

Risk of cardiovascular disease in inflammatory bowel disease

Nynne Nyboe Andersen, Tine Jess

Nynne Nyboe Andersen, Tine Jess, Department of Epidemiology Research, Statens Serum Institut, DK-2300 Copenhagen, Denmark

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Correspondence to: Nynne Nyboe Andersen, MD, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark. nyna@ssi.dk
Telephone: +45-32-683139 Fax: +45-32-683165

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Abstract

Abundant scientific evidence supporting an association between inflammatory bowel disease (IBD) and venous thromboembolic events, caused by an IBD related hypercoagulability, is acknowledged and thromboprophylactic treatment strategies are now implemented in the management of IBD patients. In contrary, the risk of arterial thromboembolic disease, as ischemic heart disease, cerebrovascular events, and mesenteric ischemia in patients with IBD remains uncertain and the magnitude of a potentially increased risk is continuously debated, with ambiguous risk estimates among studies. The evident role of inflammation in the pathogenesis of atherosclerosis forms the basis of a biological plausible link; the chronic systemic inflammation in IBD patients increases the risk of atherosclerosis and thereby the risk of thrombotic events. Further, studies have shown that the burden of traditional risk factors for atherosclerosis, such as obesity, diabetes mellitus, and dyslipidemia is lower in IBD populations, thus further strengthen the role of non-traditional risk factors, as chronic inflammation in the linking of the two disease entities. Likewise, mortality from cardiovascular disease in IBD remains questioned. The aim of the current review is to give an up-date on the existing evidence of the possible

association between IBD and cardiovascular disease and to discuss traditional and non-traditional risk factors.

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Key words: Inflammatory bowel disease; cardiovascular disease; Risk; Ulcerative colitis; Crohn's disease

Core tip: The increased risk of venous thromboembolic events in inflammatory bowel disease (IBD) patients is well-established and prophylactic strategies are implemented in current guidelines. The risk of arterial thromboembolic complications in IBD remains uncertain. Together, the systemic inflammation in patients with IBD and the inflammation-driven development of atherosclerosis form the basis of a potential association between the two disease entities. The present review will provide a summary of the existing literature on the association between IBD and thromboembolic diseases and discuss potential risk and preventive factors.

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INTRODUCTION

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD) are systemic, chronic inflammatory conditions that predominately affect the gastrointestinal tract but are also characterized by numerous extraintestinal manifestations, assumedly caused by concomitant systemic inflammation. It is well-established that the risk of venous thromboembolic event is increased in IBD patients^[1], primarily during flares^[2], potentially due to an inflammation induced state

of hypercoagulability. However, the true magnitude of this risk and the associated mortality rate remains debated.

In the last decade, it has become increasingly evident that chronic systemic inflammation plays a pivotal role in the pathogenesis of atherosclerosis^[3]. Further, the observation of increased thickness of the carotid intimal-media (a measure of atherosclerotic burden), endothelial dysfunction, and atherogenic alterations in the lipid profile of patients with IBD has further fuelled the hypothesis of a potential increased risk of atherosclerosis-driven vascular diseases in IBD^[4-6]. Likewise, an increased risk of cardiovascular diseases (CVD) in other inflammatory conditions as rheumatoid arthritis^[7], psoriasis^[8] and systemic lupus erythematosus^[9] is now established, independent of traditional cardiovascular risk factors. Currently, reported results on risk of CVD in IBD have been ambiguous with studies revealing an increased risk of both ischemic heart disease (IHD) and cerebrovascular accidents (CVA) while others have shown no association^[10-13]. Additionally, a few studies have suggested that IBD patients have a lower burden of some of the traditional risk factors for CVD, such as hypertension, diabetes mellitus, dyslipidemia, and obesity, and that non-traditional risk factors could play an important role for IBD patients^[13,14]. Overall, this has led to an ongoing debate of whether the risk of arterial thrombotic disease is increased in IBD patients, what the underlying mechanisms are, and whether a strategy for disease specific risk assessment should be implemented in the management of IBD patients.

The aim of the current review is to give an update on the existing evidence on risk of atherosclerosis-related vascular disease, including ischemic heart disease, cerebrovascular accidents, mesenteric thrombosis, and venous thromboembolic events and associated risk factors and mortality rates in patients with IBD and further to evaluate on future prospects and preventive factors.

