Cardiovascular disease and venous thromboembolism in inflammatory bowel disease

Inflammatory bowel disease appears to increase the risk of both cardiovascular and thromboembolic events. This seems to occur despite the fact that many of these patients have a lower burden of traditional risk factors. There are several theories as to what drives this heightened risk, most of which highlight the role of chronic inflammation. More studies should be undertaken to decide in what context to most optimally protect inflammatory bowel disease patients against cardiovascular and thromboembolic events, for how long these patients should be treated once diagnosed, and how best to prevent further events, including avoidance of concomitant risk factors.

KEYWORDS: cardiovascular event ▪ Crohn's disease ▪ inflammatory bowel disease ▪ thromboembolic disease ▪ thrombosis ▪ ulcerative colitis ▪ venous thromboembolism

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The precise pathways that lead to Crohn's disease (CD) and ulcerative colitis (UC) are still unknown; however, as in other inflammatory and immune disorders like rheumatoid arthritis and systemic lupus erythematosus, inflammatory bowel disease (IBD) has an increased risk of both cardiovascular (CV) and thromboembolic events [1,2]. This has tremendous implications, since CV disease is the leading cause of death and third leading cause of disability in the USA [3,4]. We have historically looked at traditional risk factors to assess CV and thromboembolic risk, but compared to healthy age-matched controls, IBD patients have early stages of vascular disease without having the traditional CV risk factors. Similarly, patients with IBD have an increased risk of venous thromboembolic disease, even without carrying some of the common genetic mutations. Here, we describe the studies supporting the association between IBD and CV and thromboembolic disease.

IBD & CV disease

The IBD population has been shown to be at increased risk for early CV disease [5–7], which led to studies identifying the potential risk factors associated with these complications. A study by Papa *et al.* measured the intima-media thickness (IMT) of the carotid artery by high-resolution ultrasound in a total of 72 patients; 52 had IBD (18 UC and 34 CD) and 20 controls were matched for age and sex [8]. None of the patients had prior cerebrovascular events or risk factors for atherosclerosis (i.e., hypertension, dyslipidemia, diabetes mellitus, or smoking history). The study showed that the mean carotid IMT was statistically significantly higher in IBD patients compared to controls. When CD and UC patients were analyzed separately, UC appeared to be driving that difference. However, Maharshak *et al.* did not find a difference in mean IMT 2 years later, though the two studies had several demographic differences; based on these two studies, no definitive conclusions can be made [9].

Oldenburg *et al.* analyzed the relationship between hyperhomocysteinemia and thrombosis in IBD [10]. An elevated homocysteine level is known to be an independent risk factor for venous and arterial thrombosis [11–15] and can be secondary to acquired deficiencies such as low folate, vitamin B12 or B6, or from genetic causes; homocysteine has been shown to be increased in patients with IBD [16]. The most common genetic defect leading to elevated levels of homocysteine is the methylenetetrahydrofolate reductase C677T variant [17], which was shown to be highly prevalent in the IBD population as well [18], supporting a genetic linkage to hyperhomocysteinemia in IBD. However, Oldenberg *et al.* found that although the prevalence of hyperhomocysteinemia in IBD was 11%, there was no correlation between elevated homocysteine and developing venous or arterial thrombosis in the IBD population [10].

Dagli *et al.* compared some nontraditional CV risk factors (high sensitivity C-reactive protein, homeostasis model assessment of insulin resistance, homocysteine, and carotid IMT) in 40 IBD cases and 20 controls. They found

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that these markers for early atherosclerosis were significantly more elevated in the IBD population, irrespective of disease activity or subtype of IBD [19].

