Cardiovascular Comorbidities and Inflammatory Bowel Disease: Causes and Consequences

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Abstract: Patients with inflammatory bowel disease (IBD) have an increased risk of cardiovascular disease (CVD) such as myocardial infarction and stroke. CVD in patients with IBD might occur in those with younger age and active disease, which are not traditional risk factors of CVD. Atherosclerotic CVD (ASCVD) and IBD are both proinflammatory conditions, and the underlying chronic inflammation might drive ASCVD risk. Decreasing inflammation might reduce this risk; however, data are limited. IBD medications can increase or decrease ASCVD risk. There are no specific guidelines or modalities to assess ASCVD in IBD. Early detection and risk stratification strategies have been established in other chronic inflammatory disorders. This article discusses causes of CVD in IBD and strategies to modify the consequences.

Cardiovascular disease (CVD) is the leading cause of mortality in the United States.[1] Increased risk of CVD such as myocardial infarction (MI) and stroke as well as CVD mortality are well established in chronic inflammatory disorders (CIDs) such as rheumatoid arthritis (RA), psoriasis, and lupus, and early risk stratification and strategies to minimize this risk are recommended.[2] Several studies have demonstrated an increased risk of CVD in patients with inflammatory bowel disease (IBD), which affects approximately 3 million Americans and 6.8 million people worldwide.[3-5] Currently, there are no guidelines to risk stratify CVD in patients with IBD. CVD, in particular atherosclerotic CVD (ASCVD), in IBD does not correlate well with traditional risk factors of ASCVD such as advanced age, obesity, and hyperlipidemia.[6-8] Nontraditional risk factors such as younger age, female sex, and IBD activity have been associated with ASCVD events.[6,7,9,10] IBD and atherosclerosis are both proinflammatory conditions with common independent underlying mechanisms of immune, endothelial, and platelet dysfunction in genetically predisposed individuals. Understanding the link between the 2 processes will help risk stratify IBD patients with

Table 1. Classification of Cardiovascular Disease in Inflammatory Bowel Disease

Venous cardiovascular disease	Arterial cardiovascular disease	
	Ischemic/atherosclerotic cardiovascular disease	Nonischemic cardiovascular disease
• Deep venous thrombosis • Pulmonary embolism • Budd-Chiari syndrome • Retinal vein thrombosis • Pseudotumor cerebri • Cerebral venous sinus thrombosis	• Coronary artery disease • Cerebrovascular disease • Peripheral arterial disease • Mesenteric ischemia • Heart failure	• Arrhythmia • Pericarditis/myocarditis • Vasculitis • Nonischemic cardiomyopathy • Heart failure

respect to their heart disease and help providers select the most appropriate treatment strategy. Current data are limited, and in-depth information regarding mechanisms and factors that influence CVD in IBD remains a major knowledge gap.[11-14] There are also limited data regarding the role of medications in reducing CVD risk. This article aims to enhance understanding of CVD in patients with IBD by classifying it as ischemic (ASCVD) or nonischemic (Table 1); discusses epidemiologic data related to risk factors and mechanisms of CVD in IBD (Table 2); and examines assessment tools, medication data, and proposed strategies to modify this risk (Table 3). Review of these aspects and identifying knowledge gaps will likely help alter the consequences of CVD in patients with IBD.

Table 2. Risk Factors for ASCVD in IBD[3,7,9,27]

Traditional risk factors[1]
• Age (>45 years in men, >55 years in women) • Male sex[a] • Race[b] • Family history of ASCVD event • Smoking • Hypertension • Hyperlipidemia • Diabetes • Obesity • Chronic kidney disease
IBD-related risk-enhancing factors[7,9,27]
• IBD activity • Younger age (<45 years)

[a]Some studies have reported a higher prevalence of ASCVD in female IBD patients, although data are conflicting.[9,10]
[b]African American adults are at higher risk of ASCVD compared with White adults.[1]

ASCVD, atherosclerotic cardiovascular disease; IBD, inflammatory bowel disease.

Causes of Cardiovascular Disease in Inflammatory Bowel Disease

To better understand the risk and common mechanisms, this article categorizes CVD in IBD into venous or arterial disorders and focuses on the latter (Table 1). Arterial CVD can be further classified as (1) ischemic CVD or ASCVD such as coronary artery disease, cerebrovascular disease (stroke), peripheral arterial disease (PAD), and mesenteric ischemia; and (2) nonischemic CVD such as arrhythmias, pericarditis, nonischemic cardiomyopathies, and valvular heart disease. Heart failure (HF) can be ischemic from ASCVD or nonischemic from cardiomyopathies or congenital causes. Epidemiologic data, risk factors, and possible mechanistic links are examined in the following sections.

