Inflammatory Bowel Disease and Atherosclerotic Cardiovascular Disease

JACC Review Topic of the Week

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ABSTRACT

Chronic inflammatory diseases including human immunodeficiency virus infection, psoriasis, rheumatoid arthritis, and systemic lupus erythematosus predispose to atherosclerotic cardiovascular disease (ASCVD). Inflammatory bowel disease (IBD) is a common chronic inflammatory condition, and the United States has the highest prevalence worldwide. IBD has so far been overlooked as a contributor to the burden of ASCVD among young and middle-age adults, but meta-analyses of cohort studies suggest that IBD is an independent risk factor for ASCVD. This review discusses the epidemiological links between IBD and ASCVD and potential mechanisms underlying these associations. ASCVD risk management of patients with IBD is challenging because of their young age and the inability of current risk scores to fully capture their increased risk. The role of IBD in current primary prevention guidelines is evaluated, and strategies for enhanced ASCVD risk reduction in patients with IBD are outlined. Finally, the authors discuss knowledge gaps and future research directions in this innovative field. (J Am Coll Cardiol 2020;76:2895–905) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide, and further efforts are warranted to enhance its prevention among young adults (1). Certain conditions and features typical of young and middle-age adulthood, such as chronic inflammatory conditions and adverse gestational features, are independently associated with incident ASCVD (2–6). In recent years, these conditions are gaining increasing visibility as potential targets for personalized, timely preventive interventions.

Chronic inflammation is a powerful driver of atherogenesis, thrombosis, and ASCVD events (2–5). Patients with conditions such as human immunodeficiency virus infection, psoriasis, and rheumatoid arthritis experience accelerated atherosclerosis (3–5). These patients have an increased burden of subclinical carotid and coronary plaque, more frequent high-risk plaque features, and higher rates of ASCVD events compared with healthy controls (7–10). Recently, CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) and COLCOT (Colchicine Cardiovascular Outcomes Trial) provided further high-quality evidence of the causal link between systemic inflammation and ASCVD (11,12).

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Inflammatory bowel disease (IBD) is a chronic condition encompassing ulcerative colitis (UC), Crohn’s disease (CD), and indeterminate colitis, all of which involve chronic inflammation of the intestinal tract, often with evidence of increased systemic inflammation and other extraintestinal manifestations (13). IBD currently affects 6.8 million globally (14), and large meta-analyses of cohort studies have reported associations between IBD and coronary heart disease (CHD) or ASCVD events, adjusting for traditional risk factors (15-17). The potential underlying mechanisms are multiple and are further sustained by microbiome disturbances, as well as by the frequent use of steroids in these patients.

Preventive cardiologists face important challenges when managing cardiovascular risk in patients with IBD. These include limited available guidance and the inability of commonly used clinical risk estimators to fully capture their excess ASCVD risk. To shed light on these aspects, in this review we describe the epidemiological links between IBD and ASCVD and potential mechanisms underlying these associations. We then discuss the role of chronic inflammatory conditions in current primary prevention guidelines and targeted strategies for ASCVD risk reduction specifically in patients with IBD. Finally, we outline knowledge gaps and future directions in this field.

IBD: THE BASICS

EPIDEMIOLOGY. Globally, more than 6.8 million patients are affected by IBD (14). Overall, the prevalence has increased as a result of low mortality rates, while the incidence of IBD has been stable or has decreased in North America and Europe (18). However, since 1990 the incidence has been rising in large, newly industrialized countries in Africa, Asia, and South America (18). In 2017, the global age-standardized prevalence of IBD was 84.3 per 100,000 population, up from 79.5 in 1990 (14). The United States had the highest age-standardized prevalence at 464.5 per 100,000, followed by the United Kingdom at 449.6 per 100,000 (14). The peak incidence of IBD occurs between the second and fourth decades of life, resulting in a long lifetime exposure to chronic systemic inflammation in these patients.

