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Prevention of Venous Thromboembolism in Patients with Inflammatory Bowel Disease

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Key Takeaways:

- When reviewing inflammatory bowel disease (IBD) patients in the clinical setting, remember to review their medical history and screen for venous thromboembolism (VTE) risk factors. This will help to risk stratify them for future decision-making.
- IBD patients admitted to hospital are at the highest risk of VTE. All IBD patients, regardless of reason for admission and disease activity, should receive VTE prophylaxis.
- In the post-operative and post-discharge setting, all IBD patients should be classified as low, intermediate, or high risk of VTE. After carefully weighing the risks and benefits, high risk patients should be considered for extended VTE prophylaxis beyond hospital discharge.

Introduction

Venous thromboembolism (VTE) is a major cause of morbidity and mortality worldwide and remains a preventable cause of death among hospitalized patients.¹ Given its potential devastating health consequences, VTE is one of the most important intestinal manifestations to monitor and prevent in patients with Inflammatory Bowel Disease (IBD). IBD patients are at an increased risk for VTE due to their underlying inflammatory state, which contributes to aberrant

platelet and procoagulant alterations, dysregulated fibrinolysis, and endothelial dysfunction.² In addition to this hypercoagulable state, the risk of VTE in IBD patients is often compounded by other co-existing risk factors such as hospitalization or surgery.³

At baseline, IBD patients have an up to 3-fold increased risk of VTE compared to those without IBD. This risk climbs even higher during hospitalization, reaching a 6-fold increase.^{4,5} The elevated risk of VTE persists after hospitalization, with population-based studies showing VTE rates

as high as 3% within 6 months after discharge.^{6,7} Although the incidence is highest during hospitalization, the relative risk of VTE during an ambulatory flare is almost 16-fold greater than that of the general population.⁴

Identifying high-risk patients and providing prophylaxis in the appropriate clinical settings is critical for preventing thrombosis in this susceptible patient group. In this article, I will review the current evidence and recommendations, as well as highlight existing knowledge gaps related to VTE prophylaxis in IBD patients.

What Do the Guidelines and Current Evidence Recommend?

The Toronto and International Consensus guidelines acknowledge the significantly elevated risk of VTE in IBD patients, particularly during periods of active disease and hospitalization.^{8,9} Although the highest risk groups are those hospitalized with active disease flares, even patients in clinical remission who are hospitalized for unrelated reasons carry an up to 3-fold risk of VTE compared to non-IBD patients.⁵ For this reason, both sets of guidelines have clear recommendations for thromboprophylaxis for hospitalized patients, irrespective of the reason for admission. These recommendations are in line with the most recent guidelines from the American College of Chest Physicians and the American Society of Hematology (ASH) on the prevention and prophylaxis of VTE in medical patients.^{10,11}

Previous studies have demonstrated that chemical prophylaxis with anticoagulants is safe for IBD patients without a significant increased risk of bleeding, even among those presenting with rectal bleeding on admission.¹² Apart from clinical situations with severe IBD-related gastrointestinal bleeding, chemical prophylaxis remains the recommended primary treatment. In cases of severe bleeding, mechanical prophylaxis with intermittent pneumatic compression should be used instead until the bleeding is no longer severe.⁸

Although VTE risk is highest during hospital admission, it does not immediately return to baseline upon discharge from hospital. However, considering the diminished risk after hospitalization, there are no guideline recommendations supporting universal extended prophylaxis for all patients. Instead, the International Consensus Guidelines recommend

considering extended prophylaxis for those with a “very high risk of VTE”.⁹ Similarly, the American Society of Colon and Rectal Surgeons recommends considering extended prophylaxis in the postoperative setting for IBD patients deemed to be at high risk.¹³ A retrospective study by McCurdy et al. developed a risk prediction model to identify patients with IBD at increased risk for post discharge VTE.⁶ This model enabled the authors to better identify patients at high risk of VTE who might benefit from anticoagulation. However, further external validation of this model is required before universal use. Based on available evidence, no guideline recommendations have clearly outlined which specific risk factors should be considered, or how many must be present before initiation of extended prophylaxis is warranted. Physicians caring for IBD patients must use clinical gestalt and shared decision making when considering the need for extended prophylaxis on a case-by-case basis.