Ischemic or Atherosclerotic Cardiovascular Disease
Epidemiologic Data ASCVD or ischemic CVD is related to atherosclerotic plaque burden in the arterial vasculature and is often referred to with the term major atherosclerotic cardiovascular event (MACE). The classical definition of MACE comprises nonfatal MI, nonfatal stroke, cardiac revascularization (percutaneous cardiovascular stent or coronary artery bypass graft), and cardiovascular mortality. There is a 2-fold increased risk of MACE in patients with IBD.[3,6,15,16] The increased prevalence of ASCVD is now well recognized in IBD patients.[6,15,17-21] However, in patients with IBD, the role of traditional risk factors of ASCVD such as hypertension, hyperlipidemia, obesity, and smoking needs further investigation.[22,23] Multiple population-based cohort and case-control studies across different regions of the world have shown a higher prevalence of ASCVD in younger and female IBD patients without higher rates of obesity or hyperlipidemia.[3,7,10,24-26] Lee and colleagues showed higher prevalence of premature (<55 years; odds ratio [OR], 1.14; 95% CI, 1.08-1.21) and extremely premature (<40 years; OR, 1.82; 95% CI, 1.52-2.17) ASCVD in IBD patients compared with non-IBD patients in a US veteran

Table 3. Proposed Recommendations for ASCVD in IBD

Recommendations	Comments
Assess baseline risk for ASCVD at clinic visit • ACC/AHA 10-year risk calculator – United States • Systematic Coronary Risk Evaluation (SCORE2) – Europe	• Asymptomatic patients with no prior ASCVD event should undergo risk assessment by clinical risk calculators based on traditional risk factors • Chronic inflammatory conditions deserve consideration as risk-enhancing factors[a] • Patients at risk should be referred to a cardiology clinic for early risk management strategies such as noninvasive testing and initiation of statins
Lifestyle modifications should be recommended to patients with IBD to improve cardiovascular health	• Mediterranean diet • Regular exercise • Smoking cessation
Early and aggressive control of disease	• Early escalation of therapy (especially in young and female patients) is recommended • IBD flares should be avoided • Corticosteroid use should be minimized • Anti–tumor necrosis factor medications may be of benefit but need caution in patients with severe heart failure (NYHA class III and IV) at higher doses • Consider prior ASCVD risk when starting Janus kinase inhibitors • Ozanimod does not increase risk of ASCVD events, but conduction defects should be considered at initiation of therapy

[a]Risk-enhancing factors according to the ACC/AHA clinical guidelines 2019 update are RA, SLE, psoriasis, and HIV/AIDS[83] and according to the ESC guidelines for chronic coronary syndrome 2019 are IBD, RA, SLE, cancer, and cancer treatment.[84]

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; ESC, European Society of Cardiology; IBD, inflammatory bowel disease; NYHA, New York Heart Association; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

population.[7] Our recent analysis of a large cohort of US veterans showed that IBD was an independent risk factor for MI in 63,155 IBD patients compared with 252,595 non-IBD patients (adjusted hazard ratio [aHR], 1.23; 95% CI, 1.11-1.36). When stratified by age, incidence of MACE was significantly higher in patients with IBD vs controls less than 40 years of age (0.49% vs 0.40%; P=.03).[27] Aggarwal and colleagues retrospectively studied 131 IBD patients at a single center with coronary artery disease diagnosed by coronary angiogram, which is a gold standard for atherosclerosis assessment. Compared with 524 controls, IBD patients were younger, had lower prevalence of active smoking, and had lower body mass index.[24] Hence, nontraditional risk factors of IBD activity might contribute to the process of atherosclerosis.

Although there is more consistent information about ASCVD risk in IBD patients, the outcomes of MI and mortality in patients with IBD during hospitalization are unclear. CVD complications contribute to increased length of stay and cost of hospitalization, especially in older patients, but the risk of CVD mortality is debatable.[3,21,28] Several retrospective national administrative database cohort studies have shown contrary results,

and significant heterogeneity has been reported in meta-analyses.[17,19,29-32] Population-based cohort studies have the advantage of analyzing a large number of patients; however, reporting of events is based on diagnosis codes that have potential for error, and the studies lack information on biologic medications that may influence outcomes. Many studies assess CVD events during the short period of hospital admission and do not assess readmissions.[17,18] The impact of IBD on CVD mortality needs to be further investigated.

Patients with IBD, especially those who are younger, are also at increased risk of PAD and mesenteric ischemia.[17,26,33] In a French cohort study, IBD patients had an increased risk of PAD (standardized incidence ratio, 1.27; 95% CI, 1.17-1.37) that was most significant in those with Crohn's disease who were less than 35 years old.[26]

Atherosclerotic Cardiovascular Disease Is Associated With Inflammatory Bowel Disease Activity An important aspect to consider is that ASCVD has been associated with disease activity in patients with IBD.[9,28,34,35] Assessing disease activity from large retrospective cohort studies has its limitations. Objective assessment of

disease activity with serum or stool biomarkers (fecal calprotectin) and endoscopy is not available in most studies.[3,36] However, a consistent pattern that has emerged over the years is that disease flare, as assessed by surrogate markers of active inflammation (such as corticosteroid use, time since diagnosis, and hospital admissions for IBD), is associated with increased incidence of ASCVD.[9,26,28,35] A recent study from UK Biobank reported a 19% higher risk of acute arterial events, defined as coronary, cerebral, and peripheral arterial events, in IBD patients (aHR, 1.19; 95% CI, 1.08-1.31), which was most pronounced in younger patients (39% higher risk in men <55 years of age and women <65 years of age) compared with non-IBD patients. High-sensitivity C-reactive protein (hsCRP) (aHR, 1.53; 95% CI, 1.15-2.03) and disease severity as assessed by IBD-related hospitalizations and surgeries (aHR, 5.4; 95% CI, 4.03-7.22) were independent risk factors. HsCRP in this study was assessed at 1 time point, but IBD was associated with increased acute arterial events even after adjusting for hsCRP, suggesting that chronic inflammation plays a role in long-term outcomes. The median follow-up duration was 15 years in this study.[34] Aarestrup and colleagues assessed ASCVD risk profiles in a Danish cohort and reported that patients with IBD had slightly lower cholesterol but a higher level of inflammatory markers (hsCRP and fibrinogen) when assessed at random time points during the disease course of the patients.[22] Decreasing the inflammatory burden may decrease ASCVD risk; however, it would be important to determine which medical therapy can decrease ASCVD risk independent of its role in controlling inflammation.