ETIOLOGY. IBD is thought to be the result of complex interactions among the environment, microbiota, and immune system in genetically susceptible persons (Figure 1). More than 200 risk loci have been identified for IBD, many of which are associated with immune function (19). One such gene, nucleotide oligomerization domain 2 (NOD2), encodes an intracellular pattern recognition receptor that plays a role in defense against intracellular bacteria and immune response to commensal microbes (20,21). Mutations in NOD2 are associated with decreases in anti-inflammatory cytokine interleukin (IL)-10 and increased numbers of mucosa-associated bacteria (22).

There are numerous environmental factors linked to the development of IBD. Urban living, appendectomy, tonsillectomy, consumption of soft drinks, and antibiotic use have been identified as risk factors (23). Smoking is a risk factor for CD, while it seems to protect against UC, the underlying mechanisms not being fully understood (24,25). Physical activity, breastfeeding, and Helicobacter pylori infection have been found to be associated with reduced risk for IBD (23). To date, the strongest risk factor identified is a positive family history of IBD (26).

MECHANISMS. The microbiome in patients with IBD is altered compared with that of healthy controls (27). In fact, some studies have shown that there is a distinct microbial signature that can be used to identify stool samples of patients with CD from those without (28). In general, Firmicutes species are decreased while Proteobacteria species are increased. The composition of the gut microbiota in IBD is less diverse and shows greater instability over time compared with that of healthy subjects (29).
However, controversy remains as to whether the changes in the microbiota seen with IBD are causative or rather a result of inflammation.

Alterations in both the innate and adaptive immune systems are thought to occur in IBD (30). Changes in innate immunity, including antigen-presenting cell signaling, regulation of intracellular bacteria, and production of defensins, result in an exaggerated adaptive immune response to dietary, commensal, and self-antigens, culminating in inflammation. In IBD, mucosal macrophages secrete increased amounts of the proinflammatory cytokines IL-1β, IL-6, IL-23, and tumor necrosis factor (TNF) and lead to production of interferon-γ by local mononuclear cells (31). Dendritic cells express increased Toll-like receptor 2 and 4 levels and produce more of the proinflammatory cytokines IL-12 and IL-6 (32). Variations in the IL-12/IL-23 pathway shift the immune response toward inflammatory T cell pathways mediated by T helper (Th) 17 and Th1 responses (33). Th17 cells produce IL-17, a potent proinflammatory cytokine, which when treated selectively in psoriasis reduces coronary plaque (34). The Th1 response is characterized by the production of TNF and interferon-γ (35). These 2 cytokines have been shown to be synergistic in the development of atherosclerosis and cholesterol crystals in psoriasis (36,37). The secretion of cytokines from proinflammatory T cell subsets is thought to be connected to epithelial barrier dysfunction, increased expression of endothelial adhesion molecules, and collagen production, with resulting inflammation and tissue damage (35).

**CLINICAL COURSE.** Besides gastrointestinal symptoms, IBD is a systemic disease, and 40% of patients develop extraintestinal manifestations. Importantly, patients with IBD typically experience active symptoms followed by (often long) remissions with very low inflammatory activity.

**EPIDEMIOLOGICAL LINKS BETWEEN IBD AND ASCVD**

Several meta-analyses, including 2 recent ones combining up to 27 cohort studies, support an independent association between IBD and subsequent ASCVD. Specifically, a 2017 meta-analysis including 10 cohort studies demonstrated a multivariate-adjusted independent association between IBD and incident CHD (pooled relative risk [RR]: 1.24; 95% confidence interval [CI]: 1.14 to 1.36). The same was true in subgroup analyses restricted to CD (adjusted RR: 1.24; 95% CI: 1.04 to 1.48) and UC (adjusted RR:
In both IBD and cardiovascular disease (CVD), compositional changes in the gut microbiota including a decrease in communal diversity, decrease in members of the Firmicutes phylum, and decreased butyrate production occur. The latter leads to intestinal epithelial cell apoptosis and barrier dysfunction with translocation of lipopolysaccharide (LPS) and initiation of an inflammatory cascade. The resulting damage activates procoagulant pathways, and inflammatory cytokines alter glucose and lipid metabolism. HDL = high-density lipoprotein; TLR = Toll-like receptor; other abbreviations as in Figure 1.
1.21; 95% CI: 1.17 to 1.24) (15). A subsequent, larger meta-analysis reported consistent associations between IBD and CHD (pooled RR: 1.17; 95% CI: 1.07 to 1.27), myocardial infarction (RR: 1.12; 95% CI: 1.05 to 1.21), and incident cerebrovascular disease (RR: 1.25; 95% CI: 1.08 to 1.44); all of which were stronger among women (16).