VENOUS THROMBOEMBOLIC EVENTS

The association between venous thromboembolic events (VTEs), comprising deep venous thrombosis (DVT) and pulmonary embolism (PE), and IBD was indicated as early as in 1936 by Borgen *et al*^[15]. In 1986, fifty years after the suggested association, Talbot *et al*^[16] was the first to report valid results on the incidence of VTEs in 7199 IBD patients from the Mayo Clinic, US and revealed a potentially increased risk.

VTEs are a serious concern with a significant morbidity and mortality. The risk of VTEs is associated with the hypercoagulability related to IBD. The specific clotting mechanism has been attributed to a range of factors including thrombocytosis^[17], increased levels of clotting factors V/VIII/fibrinogen^[18], acquired antithrombin III deficiency^[19,20] and decreased levels of protein C and S^[21-23]. The exact mechanism, the interplay between the variable factors and whether the hypercoagulability

is a secondary phenomenon to IBD or represents an underlying pathological mechanism for IBD remain uncertain.

In 2001, the first large population-based study on risk of VTEs in IBD was reported from the Canadian Manitoba database. In a cohort of 5,529 IBD patients matched 1:10 with healthy controls from the general population, the risk of DVT and PE was significantly increased in IBD patients compared to controls (incidence rate ratio, IRR = 3.54, 95%CI: 2.9-4.3; and IRR = 3.3, 95%CI: 2.5-4.3 for DVT and PE respectively). IBD patients < 40 years of age were at particular high risk of VTEs with a six-fold increased risk (IRR = 6.02; 95%CI: 3.92-9.12). No sex or IBD subtype differences were observed^[24]. This study led to the introduction of thromboprophylaxis as the standard care for IBD patients with active inflammation admitted to hospital. A later population-based study from the United Kingdom by Grainge *et al*^[2] sought to elucidate the risk of VTEs during different stages of disease activity as they hypothesized that the more severe inflammation the greater risk of VTEs. In 13756 IBD patients, matched with 71627 non-IBD controls, the risk of developing VTEs was similar to the results from Canada with a hazard ratio (HR) of 3.4 (95%CI: 2.7-4.3). Further the study found that the risk of VTEs during a flare (defined as the period 120 d after a new corticosteroid prescription) was much more prominent with a HR of 8.4 (95%CI: 5.5-12.8). The highest relative risk of VTEs was found for IBD patients non-hospitalized during a flare with an almost 16-fold increased risk (HR = 15.8; 95%CI: 9.8-25.5). A recent meta-analysis identified 10 studies assessing the risk of VTEs in 72205 IBD patients and 891840 controls and found that the overall risk of VTEs in IBD was increased by 96% compared to the general population (RR = 1.96; 95%CI: 1.67-2.30)^[25]. No difference in risk was found between UC and CD. The meta-analysis further confirmed that the risk of VTEs was greater in studies including IBD patients in general (RR = 2.48; 95%CI: 2.04-3.00) compared to studies evaluating on hospitalized IBD patients (RR 1.47; 95%CI: 1.17-1.86). This observation is potentially due to an effect of thromboprophylactic treatment strategies for hospitalized IBD patients.

Only few studies have evaluated on mortality rates in VTE complicated IBD patients. From the Mayo Clinic, Solem *et al*^[26] reported a 22% mortality rate after a median follow-up of 1.8 years among 98 IBD patients diagnosed with VTE however, no comparison was made with post-VTE mortality rates in the general population. A large nation-wide population-based study from the United States by Nguyen and Sam^[27], including more than a hundred thousand IBD patients, revealed that the in-hospital mortality was significantly higher for IBD patients with VTE compared with non-VTE IBD patients and this was valid for both CD (17.0 *vs* 4.2 per 1000 hospitalizations, $P < 0.0001$) and UC (37.4 *vs* 9.9 per 1000 hospitalizations, $P < 0.0001$). The excess mortality associated with VTE was 2.1 fold higher for

IBD patients than non-IBD individuals with VTEs ($P < 0.0001$) thereby indicating that VTEs have a more severe prognosis in IBD patients than in non-IBD individuals.