A recent article by Yarur *et al.* analyzed traditional risk factors for CV disease (i.e., hypertension, diabetes, smoking status, dyslipidemia, family history of coronary artery disease (CAD), chronic kidney disease and obesity) and nontraditional risk factors as well (i.e., hemoglobin, platelets, white blood cell count, erythrocyte sedimentation rate, C-reactive protein and steroid exposure) [20]. This retrospective longitudinal cohort study of 356 IBD patients and 712 matched controls showed that IBD patients with known CV events were significantly less likely to have hypertension, diabetes mellitus, dyslipidemia and obesity. There was no statistically significant difference in smoking status, family history of CAD or prevalence of chronic kidney disease between IBD patients and controls. With respect to the other factors analyzed, IBD subjects had higher white blood cell and platelet counts and more anemia, with slightly more than half of the IBD population (52.5%) exposed to steroids. They found that although the IBD population had fewer risk factors for traditional CV disease than their matched controls, they had more CV events, even after adjusting for both traditional and nontraditional risk factors. There was no significant difference noted in the CAD event rate between the UC and CD groups ($p = 0.79$), and the exposure to corticosteroids did not increase the risk of CAD. They concluded that patients with IBD are at a higher risk of developing CAD than matched controls despite their lower burden of traditional CAD risk factors.

Bernstein *et al.* performed a population-based study on the incidence of arterial thromboembolic diseases in IBD [21]. They compared the incidence of ischemic heart disease, cerebrovascular disease and undifferentiated arterial thromboembolic disease in IBD and matched controls. The risk of ischemic heart disease was increased for CD and UC in both genders (incidence rate ratio [IRR]: 1.26; 95% CI: 1.11–1.44), in contrast to cerebrovascular diseases, where only CD was associated with an increased risk (IRR: 1.32; 95% CI: 1.05–1.66). In undifferentiated arterial thromboembolic disease, IBD patients of female gender (IRR: 1.96; 95% CI: 1.24–3.10), aged less than 40 years (IRR: 19.95; 95% CI: 1.81–219.92), or aged 40–59 years (IRR: 3.17; 95% CI: 1.27–7.91) had significantly increased risks. They concluded that IBD patients are more likely to have cardiac arterial thromboembolic disease, CD has an increased risk of cerebral arterial thromboembolic disease, and young and female patients with IBD have an increased risk of undifferentiated arterial thromboembolic disease.

A compilation of these studies, highlighting major end points and results, is summarized in Table 1.

IBD & venous thromboembolism

The risk of thromboembolic phenomena (both arterial and venous) has been shown to be increased in the IBD population, with the reported frequency in the literature ranging widely from 0.3 to 41% [21–25], but the mechanism of this increased prevalence remains unclear. It is known that thromboembolism in the general population can be triggered by either acquired or hereditary causes. Solem *et al.* described the clinical features and acquired and congenital risk factors of the IBD population that developed deep venous thrombosis (DVT) or a pulmonary embolus (PE) [26]. A total of 94 patients were identified (55 UC and 39 CD). Active disease was present in 80% of CD and 79% of UC subjects. The median interval from IBD diagnosis to DVT/PE was shorter for UC patients than those with CD (4 vs 15.3 years). Most of the patients (79% of CD and 81% of UC) were receiving medical therapy at the time they developed a DVT or a PE, and 24% of UC patients had undergone proctocolectomy prior to having a DVT/PE. Most patients with UC (76%) had pancolonic disease and 79% of CD patients had some colonic involvement (56% ileocolonic and 23% colonic). Thrombophilia evaluation was performed in 41% of patients. In total 11% of DVTs were in the upper extremities and were primarily intravenous catheter-associated; these were considered provoked DVTs for which no additional hypercoagulable work-up was necessary. The most commonly detected thrombophilias were factor V Leiden mutation and protein C resistance (17%), followed by hyperhomocysteinemia (14%) and antiphospholipid and anticardiolipin antibodies (11%). A total of 87% had acquired risk factors (i.e., immobility, malignancy or the post operative setting). They concluded that that the IBD population has a significantly higher rate of both DVT and PE. The extent of colonic involvement correlated with thromboembolic risk and disease activity seemed to be highly associated with the development of a DVT/PE as well.

Table 1. Inflammatory bowel disease and cardiovascular disease.