Mechanism of Atherosclerotic Cardiovascular Disease in Inflammatory Bowel Disease Atherosclerosis and IBD have a similar mechanism in which individuals with genetic predisposition develop immune, platelet, and endothelial dysfunction leading to chronic inflammation. The underlying chronic inflammatory process likely drives ASCVD in patients with IBD. Chronic inflammation in the gut can lead to systemic and extraintestinal manifestations (EIMs) of IBD such as arthropathy in the joints and uveitis in the eyes. Inflammation in the vascular bed can lead to atherosclerosis, MI, and stroke.[14]

It is now widely accepted that the underlying mechanism of atherosclerosis involves both innate and adaptive immune responses with platelet and endothelial dysfunction in genetically susceptible hosts, similar to IBD.[37] Various biomarkers of altered immune response (oxidized low-density lipoprotein, fibrinogen, nuclear factor [NF]-κB, interferon-γ, tumor necrosis factor [TNF]α) and endothelial dysfunction (CD40/CD40 ligand, endothelial precursor cells, matrix metallopeptidase, vascular cell adhesion molecule 1, intercellular adhesion molecule 1, P-selectin) have been studied and are associated with CVD events.[38] Inflammatory markers that are elevated in IBD such as CRP, interleukin (IL)-6, IL-1, IL-8, and TNFα have been shown to be predictive of future CVD events.[39] In addition, certain genetic factors such as common polymorphisms in nucleotide-binding oligomerization domain-containing protein 2/caspase recruitment domain-containing protein (NOD2/CARD15) have been independently reported in the pathophysiology of both atherosclerosis and IBD.[40] Some cytokine inhibitors, such as the IL-6 inhibitor tocilizumab, the TNF inhibitor adalimumab, and the IL-1 receptor–blocking agent anakinra (which also blocks IL-1α and IL-1β), have been studied in CVD drug trials in the general population and showed reduction in inflammatory markers such as CRP and modest benefit with respect to CVD outcomes.[41] The landmark CANTOS trial, published in 2017, showed promising results with a significant decrease in CVD events with the use of an IL-1β monoclonal antibody.[42] The take-home message was that it decreased CVD endpoints of MI and nonfatal stroke, irrespective of reduction in lipids, and this was evident in the subgroup of patients who showed significant reduction in IL-6.[43] However, the cost of the drug and higher incidence of fatal infections among the treatment group raise concerns about its clinical use.

Even though certain biomarkers such as IL-6, TNFα, and CRP are increased in both atherosclerosis and IBD, further investigation is needed to obtain a deeper understanding of the underlying mechanism to formulate specific treatment targets that address both inflammatory pathways.

Nonischemic Heart Disease
Arrhythmia

Epidemiologic Data Atrial fibrillation (AF) is the most common arrhythmia in patients with IBD. A meta-analysis by Zuin and colleagues reported a 2-fold increased risk of AF in IBD patients (OR, 2.26; 95% CI, 2.11-2.41). However, owing to the small numbers and significant heterogenicity in the 2 cohorts and 1 cross-sectional study included in the meta-analysis, further investigation is needed to determine the risk of AF in patients with IBD.[25] Kristensen and colleagues reported that the risk of AF and stroke was higher in IBD patients during flares and periods of disease activity, and this risk was not seen during periods of remission.[44] The prevalence of cardiac conduction disorders such as bradycardia in ulcerative colitis (UC) appears to be low.[45] The risk of other arrhythmias in patients with IBD has not been studied.

Mechanism Chronic inflammation has been implicated in the mechanism of AF.[46] Certain biomarkers such as IL-6

and CRP are common to the pathogenesis of both disease processes. Fibrogenesis, enhanced automaticity, atrial dilatation, and conduction defects have been implicated as possible mechanisms in other CIDs.[47] Can and colleagues performed a cross-sectional study in 79 IBD patients and found a significant delay in atrial conduction time (ACT) in IBD patients compared with controls. ACT is a risk factor for severe AF.[48] Conduction abnormalities such as increased P-wave dispersion, electromechanical delays, and QTc dispersion have been reported in adult and pediatric patients with IBD. These abnormalities predispose to atrial and ventricular arrhythmias.[49-52]

Further studies are needed to better define the baseline risk of arrhythmias in patients with IBD and its relationship to disease activity to develop appropriate tools for early detection and treatment of arrhythmias in these patients.

Pericarditis and Myocarditis

Epidemiologic Data   Pericarditis and myocarditis have been reported in patients with IBD[53-56] and may manifest as the presenting sign or even precede the diagnosis of IBD.[57,58] More commonly, they have been reported as adverse events of medications such as mesalamine, with some case reports of pericarditis induced by infliximab or thiopurine.[55,59-63]

Mechanism   Autoantigens have been implicated as a trigger for myocarditis, but complete understanding of the underlying mechanism remains unclear.[64] Acknowledging that myocarditis or pericarditis can be an EIM or complication of medical treatment of IBD will assist in early diagnosis and appropriate treatment. Collaborative efforts with a cardiologist and discontinuing or holding the possible inciting medication should be considered for timely management.