To summarize, it appears evident that IBD is a moderate independent risk factor for the development of VTEs and that the risk is highest among IBD patients with a flare in disease, not admitted to hospital. Further, there is a significant mortality associated with VTEs in IBD patients that is even greater than in non-IBD patient with VTEs. This calls for the importance of preventative and treatment strategies of VTEs in the IBD population, especially in the light of results from a recent survey involving 591 United States physicians; only 35% would give pharmacologic VTE prophylaxis to a hospitalized patient with severe UC^[28].

ARTERIAL THROMBOEMBOLISM

In contrast to the well-established association between IBD and VTE, the risk of arterial thromboembolic events (ATE) in IBD is less elucidated in the literature. In the following, for simplicity, ATE will comprehend ischemic heart disease (IHD), cerebrovascular disease (CVD) and mesenteric ischemia.

Several circumstances could suggest that IBD patients are at increased risk of ATE. First of all IBD patients, particular CD patients are more likely to be current or past smokers. Further, some IBD-related drugs, *e.g.*, corticosteroids which increases the blood pressure and change the glucose homeostasis, and in contrary, the avoidance of aspirin-containing medications (due to potential fear of exacerbating IBD) could potentially increase the risk of ATE in IBD. Additionally, the presence of a chronic systemic inflammation in IBD, a well-known independent risk factor for atherosclerosis, assumedly augments the risk.

ISCHEMIC HEART DISEASE

Ischemic heart disease is caused by atherosclerotic plaque formation in coronary arteries and it is the most common type of heart disease and the leading cause of death in the world. Several inflammatory mediators as high C-reactive protein, and further up-stream inflammation markers such as tumor necrosis factor- α , interleukin-6 and 18 and the CD40 ligand are involved in the pathogenesis of both chronic inflammatory conditions including IBD and atherosclerosis^[17,29]. Further, studies have revealed that IBD patients, compared to non-IBD individuals, have an increased carotid intima-media thickness, a surrogate marker for IHD and have a higher risk of early onset of atherosclerosis^[6,30]. Thus, it appears biologically plausible that IBD patients carry an augmented risk of IHD compared to the general population.

In 2008, the first large study on risk of IHD in IBD patients, a population-based study from the Manitoba Database, Canada conducted by Bernstein *et al.*^[31], report-

ed a 26% increased risk (IRR = 1.26; 95%CI: 1.11-1.44) of IHD in 8060 IBD patients compared to non-IBD individuals. No difference in risk was observed between sex and subtype of IBD.

In contrary, a retrospective matched cohort study from United States by Ha *et al.*^[10] including 17487 IBD patients did not reveal any overall increased risk of IHD in either CD or UC, but in sub-analyses the risk of myocardial infarction was significantly increased in IBD women aged above 40 years (HR = 1.16; $P = 0.003$).

In a matched cohort study by Yarur *et al.*^[13] from 2011, the risk of IHD was assessed among 356 IBD patients and 712 matched controls and the authors reported a nearly 3-fold increased risk of IHD in IBD (HR = 2.85; 95%CI: 1.82-4.46). A nationwide Danish population-based cohort study of 4570820 individuals by Rungoe *et al.*^[12] reported a lower, although significant increased risk of IHD (IRR = 1.59; 95%CI: 1.50-1.69) in IBD patients compared to non-IBD individuals^[12]. Analyzing risk of IHD solely in the first three months and during the first year after IBD diagnosis revealed particularly high risk estimates (IRR = 4.57; 95%CI: 3.89-5.36 and IRR = 2.13; 95%CI: 1.91-2.38 respectively), hence also reflecting the potential role of ascertainment bias when assessing two chronic diseases (*i.e.* that hospitalization for one of the diseases increases the potential for discovery and recording of the other disease). However, analyses disregarding the first year after diagnosis and fully adjusted for comorbidity related medications revealed a persistent 22% increased risk of IHD over time (IRR = 1.22; 95%CI: 1.14-1.30). A following population-based Danish study by Kristensen *et al.*^[11] reported risk of myocardial infarction (MI) in more than 20.000 IBD patients according to disease activity. Analyses revealed an increased risk of MI in IBD patients during flare (RR = 1.49; 95%CI: 1.16-1.93) and during persistent activity (RR = 2.05; 95%CI: 1.58-2.65), whereas the risk was not increased during periods of remission (RR = 1.01; 95%CI: 0.89-1.15). In accordance with the Danish findings, a meta-analysis on risk of IHD in IBD by Singh *et al.*^[32] reported a 19% increased risk of IHD in IBD patients (OR = 1.19; 95%CI: 1.08-1.31) with the risk being higher in female gender (OR = 1.26; 95%CI: 1.18-1.35). Interestingly, another meta-analysis by Fumery *et al.*^[25], solely including observational studies on risk of IHD in IBD did not (potentially due to lack of power) reveal a statistically increased risk, although the magnitude of risk was similar (RR = 1.23; 95%CI: 0.94-1.62). The main difference between the two meta-analyses was the inclusion of a cross-sectional study by Sridhar *et al.*^[33] only in the latter meta-analysis; a study that contrary to expected found an inverse association between IHD and hospitalized IBD patients with a significant protective effect of IBD on risk of IHD (OR = 0.60; 95%CI: 0.56-0.65). With results paradoxical to the hypothesis authors explained this protective association could be caused by a direct result of Berkson's fallacy^[34], a form of selection bias that causes hospital cases and non-hospital controls in a case control study to be systemati-