Authors	Study type	Number of patients	End point	Results	p-value	Conclusion	Ref.
Papa *et al.*	Prospective case–control study	72 patients: 50 with IBD, 22 controls	IMT	0.63 ± 0.15 mm vs 0.53 ± 0.08 mm	p = 0.003	IBD patients have a mean IMT statistically higher than controls	[8]
Maharshak *et al.*	Case–control study	61 with IBD and 61 matched controls	IMT	0.66 ± 0.09 mm vs 0.64 ± 0.07 mm	p > 0.05	IBD patients had IMT values similar to those of controls	[9]
Oldenburg *et al.*	Retrospective study	22 IBD patients with arterial thrombosis and 23 IBD matched controls	Hyc	40.9 ± 17.7 vs 27.2 ± 9.90	p < 0.05	IBD patients with arterial or venous thrombosis have higher levels of Hyc compared to IBD matched controls	[10]
Dagli *et al.*	Case–control study	40 IBD cases and 20 matched controls	hsCRP, HOMA-IR, Hyc and cIMT	hsCRP (13 ± 21.3 vs 4.1 ± 2.5), HOMA-IR (2.62 ± 0.15 vs 1.92 ± 0.3), Hyc (20.9 ± 7.8 vs 13.2 ± 3.8), cIMT (0.74 ± 0.08 vs 0.70 ± 0.05)	cIMT and HOMA-IR (p = 0.01), Hyc (p = 0.05), hsCRP (p = 0.02)	IBD patients have higher levels of cIMT, Hyc, hsCRP and insulin resistance	[19]
Yarur *et al.*	Retrospective cohort study	356 IBD cases and 712 matched controls	Traditional versus nontraditional risk factors for CV events	Unadjusted hazard ratio for developing CAD in the IBD group was 2.85	p < 0.01 for all traditional risk factors in IBD group	Increased incidence of CAD events in IBD patients despite having a lower burden of traditional risk factors	[20]
Bernstein *et al.*	Retrospective cohort study	8060 IBD cases and 80,489 matched controls	Ischemic heart disease, cerebrovascular disease and undifferentiated ATED	Ischemic heart disease (IRR: 1.26) cerebrovascular disease, only CD (IRR: 1.32), undifferentiated ATED only females (IRR: 1.96) and aged <40 years (IRR: 19.95) and 40–59 years (IRR: 3.17)	N/A	IBD patients more likely to have cardiac ATED	[21]

ATED: Arterial thromboembolic disease; CAD: Coronary artery disease; CD: Crohn's disease; cIMT: Carotid intima-media thickness; CV: Cardiovascular; HOMA: Homeostatic model assessment; hsCRP: High-sensitivity C-reactive protein; Hyc: Hyperhomocysteinemia; IBD: Inflammatory bowel disease; IMT: Intima-media thickness; IRR: Incidence rate ratio; N/A: Not applicable.

They also proposed that all IBD patients who have a venous thromboembolic event should have a comprehensive thrombophilia evaluation, and if the presence of a hereditary hypercoaguable condition is confirmed, then that would be a relative indication for life-long anticoagulation given the high mortality and recurrence rates associated with venous thromboembolism (VTE).

Grainge *et al.* assessed the association between having an IBD flare or being hospitalized and the risk of VTE [27]. They defined a flare as the need for corticosteroids after at least 4 months without such a prescription. 8009 patients with IBD (58%) had a flare of their disease requiring corticosteroids, and they had a total of 304 episodes of VTE. After adjusting for confounding factors, they concluded that the risk of VTE was eight-times greater at the time of a flare (p < 0.0001) and 6.5-times greater during the chronic phase of the disease compared to matched controls (p < 0.0001). In addition, they found that the absolute risk of VTE during all phases of activity of IBD was significantly higher during outpatient periods as compared to hospitalization. They found no statistical difference in the incidence of VTE between UC and CD.

Table 2. Inflammatory bowel disease and venous thromboembolism.