Heart Failure

Epidemiologic Data   HF can be caused by ischemic heart disease or nonischemic causes such as cardiomyopathies and congenital heart diseases. Patients with IBD have a 2-fold increased risk of HF, which is associated with periods of disease activity.[15,65] HF in IBD patients is associated with worse IBD and clinical outcomes.[66]

Mechanism   Inflammation can be both a cause and consequence of HF and plays a central role in disease pathogenesis and progression.[67] This has been well studied in the general population, including several clinical trials exploring inflammatory pathways as a target for HF treatment.[67] The role of the gut is of particular interest in HF due to 2 mechanisms. The first involves the release of endotoxins from the gut such as lipopolysaccharides during HF. The circulating endotoxins lead to activation of the NLRP3 inflammasome with subsequent maturation of proinflammatory cytokines (such as NF-κB, TNFα, IL-1β, IL-6, and IL-18), negative cardiac inotropic effects, fibrosis, and systolic and diastolic dysfunction.[67] Endotoxins released from the gut are elevated during episodes of decompensated HF and decreased after successful treatment of decompensation, supporting the role of the gut in the inflammatory process.[68] Second, HF is also associated with dysbiosis of the gut microbiome with low bacterial diversity.[69] Altering gut dysbiosis with dietary modifications and probiotics is being looked into as a therapeutic target for HF.[70]

Understanding the underlying mechanism of HF in patients with IBD is of particular importance due to its interplay with IBD medications such as corticosteroids and anti-TNF drugs.

Consequences of Cardiovascular Disease in Inflammatory Bowel Disease

The following sections will review modalities to assess CVD in IBD, current recommendations for CVD risk assessment in IBD and other CIDs, and the role of medications in CVD. Review of these aspects and identifying knowledge gaps will help identify areas of research that will alter the consequences of CVD in patients with IBD.

Modalities to Assess Cardiovascular Disease Risk in Inflammatory Bowel Disease

Although there are data that CVD risk is increased in IBD, there is limited information regarding modalities to assess this risk.[11] Only a few prospective studies have shown evidence of early signs of atherosclerosis in patients with IBD as measured by markers of subclinical atherosclerosis and vascular dysfunction.[71-73]

Clinical risk calculators such as the American College of Cardiology/American Heart Association (ACC/AHA) 10-year ASCVD risk calculator, Framingham Risk Score calculator, Reynolds Risk Score (RRS), and Systematic Coronary Risk Evaluation (SCORE2) are based on traditional risk factors for ASCVD. Most clinical scores do not take into account nontraditional risk factors such as disease activity and serologic markers that contribute to increased ASCVD risk in CIDs.[74,75] RRS is a risk prediction algorithm that has been used in the RA population owing to its inclusion of hsCRP, which is a marker of inflammation.[76] ASCVD or other risk prediction scores have not been validated in patients with IBD.

Modalities to assess ASCVD and vascular function can be broadly classified into those evaluating structural markers of atherosclerosis and those assessing endothelial or vascular dysfunction.[11] Structural imaging to assess for

plaque burden and coronary artery calcium deposition by computed tomography (CT) angiogram or noncontrast CT has not been widely studied in patients with IBD.[77] However, even preceding calcium or plaque deposition, chronic inflammation can lead to endothelial dysfunction as seen in patients with RA.[2] Endothelial dysfunction is an imbalance between vasodilating and vasoconstricting substances produced by endothelial cells. Endothelial dysfunction is characterized by upregulation of cellular adhesion molecules, compromised barrier function, increased leukocyte diapedesis, and increased vascular smooth muscle tone. These phenomena are related to impaired production of vasodilator substances such as nitric oxide as well as increased production of vasoconstrictor substances, including endothelin, which initiate a prothrombotic state.[39] Endothelial dysfunction is present in both IBD and atherosclerosis and is a precursor for CVD events.[39]

Arterial stiffness, which is a measure of endothelial function, is impaired in patients with IBD and can be assessed by pulse wave velocity. Endothelial or vascular dysfunction can also be classified as macrovascular or microvascular. Macrovascular (large vessel) dysfunction can be assessed by flow-mediated dilatation and carotid intima thickness via ultrasound and dysfunction in the microvasculature (small vessels) by EndoPAT.[11] However, the studies that have used these modalities in patients with IBD are small and lack long-term follow-up.

In addition, laser Doppler with microdialysis has been used to assess small vessel endothelial dysfunction in vivo.[78] This technique has not yet been studied in patients with IBD and might help in the understanding of how medications may alter vascular function in real time at a mechanistic level.

Currently, the only modalities available in the clinical setting to assess atherosclerosis are CT angiogram and noncontrast CT for the coronary artery calcium score. Even these have not been validated in IBD to determine whether they detect ASCVD or preclinical atherosclerosis appropriately, especially in younger patients with short-term disease. The assessment and treatment of ASCVD risk with clinical risk calculators in the primary care setting is suboptimal.[79] Hence, there remains a need to investigate ways to risk stratify ASCVD in IBD patients with methods that incorporate inflammation.