These meta-analyses confirmed the findings from landmark cohort studies such as a nationwide Danish study of 4.3 million people including 28,833 patients with IBD followed for up to 13 years, in which IBD was associated with CHD events adjusting for multiple potential confounders (17). More recently, a 2019 U.S. study using cross-sectional data from 26 nationwide health care systems and including about 290,000 patients with IBD 20 to 65 years of age also reported a strong association between IBD and a history of myocardial infarction. The demographics- and risk factor-adjusted odds ratio was 1.25 (95% CI: 1.24 to 1.27), and stronger associations were observed for younger ages (38). It must be noted, however, that findings from cross-sectional studies have been heterogenous. Nevertheless, most of those studies had important limitations, including not only an inherent inability to establish temporal relationships but frequent restriction of study populations to hospitalized patients (39).

Studies also suggest that active disease in IBD is associated with a particularly increased risk for cardiovascular events (40). A study of 20,795 patients from Denmark showed that the risk for myocardial infarction, stroke, and cardiovascular death was significantly higher during IBD flares, while it was similar to that in control subjects during remission (40). Furthermore, the risk for ASCVD seems to be particularly increased during the first year after IBD diagnosis, which is likely related to disease activity.

IBD is also associated with a 2- to 3-fold higher risk for venous thromboembolic events, particularly...
during acute flares (41–43), most likely the consequence of a hypercoagulable state. An increased risk for mesenteric ischemia has been reported in meta-analyses as well (43,44). Conversely, an association between IBD and cardiovascular mortality has not been observed (16,43,45). Although speculative, potential explanations to this include the relatively young age of the IBD population and low case-fatality rates of ASCVD events in this age group. More research is needed to better understand this null association.

**POTENTIAL MECHANISMS INVOLVED IN THE IBD-ASCVD LINK**

Multiple processes that are chronically activated in patients with IBD have been implicated in the pathogenesis of ASCVD. These include local and systemic inflammation (see “Mechanisms” section); gut microbiome abnormalities (27,46), endothelial dysfunction (47), thrombosis (48), lipid dysfunction (49), and the deleterious effects of some IBD therapies, particularly corticosteroids, which are associated with insulin resistance, hypertension, and dyslipidemia (17,50). Figures 2 to 5 summarize some of these potential mechanisms. More research is needed in this area, with special attention to the relative importance of each of these mechanisms, a better understanding of potential differences with those described for other chronic inflammatory conditions, and the identification of additional novel mechanisms that could serve as therapeutic targets for ASCVD risk reduction interventions.

IBD and ASCVD also share some upstream risk factors, which place patients at risk for both conditions. For instance, Western lifestyles have been linked with both diseases (13). Chronic stress is associated with an increase in inflammatory markers such as high-sensitivity C-reactive protein and IL-6, and in other inflammatory diseases, including psoriasis, elevated neural activity due to stress associates with vascular inflammation and coronary plaque (51). Anxiety and mental stress are associated with the development of ASCVD, as well as IBD among genetically predisposed persons (52,53). Chronic stress is also associated with the occurrence of symptomatic flares of IBD (52,53). Tobacco is associated with deleterious effects in CD, including higher risk for disease development, disease progression, and poor response to medical and surgical management, whereas it has protective effects in UC (24,25). It has been suggested that nicotine may inhibit cytokines such as IL-1β and IL-8 (54), and smoking may alter
smooth muscle tone and influence endothelial function through nitric oxide production. It may also affect gut barrier integrity. However, trials of nicotine replacement therapy in UC have not shown convincing results (55).

