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VIEWPOINT

Thrombosis in inflammatory bowel disease: Are we tailoring prophylaxis to those most at risk?

Robert V. Bryant [a,*], Vipul Jairath [a,b], Nicola Curry [c], Simon P.L. Travis [a]

[a] Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, United Kingdom
[b] NHS Blood and Transplant, Oxford University Hospitals NHS Trust, United Kingdom
[c] Oxford Haemophilia and Thrombosis Centre, Churchill Hospital, Oxford University Hospitals NHS Trust, United Kingdom

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Abstract

Inflammatory bowel disease (IBD) is a disease-specific risk factor for incident and recurrent venous thromboembolism (VTE). The reasons are acquired, multifactorial, and related to prothrombotic aberrations during active disease, although the mechanisms remain incompletely elucidated. VTE represents a potentially life-threatening extraintestinal manifestation of IBD, but the associated morbidity and mortality can be reduced by appropriate use of thromboprophylaxis. Nevertheless, despite international guidelines advocating thromboprophylaxis in hospitalised patients with IBD, practice is highly variable, since 65% of gastroenterologists may not use pharmacological VTE prophylaxis in hospitalised patients with acute severe colitis. Furthermore, there is no guidance on appropriate prophylaxis for ambulatory outpatients with active disease who are at an appreciable risk of VTE. Thus the question: are we tailoring thromboprophylaxis to those patients with IBD who are most at risk?

1. Introduction

Inflammatory bowel disease (IBD) is a disease-specific risk factor for incident and recurrent venous thromboembolism (VTE).[1–6] The reasons are acquired, multifactorial, and related to prothrombotic aberrations during active disease, although the mechanisms remain incompletely elucidated.[7,8]

VTE represents a potentially life-threatening extraintestinal manifestation of IBD, but the associated morbidity and mortality can be reduced by appropriate use of thromboprophylaxis.[7] Nevertheless, despite international guidelines advocating thromboprophylaxis in hospitalised patients with IBD,[9–12] practice is highly variable, since 65% of gastroenterologists may not use pharmacological VTE prophylaxis in hospitalised patients with acute severe colitis.[13–15] Furthermore, there is no guidance on appropriate prophylaxis for ambulatory outpatients with active disease who are at an

* Corresponding author at: Translational Gastroenterology Unit, John Radcliffe Hospital, University of Oxford Hospitals NHS Trust, Headley Way, Headington OX3 9DU, United Kingdom. Tel.: +44 1865 741166.
E-mail addresses: Robert.Bryant@ouh.nhs.uk (R.V. Bryant), vipul.jairath@nhsbt.nhs.uk (V. Jairath), Nicola.Curry@ouh.nhs.uk (N. Curry), simon.travis@ndm.ox.ac.uk (S.P.L. Travis).

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Table 1 Manifestations, risks and mechanisms of thrombosis in patients with IBD.

Manifestations, risks and mechanisms of thrombosis in patients with IBD		
Manifestations	Risk factors	Mechanisms
Deep venous thrombosis and pulmonary embolus	Active disease state	Inflammation
Portomesenteric thrombosis	Extent of disease	Increased procoagulant acute phase reactants
Cerebral sinus thrombosis	Surgery	Decreased anticoagulant factors
Upper limb and jugular thrombosis	Hospitalisation	Thrombocytosis
Intracardiac thrombosis	Central line placement	Increased platelet activation
Aortic mural thrombosis	Corticosteroids	Extracellular vesicles?
Retinal vein thrombosis	Pregnancy	Hyperhomocysteinaemia?
Cerebrovascular disease	Older age	
Ischaemic heart disease	Oral contraceptives	
	Previous history of VTE	
	Family history of VTE	

appreciable risk of VTE.[2] Thus the question: are we tailoring thromboprophylaxis to those patients with IBD who are most at risk?