Recommendations for Assessment of Atherosclerotic Cardiovascular Disease in Chronic Inflammatory Disorders

The 2019 update of the ACC/AHA guidelines on primary prevention of CVD identifies CIDs such as psoriasis, RA, lupus, and HIV/AIDS as risk-enhancing factors.[80] Per ACC/AHA guidelines, all adults should undergo ASCVD risk assessment by using an ASCVD risk score calculator that incorporates traditional risk factors. In patients with borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (>7.5% to <20% 10-year ASCVD risk), risk-enhancing factors such as CIDs should be used to guide clinical decision-making for primary prevention strategies such as statin therapy. IBD is not incorporated in the 2019 ACC/AHA guidelines. However, guidelines published by the European Society of Cardiology in 2019 recognized IBD, along with other proinflammatory conditions such as cancer treatment, RA, and systemic lupus erythematosus (SLE), as needing more intensive risk screening, counseling, and management.[81]

There are well-established guidelines for the assessment of ASCVD in other CIDs such as RA, psoriasis, ankylosing spondylitis, and SLE per the European Alliance of Associations for Rheumatology (EULAR).[2,82] The key take-home point from these recommendations is that all patients with RA, ankylosing spondylitis, or psoriatic arthritis should be screened for ASCVD risk using SCORE2 at least once every 5 years so that lifestyle advice and CVD preventive treatment can be initiated when indicated.[83] A multiplication factor of 1.5 is recommended in RA patients to incorporate the role of the chronic inflammatory process. Aggressive management of disease activity, as well as avoiding and minimizing use of nonsteroidal anti-inflammatory drugs and corticosteroids, is recommended. The 2017 EULAR update was notable for being the first time to include the recommendation for screening of asymptomatic atherosclerotic plaque by carotid ultrasound in RA patients because the plaque reclassifies a considerable proportion of patients with RA into a more appropriate CVD risk group, which might change the indication to start statin therapy.[84] European consensus on EIMs in IBD established CVD as an EIM; however, there is a lack of specific recommendations to risk stratify patients with IBD.[85]

Cardiovascular Disease Risk and Inflammatory Bowel Disease Medications

IBD can be treated with various medications that can be broadly classified into (1) aminosalicylates/mesalamines, (2) corticosteroids, (3) immunomodulators, (4) biologics, and (5) small molecules. The following sections highlight CVD risk associated with medications of interest in current IBD management such as corticosteroids, anti-TNF drugs, Janus kinase (JAK) inhibitors, IL-12/IL-23 inhibitors, and sphingosine-1 phosphate (S1P) receptor modulators.[11,86,87]

Corticosteroids Corticosteroid use has been associated with increased risk of HF and ASCVD in the general population.[67,88] Minimizing corticosteroid use and

transitioning to corticosteroid-sparing medications are recommended in CIDs to reduce CVD risk.[82] In SLE patients, a dose-dependent relationship was noted with an increase in long-term side effects when taking a daily dose of more than 10 mg for longer than 6 months.[89] Corticosteroids have a detrimental effect on the cardiometabolic profile and cause weight gain, fluid retention, and increases in blood glucose and blood pressure. These require close monitoring, adjustment of the corticosteroid dose, and initiation of hypoglycemic and/or antihypertensive therapy if appropriate.[90,91] Corticosteroids are frequently used to treat IBD flare. Lewis and colleagues assessed side effects of long-term corticosteroid use (>3 g or equivalent dose over a 12-month period). Long-term corticosteroid use was associated with increased mortality, compared with use of anti-TNF drugs, mainly related to MACE.[92]

Interpretation of short-term effects of corticosteroids in IBD through epidemiologic studies can be difficult. The detrimental effect of corticosteroids in IBD can be confounded by the fact that they are often used during active disease, which has been shown to be associated with ASCVD events. In addition, corticosteroid use is often utilized as a surrogate marker for disease activity in large retrospective cohort studies. Hence, the short-term effects of corticosteroids on ASCVD in patients with IBD may be best assessed by prospective studies. Yarur and colleagues did not find corticosteroids to be associated with increased risk of ASCVD in patients with IBD in a single-center retrospective case-control study.[6]

Anti–Tumor Necrosis Factor Medications TNF inhibition emerged as a potential therapeutic target for HF after preclinical data suggested harmful effects of TNF signaling in HF and improvement in left ventricle ejection fraction with TNF blockage.[67] Two large trials of anti-TNF therapy in the general population, RENEWAL and RENAISSANCE, did not show improvement in clinical outcomes.[93] The ATTACH trial found that high-dose infliximab (10 mg/kg) was associated with an increased risk of all-cause death and HF hospitalization.[94] Hence, use of anti-TNF agents is contraindicated in severe HF patients (New York Heart Association [NYHA] class III and IV). Of note, 10 mg/kg is not the usual dose in patients with IBD, and no detrimental effects were noted at standard dosing. A paradoxical effect at high dosage of anti-TNF therapy may be related to inhibition of NF-κB signaling. NF-κB is activated by TNF and, contrary to TNF, is cardioprotective. Hence, it is possible that the beneficial effects of NF-κB were lost by excessive suppression of TNFα.[67]