In addition, various studies demonstrate increased prevalence or incidence of several traditional risk factors, including diabetes and hypertension, in patients with IBD compared with healthy peers (17,38,50,56). These observations are consistent with the mechanisms described earlier and identify opportunities to enhance ASCVD prevention in these patients.

**IBD IN CURRENT PRIMARY PREVENTION GUIDELINES**

**RISK MANAGEMENT.** There is currently a lack of evidence from interventional studies defining optimal ASCVD prevention in patients with IBD. The guidelines for primary prevention of ASCVD from the American College of Cardiology/American Heart Association and the European Society of Cardiology acknowledge the relevance of chronic inflammatory conditions as independent mechanisms for ASCVD and recommend consideration of those as risk enhancers or modifiers to be used to make a stronger case for chronic statin therapy among patients at borderline or intermediate risk (57,58). Additional guideline recommendations for risk assessment and management in patients with chronic inflammatory conditions are summarized in Table 1.

**CONSIDERATIONS RELEVANT TO RISK ASSESSMENT.** Patients with IBD are often young adults, who either do not qualify for 10-year ASCVD risk assessment (<40 or 50 years of age) or are assigned low-risk estimations as a consequence of their chronological age. In addition, some mechanisms by which IBD increases the risk for ASCVD may not be captured by clinical risk scores, potentially leading to risk underestimation. Indeed, the predictive accuracy of tools such as the pooled cohort equations or the SCORE charts has not been validated in adults with IBD. Specific guidance and adapted, validated risk stratification tools are needed in this typically young patient population.

In addition, no guidance was provided in either the American or European documents in terms of risk heterogeneity among patients with inflammatory conditions such as IBD or on the use of further risk

| **TABLE 1** Recommendations in the 2018 and 2019 ACC/AHA and ESC Guidelines Relevant to IBD for ASCVD Risk Assessment |
|-----------|---------------------------------------------------------------|
| **Guideline** | **Role of Inflammatory Conditions** | **Recommendation** |
| 2018 AHA/ACC/multisociety guideline on the management of blood cholesterol | Risk-enhancing factors: “chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, or HIV/AIDS” | • Clinicians should first focus on helping patients with these diagnoses to optimize their lifestyle habits (in text). |
| | | • In adults 40–75 yrs of age with LDL-C 70-189 mg/dl (1.7–4.8 mmol/l) who have 10-yr ASCVD risk of 7.5% or higher, chronic inflammatory disorders are risk-enhancing factors, and in risk discussion, favor moderate-intensity statin therapy or high-intensity statin therapy (Class IIa, LOE: B-NR). |
| | | • In patients with chronic inflammatory disorders or HIV infection, a fasting lipid profile and assessment of ASCVD risk factors can be useful 1) as a guide to benefit of statin therapy; and 2) for monitoring or adjusting lipid-lowering drug therapy before and 4-12 weeks after starting inflammatory disease-modifying therapy or antiretroviral therapy (Class IIa, LOE: B-NR). |
| | | • The accuracy of the ASCVD risk estimator has not been well validated for adults with chronic inflammatory disorders or HIV infection. Assessment of traditional risk factors often has resulted in underestimation of actual risk and the potential for undertreatment with pharmacological therapy. Traditional risk factors should be assessed early in the disease process and then modified (in text). |
| 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease | Risk-enhancing factors: “chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, lupus, or HIV/AIDS” | • Same as above: assessing for risk-enhancing factors (including chronic inflammatory conditions) can help guide decisions about preventive interventions in select individuals. |
| | | • Clinicians should not down-classify risk in patients who have coronary artery calcium scores of zero but who are persistent cigarette smokers, have diabetes, have family histories of ASCVD, or, possibly, have chronic inflammatory conditions. In the presence of these conditions, a coronary artery calcium of zero does not rule out risk from noncalcified plaque or increased risk of thrombosis (in text). |
| 2019 ESC guidelines for the management of dyslipidemias | Risk modifiers: “chronic immune-mediated inflammatory disorders” | • There are a few specific groups of patients in whom an underlying disease confers such increased risk and in addition in whom the standard treatments may themselves cause dyslipidemia that may contribute to the risk for ASCVD. These include 1) chronic immune-mediated inflammatory disease; 2) patients with HIV infection; and 3) patients with severe mental illness. The risk management principles are the same in these patient groups, but their management may need to address specific issues related to individual dyslipidemias and drug safety (in text). |
| | | • The use of lipid-lowering drugs only on the basis of the presence of CIID is not recommended (Class III, LOE: C). |