2. Impact and manifestations of thrombosis in patients with IBD

VTE occurs in patients with IBD at a younger age than the general population[1,16] and may lead to prolonged hospitalisation, impaired quality of life and increased healthcare utilisation.[3,17] IBD has also been shown to be a risk factor for recurrent VTE, with an adjusted recurrence rate 2.5 fold (95% CI 1.4–4.2) that of the general population 5 years after cessation of anticoagulation for a first VTE.[18] Mortality rates following VTE amongst patients with IBD are considerable, ranging from 18 to 22%.[19,20] Perhaps more striking is evidence that mortality rates in hospitalised patients with IBD and VTE are 2.1 fold-higher (95% CI 1.6–2.9) than those of patients with VTE, but without IBD.[3] This study found that IBD-related bowel surgery had the greatest impact on inpatient mortality associated with VTE (OR 4.8; 95% CI 3.97–5.8), which is incongruous with the younger age and low comorbidity of patients with IBD. Although unable to define the type of VTE, the data suggest that VTE in this group may be more severe or carry a higher risk of pulmonary embolism.[3]

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most common sites of VTE in patients with IBD, representing 90% of events (Table 1).[21] The location of VTE in IBD is otherwise diverse and requires astute clinical awareness. Portal vein or superior mesenteric vein thrombosis should be considered if there is disproportionate abdominal pain or clinical deterioration in a hospitalised patient, whether with Crohn's disease (CD) or ulcerative colitis (UC).[21,22] Cerebral sinus thrombosis should be considered in the event of headache, altered consciousness, or focal neurology.[23] Other reported sites of VTE include subclavian, internal jugular, or superior vena caval thrombosis, commonly associated with central lines or parenteral nutrition. Intracardiac, aortic mural, or retinal vein thrombosis in IBD have been described.[7,8,20] Less well recognised is the association between IBD and arterial thrombotic events, including mesenteric arterial thrombosis, which may lead to catastrophic loss of small bowel, particularly in patients with UC (hazard ratio 12.5 compared to age-matched hospitalised patients, $p < 0.0001$).[24] Debate continues about an increased risk of cerebrovascular or ischaemic heart disease, despite a lower burden of conventional risk factors.[25,26]

3. When is the risk of VTE in IBD patients highest?

Incidence rates of VTE from population-based studies range from 2.4 to 4.6/1000 person years, equating to a relative risk in both ambulatory and hospitalised patients of 1.5 to 3.5 that of the general population.[1–3,6,18] A meta-analysis including 11 studies that compared risk of VTE in patients with IBD to control populations, reported a 2.2 fold (95% CI 1.83–2.65) relative risk of VTE.[4] Despite conflicting literature, the risk of VTE appears similar between UC and CD.[3,4,21] Patients with pancolitis (UC), or colonic involvement in CD appear to be at particular risk.[8] Traditional risk factors for VTE also operate in IBD, including immobility, smoking, older age, surgery, pregnancy or oral contraceptives, corticosteroids and central venous lines (Table 1).[2,3,7,27,28]

Disease activity is closely associated with VTE risk.[2,8,21] The UK General Practice Research Database was used to evaluate the association between disease activity and VTE, defining a disease flare as a requirement for corticosteroids.[2] Patients with IBD had an 8.4-fold (95% CI 5.5–12.8) increased risk of developing VTE during active disease compared with the general population. When the risk of VTE was stratified into ambulant outpatients versus hospitalised patients with active disease, the risk of VTE was 15.8-fold (95% CI 9.8–25.5) higher in ambulant outpatients compared to controls, but only 3.2-fold (95% CI 1.7–6.3) higher in hospitalised patients compared to hospitalised controls. Although the absolute risk in ambulant outpatients with active IBD is low (and lower than in hospitalised patients), this highlights active disease amongst outpatients with IBD as a greater risk than previously recognised. Thus, another question: for how long does the increased risk of VTE in patients with active IBD persist after hospitalisation?