cally different from one another, leading to a systematically higher exposure rate among hospital patients, and thereby distorting the risk estimate.

CEREBROVASCULAR DISEASE

Several case reports of ischemic stroke in remarkably young patients with CD has additionally led to the hypothesis of a potential association between IBD and CVE^[35-38].

Bernstein and colleagues reported a slightly increased risk of cerebrovascular disease in patients with CD (but not UC) in a population based setting (IRR = 1.32; 95%CI: 1.05-1.66), but adjustments were insufficient, lacking several important cerebrovascular risk factors, such as smoking, obesity and hypertension^[31]. A population-based case-control study from the United States evaluated on risk of ischemic stroke among 8054 CD patients matched with 161078 non-CD patients and results revealed an insignificant overall increased risk of ischemic stroke (OR = 1.10; 95%CI: 0.85-1.43)^[39]. A significant almost 3-fold increased risk of ischemic stroke was estimated in younger CD patients below 50 years of age (OR = 2.93; 95%CI: 1.44-5.89). A large United States conducted population-based matched cohort study found no overall increased risk of cerebrovascular disease in IBD patients, but stratified analyses revealed a significantly increased risk of stroke among women with IBD below the age of 40 compared to non-IBD controls (HR = 2.1, $P < 0.05$)^[10]. Only in a Danish setting an overall slightly increased risk of stroke in IBD patients has been estimated (RR = 1.15; 95%CI: 1.04-1.27)^[11] and during flares this risk was further increased (RR = 1.53; 95%CI: 1.22-1.92).

The meta-analysis by Singh *et al*^[32] reported pooled OR from five studies on cerebrovascular events in IBD and the meta-analysis revealed an adjusted 18% increased risk of CVE in IBD (OR = 1.18; 95%CI: 1.09-1.27), with a higher magnitude of risk estimates in women and patients at younger age.

INTESTINAL ISCHEMIA

The association between intestinal ischemia (including acute/chronic mesenteric ischemia and ischemic colitis) and IBD is vaguely elucidated. A population-based case-control study from the United Kingdom from 2011 studied risk factors for intestinal ischemia from the General Practice Research Database (GPRD)^[40]. Of the 71 cases of intestinal ischemia derived from the database only one patient had intestinal ischemia and IBD corresponding to an insignificant 4-fold increased risk (OR = 4.19; 95%CI: 0.46-38.43). From the Nationwide Inpatient Sample (NIS), the largest inpatient database in the United States, the risk of mesenteric ischemia was assessed among nearly 150000 discharges with a diagnosis of IBD and revealed a significant association between IBD and mesenteric ischemia (adjusted OR

= 3.4; 95%CI: 2.90-4.00) with a higher risk among UC patients (OR = 5.3; 95%CI: 4.24-6.74) than CD patients (2.58; 95%CI: 2.09-3.17). Young females with UC in the age group from 18 -39 years had the highest risk (OR = 15.48; 95%CI: 8.98-26.67). Likewise, a large cohort study^[10] reported increased risk of mesenteric ischemia in IBD patients with a HR of 11.2 compared with controls ($P < 0.0001$) and found the risk to be highest in UC patients (HR = 12.5; $P < 0.0001$) and females aged between 18-39 years (HR = 22.3; $P < 0.0001$). Although the absolute risk may be limited, mesenteric ischemia remains a very serious condition and IBD practitioners should be aware of the importance of recognizing these events.