**ACC** — American College of Cardiology; **AHA** — American Heart Association; **AIDS** — acquired immune deficiency syndrome; **ASCVD** — atherosclerotic cardiovascular disease; **CIID** — chronic immune-mediated inflammatory disease; **ESC** — European Society of Cardiology; **HIV** — human immunodeficiency virus; **IBD** — inflammatory bowel disease; **LDL-C** — low-density lipoprotein cholesterol; **LOE** — Level of Evidence; **NR** — nonrandomized.
assessment tools to personalize risk management in this population. Actually, the 2019 American College of Cardiology/American Heart Association document explicitly discussed the uncertainty of the prognostic implications of a coronary artery calcium score of zero, a strong negative risk marker in the general population, in patients with inflammatory conditions (57).

**PROPOSED STRATEGIES FOR ENHANCED ASCVD PREVENTION AMONG PATIENTS WITH IBD**

Despite limited recommendations in current guidelines, the following interventions may help enhance ASCVD risk prevention in patients with IBD (Central Illustration).

**TEAM APPROACH.** As the predisposing factors for accelerated atherosclerosis are likely present early in the natural history of IBD, it is imperative to start preventive care soon after diagnosis (59). Importantly, studies suggest that patients with IBD receive suboptimal ASCVD prevention care, worse than those without IBD (60,61). Given the strong link between specific IBD features, clinical stages, and therapies, and ASCVD risk, optimized ASCVD prevention among patients with IBD requires coordinated efforts with input from both gastroenterologists and preventive cardiologists. The ultimate goal should be a patient-centered approach emphasizing shared decision making with an informed and engaged patient.

**TRADITIONAL CARDIOVASCULAR RISK FACTORS.** Established cardiovascular risk factors should be screened for in all patients with IBD, including hypertension, diabetes, and dyslipidemia, followed by aggressive management. Importantly, a deeper
understanding of treatment targets of specific risk factors such as hypertension is needed in patients with IBD, given the possibility of marked volume losses during flares. Frequent rescreening of such risk factors should be considered among apparently cardiovascular-healthy patients. Also, given the multitude of harmful effects of tobacco smoking, we pose that tobacco cessation should be pursued in all patients with IBD (including UC), and other approaches to improve the course of UC should be prioritized. Lifestyle modification with regular exercise and stress and anxiety management should be emphasized too. These interventions are not only beneficial for ASCVD prevention but may improve the course of IBD and reduce risk for relapse (62,63).

**IBD Modification for ASCVD Risk Reduction.** Disease activity is an important risk marker for ASCVD, and optimization of IBD management in all patients should be pursued as recommended in relevant guidelines (64), particularly during active flares. The IBD-ASCVD link also raises the question of whether disease-modifying therapies such as anti-inflammatory and immunomodulatory agents could help mitigate ASCVD risk. A large Danish cohort study showed that 5-aminosalicylate use was associated with a lower risk for ischemic heart disease (17). Interestingly, this association was dose dependent and present only in patients taking corticosteroids, which was used as a proxy of disease severity.

Novel therapies such as immunomodulators and biologic agents have shown potential for ASCVD risk reduction in chronic inflammatory diseases such as rheumatoid arthritis and human immunodeficiency virus infection (59,65). In psoriasis, treatment of skin disease with biologic therapy has been associated with reductions in coronary inflammation (66), non-calcified plaque burden (34), and vascular inflammation (67), suggesting that treatment of primary sources of inflammation is beneficial to vascular health. In IBD, in a recent French observational study including 177,827 patients, use of anti-TNF agents was associated with decreased risk for acute arterial events, including CHD, cerebrovascular disease, and peripheral artery disease (68). Despite the large sample size and the use of complex multivariate models, these promising results need to be confirmed in experimental settings. Such studies will also provide valuable insights into the cardiovascular safety of these medications.