Anti-TNF drugs, however, have not been associated with worsening of HF in the RA population.[95] Several studies have shown a beneficial effect of anti-TNF agents in RA and psoriasis patients, especially if the disease is controlled in the first 6 months.[89,96,97] Data in IBD are limited, but several studies indicate the beneficial effect of anti-TNF drugs in reducing CVD risk and mortality.[92,98,99] Kirchgesner and colleagues reported decreased risk of acute arterial events in a French IBD cohort exposed to anti-TNF drugs (HR, 0.79; 95% CI, 0.66-0.95) but not to thiopurines (HR, 0.54; 95% CI, 0.82-1.05).[98] Analysis of US Medicare and Medicaid data showed significant mortality benefit in Crohn's disease patients treated with anti-TNF drugs compared with patients who were treated with prolonged courses of corticosteroids (21.4 vs 30.1 per 1000 person-years; OR, 0.78; 95% CI, 0.65-0.93).[92] A prospective study assessing subclinical atherosclerosis by pulse wave velocity showed that anti-TNF use was associated with reduction in arterial stiffness to a level comparable to that of controls after 4 years of treatment.[100] Anti-TNF agents have been associated with dyslipidemia in case reports.[101] Although anti-TNF agents show promise in reducing CVD risks, studies are needed to assess their effect on lipid patterns and HF in patients with IBD. In addition, whether the protective effect is due to control of disease activity or a mechanistic effect regardless of control of disease activity needs to be investigated.

Interleukin-12/Interleukin-23 Antagonists IL-12 and IL-23 inhibition in mouse models has been shown to be protective against atherosclerosis.[67,102] However, an increased risk of MACE was seen with the IL-12/IL-23 inhibitor briakinumab, which led to study discontinuation in 2011.[103] The IL-12/IL-23 inhibitor ustekinumab (Stelara, Janssen) is now available for Crohn's disease and UC patients. Ustekinumab was not associated with an increased risk of MACE in psoriasis or psoriatic arthritis, and current data in IBD patients have not shown any signals of increased CVD risk.[104,105] Cardioprotective effects of ustekinumab, including improvements in left ventricular and vascular function, were seen in a small clinical trial of psoriasis patients.[106] Risankizumab (Skyrizi, AbbVie), an IL-23 inhibitor, has no safety concerns regarding MACE in clinical trials for IBD or other CIDs.[107] Long-term data in IBD are awaited. Given the molecular mechanism of cardioprotection, its effectiveness for reducing CVD risk would be worth exploring.

Janus Kinase Inhibitors Tofacitinib (Xeljanz, Pfizer) is a pan-JAK inhibitor and the first oral small molecule approved for UC. Subsequently, the JAK1-selective inhibitor upadacitinib (Rinvoq, AbbVie) was approved for UC and Crohn's disease, and the JAK1-selective inhibitor filgotinib is being studied in patients with IBD.

JAK inhibitors are currently indicated as second-line agents in UC and Crohn's disease owing to safety concerns regarding thromboembolism, MACE, and malignancy. In 2019, the US Food and Drug Administration (FDA) reviewed initial results of the postmarketing Oral Rheumatoid Arthritis Trial (ORAL) Surveillance, which randomized RA patients 50 years and older on methotrexate with at least 1 CVD risk factor into 3 groups (tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or anti-TNF therapy [adalimumab or etanercept]).[108] An increased risk of MACE (HR, 1.33; 95% CI, 0.91-1.94) was found in patients on tofacitinib. This was most pronounced in patients older than 65 years and smokers. Subsequent post hoc analysis of ORAL Surveillance published in January 2023 showed an increased risk of MACE in the group that had prior history of ASCVD.[109]

In patients with IBD, data from more than 7 years of follow-up of randomized controlled trials (RCTs) have not shown any adverse signals for MACE with JAK inhibitors.[110] Pooled analysis from RCTs of tofacitinib in UC found 8 CVD events in 1124 patients. Five of the 7 patients with MACE had multiple CVD risk factors at baseline with intermediate to high ASCVD risk as calculated by the ACC/AHA 10-year risk calculator.[111,112] One patient had an aortic dissection that resulted in death, but that was not considered to be related to the drug. It is notable that the total incidence of MACE in RCTs of tofacitinib over a 7-year period in IBD was low (0.7%; 0.26/100 patient-years; 95% CI, 0.11-0.54). This is similar to pooled data from RCTs in the RA population with 9.5 years of follow-up (incidence rate, 0.4; 95% CI, 0.3-0.5).[113]

Several studies have investigated the risk of MACE with tofacitinib in real-world settings and have not found it increased, although most studies had a small number of patients.[87,114] Kochar and colleagues reported a 2% risk of MACE (HR, 2.5; 95% CI, 0.37-6.18) in 305 patients receiving tofacitinib in a study from a large US claims database; this was not significantly different from patients receiving anti-TNF therapy.[115]

In clinical trials of upadacitinib in UC, there was 1 MACE in the placebo group and none in the treatment group with 52 weeks of follow-up.[116] One MACE was reported at 30-month follow-up in a clinical trial of upadacitinib for Crohn's disease in a patient who had multiple CVD risk factors.[117] RCTs of filgotinib in patients with IBD have reported few cerebrovascular events, but long-term data are awaited.[118] Data on upadacitinib and filgotinib from RCTs in RA, psoriasis, and atopic dermatitis reported infrequent MACEs, and the exposure-adjusted incidence rates remained stable over time.[119-123] Real-world data of patients with IBD are still awaited for upadacitinib and filgotinib, and whether selective JAK inhibition confers protection against CVD adverse effects remains to be determined.