Author	Study type	Number of patients	End points	Results	p-value	Conclusion	Ref.
Solem *et al.*	Retrospective study	94 patients with IBD with DVT or PE	Risk factors to develop recurrent DVT or PE	Extent of involvement CD: ileocolonic (56%), colonic (23%) UC: (76%), pancolonic (2%) isolated proctitis Active disease: 80% in CD and 79% in UC 1/4 UC s/p proctocolectomy	N/A	IBD activity and extent of disease positively correlates with venous thromboembolic risk Proctocolectomy does not appear to prevent recurrent thromboembolic events	[26]
Grainge *et al.*	Prospective cohort study	139 IBD patients and 165 controls that developed VTE	Risk of VTE during the different phases of the disease	IBD higher risk of VTE than controls (HR: 3.4) During a flare (HR: 8.4) During a flare during nonhospitalized periods (HR: 15.8)	IBD higher risk of VTE than controls ($p < 0.0001$), Flare ($p < 0.0001$), Flare during nonhospitalized periods ($p < 0.0001$)	Overall, IBD patients are at increased risk for VTE, especially Nonhospitalized patients having a flare of their disease	[27]
Novacek *et al.*	Multicenter cohort study	116 IBD patients and 1255 non-IBD patients with previous VTE	Risk factors for recurrent VTE	In IBD patients: male sex (HR: 3.0) and age at first VTE (HR: 1.03) associated with increased risk of recurrent VTE	Male sex ($p = 0.003$), Age at first VTE ($p = 0 .031$)	Patients with IBD and VTE are at high risk for recurrent VTE	[28]
Bernstein *et al.*	Case–control study	327 with CD, 165 with UC and 412 controls	Determination of the presence of mutations in clotting factors in IBD	Only in Factor XIII, more homozygous carriers in CD (8.7%) compared with controls (4.3%)	$p = 0.02$	No gene mutation in clotting factors explains the greater risk of VTE in IBD	[29]

CD: Crohn's disease; CV: Cardiovascular; DVT: Deep venous thrombosis; Hyc: Hyperhomocysteinemia; IBD: Inflammatory bowel disease; IMT: Intima-media thickness; N/A: Not applicable; PE: Pulmonary embolus; UC: Ulcerative colitis; VTE: Venous thromboembolism.

Novacek *et al.* recently described the recurrence risk of VTE in patients with IBD [28]. It was a multicenter study that included 116 IBD patients with a history of previous VTE, 86 of which were deemed unprovoked. They found that 35 (25 CD and ten UC) out of 116 (30.2%) IBD patients had recurrent VTE (22 DVT and 13 PE) compared to 204 out of 1255 (16.3%) non-IBD patients ($p = 0.01$). When they analyzed risk factors for recurrent VTE in IBD patients, only male sex ($p = 0.003$) and age at first VTE ($p = 0.031$) were associated with a significantly increased risk of recurrent VTE. Other factors, including unprovoked first VTE, factor V Leiden deficiency, location of VTE (i.e., proximal DVT and PE vs distal DVT), type of IBD, basal metabolic index, duration of anticoagulation and elevated levels of factor VIII were not found to be independent predictors of recurrence risk. Their conclusion was that patients with IBD and VTE are at high risk of recurrent VTE, but it is unclear, which patients need to be on prolonged anticoagulation therapy, balancing the risk of VTE recurrence with the risk of bleeding complications.

Bernstein *et al.* sought to determine if patients with IBD have mutations in clotting factors that could explain their three- to four-fold increased risk of venous thrombosis [29]. Theirs was a case–control study with 327 patients with CD, 165 with UC and 412 healthy controls. The four most common prothrombotic genetic mutations (i.e., Factor II G20210A, Factor V Leiden, methylenetetrahydrofolate reductase C677T, and Factor XIII) were measured in all patients. A total of 18 subjects (ten CD, four UC and four controls) had venous thrombosis. For Factor II, there were no homozygous mutation carriers, and there were no significant differences between CD, UC and controls for being heterozygous. For Factor V Leiden, only one patient with CD was a homozygous mutation carrier and none of the patients in either of the two other

groups was a carrier; there was no significant difference among the three groups for being heterozygous for the mutation. For methylenetetrahydrofolate reductase C677T, the risk of carrying a mutated allele (either homozygous or heterozygous) was no different in the three groups. Finally, for Factor XIII, there were more homozygous carriers among CD (8%) than controls (4.3%), but the three groups had a similar overall carriage of any mutation (heterozygous or homozygous; 48% in CD, 43.3% in UC and 46.3% in controls). The conclusion of this study was that the higher risk of thrombosis in patients with IBD compared to controls is not related to the four most common prothrombotic genetic mutations, despite the slightly greater prevalence of Factor XIII mutation carriership in CD.