Consensus guidelines do not routinely recommend prophylactic anticoagulation for patients with IBD flares undergoing treatment in the outpatient setting. Although the relative risk of VTE during an outpatient flare can be up to 16-fold higher compared to the general public, the absolute risk remains too low to recommend prophylaxis in the absence of other risk factors.^{8,9} In addition, a previous Markov decision analysis found that this intervention is not cost effective.¹⁴ However, certain cases may warrant prophylaxis in the ambulatory setting. Considering that the risk of recurrent VTE in IBD patients is 2.5-fold higher compared with non-IBD patients, the Toronto Consensus recommends thromboprophylaxis to prevent recurrent VTE during moderate-to-severe ambulatory disease flares.⁸ Patients omitted from this recommendation include those whose initial episode of VTE was provoked by surgery, as these patients are considered to have a lower risk of recurrence.¹⁵ In contrast, the International Consensus Guidelines recommend considering prophylaxis in ambulatory patients who have known major or multiple risk factors, not just those with a previous VTE history.⁹ Given inflammation is a key driver of VTE risk in these cases, prophylaxis, if initiated, should be continued until remission is achieved. As with post discharge management, the decision to initiate VTE prophylaxis in the outpatient setting should be at the discretion of the treating physician on a case-by-case basis after an assessment of the patient’s individualized risk.

Where Do Our Guidelines Fall Short?

Evidence and guideline recommendations are clear on the benefits of inpatient VTE prophylaxis and recommend its use for most patient populations. However, the role of extended and ambulatory VTE prophylaxis, is less clearly defined. Although current guidelines recommend consideration of prophylaxis for high-risk patients in these settings, there is a paucity of high-quality evidence to guide clinicians in identifying which patients are most likely to benefit. Key questions remain unanswered, such as which risk factors are most relevant, how many are needed to justify intervention, and what clinical decision tools should be used? Further evidence and guidance is needed to aid in identifying which patients are most likely to benefit from VTE prophylaxis.

How Do We Identify the High-risk Patients?

The challenge in implementing extended prophylaxis is identifying the patient group most likely to benefit. A review of this topic by Murthy et al. proposed an algorithm in which patients are classified into low (<1%), intermediate (1–5%) or high risk (>5%) categories, which recommended extended prophylaxis for the high-risk patient group.⁷ This appears to be a reasonable approach, particularly considering a previous study had identified that extended prophylaxis with enoxaparin is cost effective when the risk of VTE exceeds 4.9%.¹⁶ Although several clinical predictive models, such as Padua, IMPROVE, and Caprini are available to help identify high-risk patients, these tools were developed for the general population and are not specific to IBD patients.^{17–19} A recent systematic review characterized IBD risk factors across multiple phases of care.³ While many of the risk factors identified, such as a previous history of VTE and age, are well-established in the general population, the review also identified significant IBD-specific risk factors, such as corticosteroid exposure, *Clostridioides difficile* infection, malnutrition, and inflammatory disease extent. Of note, IBD-related medications were an important group of factors reviewed in the study. Corticosteroids were associated with increased VTE risk, although this is difficult to interpret considering these medications are typically used during active disease flares.

Considering that active disease is a known independent risk factor for VTE, this association may simply be a surrogate marker for active disease. Importantly, other IBD therapies, including biologics, Janus kinase (JAK) inhibitors, 5-ASA, and immunomodulators, were not associated with an increased risk of VTE. In fact, anti-tumour necrosis factor (TNF) biologics were found to be protective against VTE with an odds ratio of 0.66 (95% confidence interval 0.46–0.97), which is consistent with previous studies and animal models suggesting that anti-TNF therapy may directly reduce VTE risk.^{20,21} Notably, JAK inhibitor therapy was not associated with an increased risk of VTE in this systematic review, despite a potential risk identified in rheumatoid arthritis patients that resulted in an FDA warning.²² The review examined multiple risk factor categories, including medical comorbidities, IBD characteristics, and surgical characteristics, among others. Many of these risk factors are specific to IBD, and can serve to guide future prospective studies and the development of IBD-specific clinical predictive models. Once developed and validated, these models can better inform clinicians when considering VTE prophylaxis.