Two meta-analyses, comprising a total of 20 RCTs across all CIDs (including IBD), showed no significant increased risks in mortality, MACE, and venous thromboembolism with use of selective (upadacitinib and filgotinib) and nonselective (tofacitinib and baricitinib) JAK inhibitors.[124,125]

There are a few other aspects to consider regarding JAK inhibitors and cardiovascular risk. First, even though ORAL Surveillance reported an increased risk of MACE in patients with RA, the absolute incidence of MACE is low and was not statistically significant in RCTs and real-world studies across multiple CIDs, including IBD. Second, most patients who had MACE had known CVD risks or prior ASCVD, which appears to be a more important factor than the drug. Hence, JAK inhibitors should be used with caution in older patients with multiple CVD risk factors.

Lipid alterations have been reported with tofacitinib in IBD trials, especially with higher doses. These are reversible, and the long-term implications in patients with IBD are still to be investigated.[111] In the RA population, review of data from RCTs found that hypertension, age, and total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio were associated with risk of MACE. Increase in HDL-C and decrease in total cholesterol over a 24-week period were associated with lower future MACE risk.[126]

A recently published international consensus statement regarding venous and arterial thromboembolism in patients with IBD recommended use of strategies to establish and control traditional ASCVD risk factors and IBD activity to improve CVD outcomes in patients with IBD. Tofacitinib was not considered to be a risk factor for MACE in IBD.[16] However, intermediate or high baseline ASCVD risk appears to be associated with MACE in patients treated with tofacitinib.[112] Both the FDA and European Medicines Agency have issued guidelines regarding small molecules (JAK inhibitors and S1P receptor modulators) in IBD treatment recommending the use of JAK inhibitors as second-line agents and with caution in patients with baseline risk of ASCVD.[127,128]

Sphingosine-1 Phosphate Receptor Modulators The S1P molecule binds to S1P receptors in different cell types. Their highest density is on leukocytes, and S1P receptor modulators prevent trafficking of lymphocytes from the spleen and lymph nodes into the systemic circulation leading to decrease in inflammation.[129] S1P receptors have 5 subtypes (1-5), and 3 (1-3) are present ubiquitously, including in the CVD system possibly leading to arteriovenous block and transient bradycardia.[130]

Three S1P receptor modulators have been studied in IBD (ozanimod [Zeposia, Bristol Myers Squibb], etrasimod [Velsipity, Pfizer], and amiselimod), and ozanimod (S1P1/5 receptor modulator) and etrasimod have been approved for use in UC. Ozanimod is contraindicated in patients who have experienced MI, unstable angina, cerebrovascular accident, or NYHA class III or IV HF in the 6 months prior to initiation of therapy and patients with significant conduction abnormalities (Mobitz type II second-degree or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial block) unless the patient has a functioning pacemaker. Given cardiac considerations, it is recommended that patients obtain a baseline electrocardiogram to screen for any conduction abnormalities. Follow-up cardiac monitoring is not recommended. Pooled data from RCTs in UC and multiple sclerosis did not show increased risk of MACE, and the incidence of bradycardia was low (mean decrease in heart rate by 0.7 beats per minute from baseline) and primarily in the induction period (within the first 5 hours and returned to baseline after 6 hours).[131] Ozanimod is not associated with increased risk of MACE, QTc prolongation, or clinically significant bradycardia.

Conclusion

Patients with IBD are at increased risk of ASCVD events such as MI and stroke. Traditional risk factors such as obesity, hyperlipidemia, and advanced age may not completely explain the higher risk of ASCVD in the IBD population. Disease activity and chronic inflammation appear to drive the risk. Modalities to assess ASCVD in IBD are needed to appropriately risk stratify patients so that early intervention and risk modification strategies can be implemented. Anti-TNF medications may decrease ASCVD risk; however, it is unclear whether this is due to underlying mechanisms of the drugs or due to control of inflammation. Corticosteroids increase ASCVD risk, and small molecules such as tofacitinib, upadacitinib, and ozanimod must be used with caution in patients with prior ASCVD risk factors or conduction defects of the heart. Patients with IBD should be assessed for baseline ASCVD risk; however, whether ASCVD clinical risk scores or imaging modalities appropriately risk stratify CVD in IBD needs further investigation. Table 3 lists our recommendations for CVD risk assessment in patients with IBD.

Disclosures

Dr Sinh has no relevant conflicts of interest to disclose. Dr Cross has participated in consulting and advisory boards for AbbVie, Adiso, BMS, Fresenius Kabi, Fzata, Janssen, Magellan Health, Pfizer, Pharmacosmos, Samsung Bioepis, Sebela,

and Takeda. He has a research grant with Janssen. He is also the Scientific Co-Director of the CorEvitas registry and is a member of the executive committee for the IBD Education Group.

References

1. Virani SS, Alonso A, Benjamin EJ, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139-e596.

2. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis*. 2017;76(1):17-28.

3. Panhwar MS, Mansoor E, Al-Kindi SG, et al. Risk of myocardial infarction in inflammatory bowel disease: a population-based national study. *Inflamm Bowel Dis*. 2019;25(6):1080-1087.

4. Luther J, Dave M. Rising inflammatory bowel disease prevalence highlights the need for effective, cost-effective therapies. *Inflamm Bowel Dis*. 2020;26(4):626-627.

5. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(1):17-30.

6. Yarur AJ, Deshpande AR, Pechman DM, Tamariz L, Abreu MT, Sussman DA. Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. *Am J Gastroenterol*. 2011;106(4):741-747.

7. Lee MT, Mahtta D, Chen L, et al. Premature atherosclerotic cardiovascular disease risk among patients with inflammatory bowel disease. *Am J Med*. 2021;134(8):1047-1051.e2.

