. Comparison of a novel predictor of venous thromboembolic complications in inflammatory bowel disease with current predictors. *J Gastroenterol Hepatol* 2019; **34**: 870-879 [PMID: 30225931 DOI: 10.1111/jgh.14472]

54 **Alatri A**, Schoepfer A, Fournier N, Engelberger RP, Safroneeva E, Vavricka S, Biedermann L, Calanca L, Mazzolai L; Swiss IBD Cohort Study Group. Prevalence and risk factors for venous thromboembolic complications in the Swiss Inflammatory Bowel Disease Cohort. *Scand J Gastroenterol* 2016; **51**: 1200-1205 [PMID: 27211077 DOI: 10.1080/00365521.2016.1185464]

55 **Benlice C**, Holubar SD, Gorgun E, Stocchi L, Lipman JM, Kalady MF, Champagne BJ, Steele SR. Extended Venous Thromboembolism Prophylaxis After Elective Surgery for IBD Patients: Nomogram-Based Risk Assessment and Prediction from Nationwide Cohort. *Dis Colon Rectum* 2018; **61**: 1170-1179 [PMID: 30192325 DOI: 10.1097/DCR.0000000000001189]

56 **Kaplan GG**, Lim A, Seow CH, Moran GW, Ghosh S, Leung Y, Debruyn J, Nguyen GC, Hubbard J, Panaccione R. Colectomy is a risk factor for venous thromboembolism in ulcerative colitis. *World J Gastroenterol* 2015; **21**: 1251-1260 [PMID: 25632199 DOI: 10.3748/wjg.v21.i4.1251]

57 **Dwyer JP**, Javed A, Hair CS, Moore GT. Venous thromboembolism and underutilisation of anticoagulant thromboprophylaxis in hospitalised patients with inflammatory bowel disease. *Intern Med J* 2014; **44**: 779-784 [PMID: 24893756 DOI: 10.1111/imj.12488]

58 **Tinsley A**, Naymagon S, Trindade AJ, Sachar DB, Sands BE, Ullman TA. A survey of current practice of venous thromboembolism prophylaxis in hospitalized inflammatory bowel disease patients in the United States. *J Clin Gastroenterol* 2013; **47**: e1-e6 [PMID: 22476043 DOI: 10.1097/MCG.0b013e31824c0dea]

59 **Tinsley A**, Naymagon S, Enomoto LM, Hollenbeak CS, Sands BE, Ullman TA. Rates of pharmacologic venous thromboembolism prophylaxis in hospitalized patients with active ulcerative colitis: results from a tertiary care center. *J Crohns Colitis* 2013; **7**: e635-e640 [PMID: 23706933 DOI: 10.1016/j.crohns.2013.05.002]

60 **Faye AS**, Hung KW, Cheng K, Blackett JW, Mckenney AS, Pont AR, Li J, Lawlor G, Lebwohl B, Freedberg DE. Minor Hematochezia Decreases Use of Venous Thromboembolism Prophylaxis in Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2019 [PMID: 31689354 DOI: 10.1093/ibd/izz269]

61 **Lewin SM**, McConnell RA, Patel R, Sharpton SR, Velayos F, Mahadevan U. Improving the Quality of Inpatient Ulcerative Colitis Management: Promoting Evidence-Based Practice and Reducing Care Variation With an Inpatient Protocol. *Inflamm Bowel Dis* 2019; **25**: 1822-1827 [PMID: 30980712 DOI: 10.1093/ibd/izz066]

62 **Ra G**, Thanabalan R, Ratneswaran S, Nguyen GC. Predictors and safety of venous thromboembolism prophylaxis among hospitalized inflammatory bowel disease patients. *J Crohns Colitis* 2013; **7**: e479-e485 [PMID: 23537817 DOI: 10.1016/j.crohns.2013.03.002]