CARDIOVASCULAR MORTALITY

Several studies have assessed the mortality rate from CVD in IBD and reports on both increased and decreased mortality rates exist^[41,42]. In a recent meta-analysis by Bewtra *et al*^[43] of cause-specific standardized mortality ratios in both population-based and inception cohort studies of IBD patients, no increased mortality from cardiovascular disease in neither UC nor CD was found (SMR_{UC} = 0.90; 95%CI: 0.80-1.02 and SMR_{CD} = 1.00; 95%CI: 0.88-1.13). Similar insignificant risk estimates of cardiovascular mortality in IBD patients was reported in the meta-analysis by Fumery and colleagues (pooled SMR = 1.03; 95%CI: 0.93-1.14)^[25]. Nevertheless, it is important to keep in mind that although cardiovascular mortality is a hard end-point and less prone to ascertainment bias it does not capture the entire spectrum of cardiovascular disease and with improving therapeutic options the mortality rate is decreasing and observational studies on the association between IBD and cardiovascular mortality often does not reach statistical significance due to the low mortality rates. In the large-scale population-based study by Kristensen *et al*^[11] with non-increased overall CV mortality among patients in remission (RR = 0.98; 95%CI: 0.89-1.09), authors were able to show increased CV mortality during flares (RR = 2.32; 95%CI: 2.01-2.68) and in patients with persistent disease activity (RR = 2.50; 95%CI: 2.14-2.92).

RISK FACTORS

The traditional risk factors for CVD are hypertension, diabetes mellitus, obesity, smoking, dyslipidemia, and physical inactivity.

A small Indian study by Sappati Biyyani *et al*^[14] aimed at evaluating the presence of traditional atherosclerotic risk factors in patients with IBD and coronary artery disease (CAD) compared to a control group (only CAD) by using the Framingham risk score. The Framingham risk score is a 10-year risk of CAD score based on the following risk factors: age, hypertension, diabetes mellitus, tobacco use and dyslipidemia. Among 42 cases and 137 controls the Framingham risk score was significantly

lower in patients with both IBD and CAD compared to controls (8.1 *vs* 10.0; $P = 0.002$). Yarur *et al*^[13] further assessed traditional and nontraditional risk factors in IBD related CAD and found that several traditional risk factors usually linked with patients' anthropometric status were less common in IBD. Kristensen *et al*^[11] made subgroup analyses stratifying IBD patients according to presence of traditional risk factors and showed a strong association between the number of risk factors and the risk of cardiovascular events. Additionally it is interesting that this study found an association between disease activity and risk of CV events, thereby supporting the hypothesis that the chronic inflammation acts as a risk factor for CVD in IBD patients. This is in accordance with another Danish study by Rungoe and colleagues stratifying risk according to use of oral corticosteroids, used as a proxy for both current and later disease activity, and the study revealed a higher risk of IHD in IBD patients with a history of oral corticosteroids compared to never users (IRR = 1.37 *vs* 1.23 respectively; $P < 0.01$)^[12].

POTENTIAL PREVENTIVE TREATMENTS

Considering chronic systemic inflammation as a potential nontraditional risk factor for CVD in IBD, it is interesting to evaluate the effect of treatments lowering the inflammatory burden on risk of CVD; despite the fact that anti-inflammatory therapy as treatment for atherosclerosis has received little attention. However, only few studies have addressed the impact of inflammation lowering drugs use in the management of IBD on risk of CVD.