**EVIDENCE GAPS AND FUTURE DIRECTIONS**

A number of evidence gaps remain to be addressed (Table 2). A better understanding of the mechanisms involved in the development of ASCVD in patients with IBD is needed. This is particularly true for intermediate mechanisms and early coronary atherosclerotic changes. Such research will help better characterize ASCVD risk heterogeneity among patients with IBD, aiding the early identification of highest risk patients, as well as of atherosclerosis-resilient phenotypes in which aggressive ASCVD preventive therapies may not be justified. Also, more detailed knowledge of these mechanisms will inform the development of tailored risk assessment tools. In addition, this research will help define the potential role that cardiovascular imaging tools such as computed tomographic angiography might have in characterizing coronary plaque burden and characteristics associated with higher risk for future ASCVD events specifically in these patients. Given the increased burden of plaque and of high-risk plaque features in patients with chronic inflammatory conditions, whether such techniques can improve the identification of IBD candidates for intensive ASCVD preventive interventions beyond traditional risk factors and the coronary artery calcium score needs to be evaluated.

Randomized trials are warranted to better understand the potential role of IBD-modifying therapies in the reduction of ASCVD risk. Among highest risk patients, a better understanding of the value of preventive interventions targeting key pathophysiological

| **TABLE 2** Key Evidence Gaps and Future Research Pathways in IBD and ASCVD |
|---------------------------------|---------------------------------|
| **Epidemiology**                |                                 |
| Identification of IBD patient subgroups with highest risk for ASCVD | Characterize the reasons underlying the lack of association between IBD and CVD death |
| **Pathophysiological and mechanistic research**                  |                                 |
| Better understanding of mechanistic links between IBD and ASCVD, with special attention to genetics, micro-RNA, and lipid dysfunction | Evaluation of similarities and differences in underlying mechanisms involved in the IBD-ASCVD connection compared with those in other chronic inflammatory conditions |
| Determinants of ASCVD risk heterogeneity among patients with IBD | Burden of coronary atherosclerotic plaque at different stages of IBD |
| Characterization of the architectural and compositional features of coronary plaque associated with highest risk for ASCVD events in patients with IBD | |
| **Risk assessment**             |                                 |
| Develop risk assessment tools that account for increased ASCVD risk in patients with IBD | Risk stratification tools that allow the identification of patients with IBD at highest ASCVD risk |
| Clarify the prognostic value of the CAC score in this patient population, particularly CAC – 0 | Characterize the role that advanced cardiovascular imaging techniques (e.g., coronary computed tomographic angiography) can have in the ASCVD risk assessment of these patients |
| **Risk management**             |                                 |
| Clarify the value of IBD-modifying therapies in ASCVD risk reduction | Definition of most effective cardiovascular preventive interventions in high-risk patients with IBD |
| Identification of cost-effective ASCVD risk management approaches in IBD populations | |

CAC = coronary artery calcium; RNA = ribonucleic acid; other abbreviations as in Table 1.
mechanisms, such as lipid dysfunction mechanisms or prothrombosis, will also be needed.

CONCLUSIONS

IBD affects 6.8 million patients globally and is independently associated with increased risk for ASCVD events. This connection likely operates through various mechanisms and is not fully captured by traditional risk scores. A strong collaboration between gastroenterologists and preventive cardiologists, aggressive screening and management of traditional risk factors, and optimal management of IBD, particularly during flares, can help decrease ASCVD risk in this patient population. Upcoming research into novel mechanisms underlying the IBD-ASCVD connection, cardiovascular risk heterogeneity among patients with IBD and its determinants, and the effects of disease-modifying IBD therapies will help inform targeted preventive interventions aimed at further reducing ASCVD risk in patients with IBD most likely to have events.

AUTHOR DISCLOSURES

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