63 **Shen J**, Ran ZH, Tong JL, Xiao SD. Meta-analysis: The utility and safety of heparin in the treatment of active ulcerative colitis. *Aliment Pharmacol Ther* 2007; **26**: 653-663 [PMID: 17697199 DOI: 10.1111/j.1365-2036.2007.03418.x]

64 **Baser O**, Sengupta N, Dysinger A, Wang L. Thromboembolism prophylaxis in medical inpatients: effect on outcomes and costs. *Am J Manag Care* 2012; **18**: 294-302 [PMID: 22774997]

65 **Vedovati MC**, Becattini C, Rondelli F, Boncompagni M, Camporese G, Balzarotti R, Mariani E, Flamini O, Pucciarelli S, Donini A, Agnelli G. A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Ann Surg* 2014; **259**: 665-669 [PMID: 24253138 DOI: 10.1097/SLA.0000000000000340]

66 **Leeds IL**, DiBrito SR, Canner JK, Haut ER, Safar B. Cost-Benefit Limitations of Extended, Outpatient Venous Thromboembolism Prophylaxis Following Surgery for Crohn's Disease. *Dis Colon Rectum* 2019; **62**: 1371-1380 [PMID: 31596763 DOI: 10.1097/DCR.0000000000001461]

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**Table 1 Age and venous thromboembolism risk**

|  |  |  |
| --- | --- | --- |
| **Ref.** | **Findings** | **Statistics** |
| Kappelman *et al*[19] | 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 DVTHazard 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 | Incidence  |
| ≤ 20 yr | 8.9/10000 persons-years |
| > 60 yr | 54.6/10000 persons-years |
| Nylund *et al*[20]  | 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 *et al*[22] | IBD patients > 50 have an increased odds of developing VTE | Odds ratio 3.52 (95%CI: 1.25-9.94) |
| Nguyen *et al*[5] | Each incremental decade in age was associated with increased odds of developing VTE | Odds ratio 1.20 (95%CI: 1.15-1.25) |
| Faye *et al*[23] | Age > 30 had an increased risk of VTE readmission compared with patients younger than 18 years of age | Age (yr) | Relative risk |
| 31-40 | 2.10 (95%CI: 1.29-3.42) |
| 41-50 | 2.08 (95%CI: 1.28-3.37) |
| 51-65 | 3.74 (95%CI: 2.35-5.94) |
| 66-80 | 4.04 (95%CI: 2.54-6.44) |
| > 80 | 3.06 (95%CI: 1.87-5.02) |
| McCurdy *et al*[24] | 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.

**Table 2 Pregnancy and venous thromboembolism risk**

|  |  |  |
| --- | --- | --- |
| **Ref.** | **Findings** | **Statistics** |
| Hansen *et al*[29] | 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) |
| Postpartum IBD | 7.03 (95%CI: 3.87-10.20) |
| Kim *et al*[30] | 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 *vs* CD patients | 2.24 (95%CI: 1.60-3.11) |
| Postpartum UC *vs* CD patients  | 2.85 (95%CI: 1.79-4.52)  |

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

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

|  |  |  |
| --- | --- | --- |
| **Ref.** | **Findings** | **Statistics** |
| Grainge *et al*[3] | 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 *et al*[29] | 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 *et al*[32] | 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.

**Table 4 Hospitalization and venous thromboembolism risk**

|  |  |  |
| --- | --- | --- |
| **Ref.** | **Findings** | **Statistics** |
| Grainge *et al*[3] | 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 |
| Ambulatory  | 1.8/1000 person-years |
| Nguyen *et al*[5] | Hospitalized IBD patients with VTE had greater mortality compared to those without VTE | 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 |
| Hospitalized non-IBD | 14% rise over 7 yr |
| Kim *et al*[35] | Hospitalized IBD patients without a disease flare had higher risk of VTE as compared to age- and sex-matched non-IBD patients | Hazard ratio 12.97 (95%CI: 8.68-19.39) |

VTE: Venous thromboembolism; IBD: Inflammatory bowel disease.

**Table 5 Medications and venous thromboembolism risk**

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

VTE: Venous thromboembolism.