In the study by Bewtra *et al*^[44] sub-analyses stratifying between users and non-users of 5-aminosalicylic (5-ASA), a drug potentially possessing aspirin like properties, revealed a significant decreased risk of IHD in IBD patients receiving 5-ASA compared to never users (IRR = 1.16 *vs* 1.36 respectively; $P = 0.02$)^[12]. Restricting analyses to long-term use of 5-ASA (defined as three or more redeemed prescriptions) further strengthened the finding of a preventive effect of 5-ASA on IHD (further decrease in IRR = of IHD to 1.08; 95%CI: 0.98-1.19). Interestingly, this observation of a preventive effect of 5-ASA on IHD was only present in IBD patients receiving oral corticosteroids which in this case was used as a proxy for disease severity. These results could indicate that only IBD patients with more severe disease or increased disease activity, are at increased risk of IHD and in this case the aspirin-like moiety of 5-ASA may have preventive properties.

As stated previously, the pro-inflammatory cytokine TNF- α plays an important role in the inflammatory process in both the intestine and in development of atherosclerosis. Accordingly, biological drugs impairing this cytokine, *e.g.*, infliximab and adalimumab, have been outlined not only as potential preventive treatments lowering the risk of CVD in IBD but also as a potential treatment for atherosclerotic disease as IHD

in the general population. The direct and indirect effects of the TNF- α cytokine on the cardiovascular system is very complex and to some extent paradoxical. It is beyond the scope of the present review to give a detailed description of the pathological effects of TNF- α , but overall TNF- α tends to have both beneficial and harmful effects on the cardiovascular system, both in *in vitro* and *in vivo* studies; suggestively caused by a TNF- α concentration-related difference in effect and activation of different receptors^[45-49]. This might also be the reason for conflicting results in studies evaluating the effect of TNF- α antagonist as a potential treatment option for atherosclerosis and IHD^[48,50].

A study by Greenberg *et al*^[51] evaluated on CV events associated with TNF- α antagonist treatment among more than 10000 patients with rheumatoid arthritis (RA) and found that TNF- α antagonists treatment was associated with a reduced risk of cardiovascular events compared to RA patients treated with traditional disease-modifying antirheumatic drugs (HR = 0.39; 95%CI: 0.19-0.82). The risk of CVD, including both IHD and CVE, in IBD patients treated with TNF- α antagonists was elucidated in a Danish population-based study including more than 50000 IBD patients. Thirty-one TNF- α antagonist-exposed patients and 2641 unexposed patients developed IHD, yielding an adjusted RR of 0.85 (95%CI: 0.59-1.24) whereas the risk of CVE associated with TNF- α antagonists was 1.42 (95%CI: 0.82-2.45)^[52]. Thus, point estimates indicate a protective effect of TNF- α antagonist on IHD but at the same time suggest TNF- α antagonists to be a risk factor for CVE, though noteworthy none of the estimates reached statistical significance. The complexity of TNF- α and the therapies targeting the cytokine demands for forthcoming intensive and thorough research in the field before any clear evaluation can be fulfilled.

A recent interest has been raised to the HMG-CoA-reductase inhibitors (statins), drugs mainly used for hyperlipidemia but comprise pleiotropic properties as pro-apoptotic, anti-angiogenic, and anti-inflammatory effects. The anti-inflammatory capacity of statins has been evaluated in IBD patients in a large retrospective study by Crockett *et al*^[53] revealing a 18% reduction in initiation of oral steroids in IBD patients (HR = 0.82; 95%CI: 0.71-0.94) and an even greater reduction for UC patients (HR = 0.75; 95%CI: 0.62, 0.91). Future studies are needed to clarify the beneficial effect of statins in IBD and whether a potential synergetic effect may develop due to the potential of both lowering the risk of atherosclerosis and the inflammation in IBD.

CONCLUSION

The association between venous thromboembolic events and IBD is well-established and may cause significant morbidity and mortality. Although antithrombotic prophylactic treatment is recommended for hospitalized IBD patients, surveys have shown that these recommendations are by far not followed in practice and greater

attention to this issue is warranted.

Regarding arterial thromboembolic diseases, it seems plausible and it is further supported by recent literature, that the risk of CVD is increased in IBD patients, particularly during flares. The elevated risk is most likely due to an increased atherosclerotic burden triggered by inflammatory mediators, such as CRP, interleukin 6, and TNF- α .

Future large, prospective longitudinal studies are needed to determine the true risk of CVD in IBD and to further characterize preventive and risk factors. It is of particular interest whether tight control of the IBD-related inflammation could lower the progression and early development of atherosclerosis in these patients.

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