A compilation of these studies, highlighting major end points and results, is summarized in Table 2.

Future perspective

There is mounting evidence that patients with IBD have higher CV and thromboembolic risk than matched controls despite fewer traditional risk factors; however, it is still unclear what makes the IBD patients more prone to these complications. Tobacco, known to worsen the course of CD and perhaps ameliorate UC, is associated with CV disease and VTE; however, most studies quoted in this review controlled for this factor. Though some chronic inflammatory diseases like rheumatoid arthritis have the confounding factor of age possibly contributing to their increased rate of CV disease, others diseases with increased rates of CV disease like systemic lupus erythematosus afflict younger patients in the way IBD does. Multiple studies have come to different, and sometimes contradictory, conclusions about the mechanism of atherosclerosis and thrombosis in IBD, from the role of IMT and homocysteine, to various genetic markers found in non-IBD patients with CV disease and VTE, to severity, location and nature of disease. It has been hypothesized that there is a somewhat shared mechanism between inflammation induced in the gastrointestinal and CV systems leading to increased CV disease and VTE in IBD patients, though further elucidation of this is necessary. Other factors, such as the use of oral contraceptives, nutrient malassimilation, and venous instrumentation for vascular access may play a role, and this certainly warrants further study.

Even though the exact etiology has not been found, there is no doubt that IBD should be considered a hypercoaguable state and prevention of VTE should be administered when those patients have another VTE risk factor, such as immobility due to hospitalization; whether anticoagulation should be given for active disease not well-controlled with the patient's current medical therapy is still controversial. Given the predisposition to gastrointestinal bleeding due to mucosal defects in patients with IBD, it is still unclear if the benefits of long-term VTE prophylaxis outweigh the risk of bleeding. Similarly, for CV events, studies in IBD patients examining the potentially protective role of aspirin weighed against

Executive summary

Inflammatory bowel disease & cardiovascular disease

- Inflammatory bowel disease (IBD) has an increased risk of both cardiovascular (CV) and thromboembolic events, with CV disease being a leading cause of death and disability in the USA.
- An elevated homocysteine level is known to be an independent risk factor for venous and arterial thrombosis, but the association is not as strong in IBD patients.
- Markers for early atherosclerosis are significantly more elevated in the IBD population, irrespective of disease activity or subtype of IBD.
- IBD patients have more CV events than matched controls despite fewer traditional CV risk factors.
- Subgroups of IBD patients are more likely to have cardiac, cerebral and undifferentiated arterial thromboembolic disease than controls.

IBD & venous thromboembolism

- The risk of venous thromboembolism (VTE) is increased in the IBD population.
- The extent of colonic involvement in IBD correlates with thromboembolic risk and disease activity is highly associated with the development of a deep venous thrombosis/pulmonary embolus.
- Risk of VTE is greater at the time of a flare but also during the chronic phase of the disease compared to matched controls, and most of this risk appears to occur in the outpatient setting.
- The higher risk of thrombosis in patients with IBD does not appear to be related to the most common prothrombotic genetic mutations.

Future perspective

- IBD should be considered a hypercoaguable state and prevention of VTE should be considered in patients with other risk factors for VTE.
- It is still unclear if the benefits of long term CV disease and VTE prophylaxis outweigh the risk of bleeding in those without other risk factors for these disease states.

its possible adverse gastrointestinal side effects should be undertaken. Since some of the data discussed previously suggests that the degree of inflammation (particularly colonic) may predispose to cardiac and vascular complications, perhaps the most effective pre-emptive therapy is adequate control of disease with aggressive medical treatment of the IBD itself; clearly, larger scale studies will be needed to address all of these issues.

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▪ **The increased risk of thrombosis in IBD is not accounted for by some of the most common prothrombotic genetic mutations alone.**