How Can We Make VTE Prophylaxis Cost Effective?

To expand the use of VTE prophylaxis among IBD patient groups, it needs to demonstrate effectiveness in preventing VTE, maintain a favourable safety profile, and be cost effective. A 2019 Canadian study showed that a 28-day course of extended prophylaxis with enoxaparin, while associated with higher costs, improved quality-adjusted life-years along with incremental cost-effectiveness ratios in IBD patients undergoing colorectal surgery.²³ However, two additional cost-benefit decision analyses in IBD patients undergoing surgery found that extended prophylaxis was not a cost-effective intervention.^{24,25} As discussed earlier, a previous decision analysis assessing the cost-effectiveness of VTE prophylaxis in ambulatory patients also concluded that it was not a cost-effective strategy.¹⁴

Several therapeutic options for anticoagulation prophylaxis exist, each with widely variable costs. Historically, studies on the cost-effectiveness of VTE prophylaxis in IBD

patients have largely investigated low molecular weight heparin (LMWH). However, alternative agents such as direct oral anticoagulants (DOACs) offer effective VTE prevention and treatment at significantly lower costs compared to LMWH. In the orthopedic literature, DOACs have been shown to be effective in preventing VTE after surgery,²⁶ and have been incorporated into Thrombosis Canada guidelines for extended prophylaxis.²⁷ Regarding non-orthopedic surgery, a 2022 study showed that oral rivaroxaban was more effective than placebo for extended VTE prophylaxis after laparoscopic surgery for colorectal cancer without an increase in major bleeding.²⁸ Finally, the ASH guidelines on VTE prevention in hospitalized surgical patients suggests using extended prophylaxis over short-term prophylaxis, citing a likely modest benefit in reducing VTE with comparable bleeding rates.²⁹ Importantly, the guidelines recognized that the evidence was limited to orthopedic and major oncologic surgeries.

In medical patients, there is currently no confirmed benefit to using DOACs for extended VTE prophylaxis after hospital discharge.^{30,31} It is important to note that IBD patients are underrepresented in these studies, despite their inflammatory burden that places them at a greater risk for VTE compared to the general medical population. As such, more evidence is needed before these therapies can be recommended for routine use in IBD patients. However, if DOACs are shown to be effective for VTE prevention in carefully selected high-risk patient groups, they could offer a more cost-effective intervention compared to LMWH.

Conclusion

While the evidence and guidelines on inpatient VTE prophylaxis is clear, this does not always translate into clinical practice. Despite clear recommendations, adherence rates for VTE prophylaxis is suboptimal, with some studies reporting prophylaxis rates as low as 39.7% among hospitalized patients.³² Physicians who care for patients with IBD should be aware of the benefits and safety of VTE prophylaxis for hospitalized patients.

To expand the use of extended VTE prophylaxis in IBD populations, it is essential to identify those who may benefit from targeted prophylaxis. This requires further research to stratify patients by risk and guide targeted prophylaxis. As our knowledge of IBD risk factors continues to grow, prospective studies will be needed for creating and validating clinical predictive models that can accurately and reliably identify these high-risk patients. To optimize the cost-benefit of extended and ambulatory prophylaxis interventions, future studies could investigate the use of low dose DOACs, particularly in the post surgical setting where evidence already exists for some patient populations. For now, clinicians will need to consider the known risk factors identified in the literature and assess patients on a case-by-case basis.

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Financial Disclosures

Speaker Fees: Pfizer, Janssen;

Consultancy/Advisory Board Fees: Abbvie,

Takeda, Celltrion, Ferring; **Educational grant:** Pfizer

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Canadian IBD Today
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