8. Soh H, Im JP, Han K, et al. Crohn's disease and ulcerative colitis are associated with different lipid profile disorders: a nationwide population-based study. *Aliment Pharmacol Ther*. 2020;51(4):446-456.

9. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death—a Danish nationwide cohort study. *PLoS One*. 2013;8(2):e56944.

10. Fang L, Gao H, Gao X, et al. Risks of cardiovascular events in patients with inflammatory bowel disease in China: a retrospective multicenter cohort study. *Inflamm Bowel Dis*. 2022;28(suppl 2):S52-S58.

11. Sinh P, Cross R. Cardiovascular risk assessment and impact of medications on cardiovascular disease in inflammatory bowel disease. *Inflamm Bowel Dis*. 2021;27(7):1107-1115.

12. Cainzos-Achirica M, Glassner K, Zawahir HS, et al. Inflammatory bowel disease and atherosclerotic cardiovascular disease: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2020;76(24):2895-2905.

13. Al-Kindi S, Tashtish N, Bevan G, et al. Abstract 16584: Inflammatory bowel disease is independently associated with elevated coronary artery calcium score in young patients: insights from CLARIFY study. *Circulation*. 2020;142(suppl 3):A16584.

14. Weissman S, Sinh P, Mehta TI, et al. Atherosclerotic cardiovascular disease in inflammatory bowel disease: the role of chronic inflammation. *World J Gastrointest Pathophysiol*. 2020;11(5):104-113.

15. Aniwan S, Pardi DS, Tremaine WJ, Loftus EV Jr. Increased risk of acute myocardial infarction and heart failure in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2018;16(10):1607-1615.e1.

16. Olivera PA, Zuily S, Kotze PG, et al. International consensus on the prevention of venous and arterial thrombotic events in patients with inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2021;18(12):857-873.

17. Fumery M, Xiaocang C, Dauchet L, Gower-Rousseau C, Peyrin-Biroulet L, Colombel J-F. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. *J Crohns Colitis*. 2014;8(6):469-479.

18. Singh S, Kullo IJ, Pardi DS, Loftus EV Jr. Epidemiology, risk factors and management of cardiovascular diseases in IBD. *Nat Rev Gastroenterol Hepatol*. 2015;12(1):26-35.

19. Singh S, Singh H, Loftus EV Jr, Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic

review and meta-analysis. *Clin Gastroenterol Hepatol.* 2014;12(3):382-393.e1.

20. Mitchell NE, Harrison N, Junga Z, Singla M. Heart under attack: cardiac manifestations of inflammatory bowel disease. *Inflamm Bowel Dis.* 2018;24(11):2322-2326.

21. Golovics PA, Verdon C, Wetwittayakhlang P, et al. Increased prevalence of myocardial infarction and stable stroke proportions in patients with inflammatory bowel diseases in Quebec in 1996-2015. *J Clin Med.* 2022;11(3):686.

22. Aarestrup J, Jess T, Kobylecki CJ, Nordestgaard BG, Allin KH. Cardiovascular risk profile among patients with inflammatory bowel disease: a population-based study of more than 100 000 individuals. *J Crohns Colitis.* 2019;13(3):319-323.

23. He J, Zhang S, Qiu Y, et al. Ulcerative colitis increases risk of hypertension in a UK biobank cohort study. *United European Gastroenterol J.* 2023;11(1):19-30.

24. Aggarwal A, Atreja A, Kapadia S, Lopez R, Achkar JP. Conventional risk factors and cardiovascular outcomes of patients with inflammatory bowel disease with confirmed coronary artery disease. *Inflamm Bowel Dis.* 2015;21(1):E2.

25. Zuin M, Zuliani G, Rigatelli G, Favero GD, Roncon L. Atrial fibrillation in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Eur J Intern Med.* 2020;76:120-122.

26. Kirchgesner J, Beaugerie L, Carrat F, Andersen NN, Jess T, Schwarzinger M; BERENICE study group. Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study. *Gut.* 2018;67(7):1261-1268.

27. Sinh P, Sherman K, Rosenthal A, et al. 16: Incidence of cardiovascular disease in veterans with inflammatory bowel disease: data from a large cohort of United States veterans from 2002 to 2015. *Gastroenterology.* 2022;162(7)(suppl):S-6.

28. Le Gall G, Kirchgesner J, Bejaoui M, et al. Clinical activity is an independent risk factor of ischemic heart and cerebrovascular arterial disease in patients with inflammatory bowel disease. *PLoS One.* 2018;13(8):e0201991.

29. Dorn SD, Sandler RS. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. *Am J Gastroenterol.* 2007;102(3):662-667.

30. Barnes EL, Beery RM, Schulman AR, McCarthy EP, Korzenik JR, Winter RW. Hospitalizations for acute myocardial infarction are decreased among patients with inflammatory bowel disease using a nationwide inpatient database. *Inflamm Bowel Dis.* 2016;22(9):2229-2237.

31. Ha C, Magowan S, Accortt NA, Chen J, Stone CD. Risk of arterial thrombotic events in inflammatory bowel disease. *Am J Gastroenterol.* 2009;104(6):1445-1451.

32. Sinh P, Tabibian JH, Biyani PS, et al. Inflammatory bowel disease does not impact mortality but increases length of hospitalization in patients with acute myocardial infarction. *Dig Dis Sci.* 2021;66(12):4169-4177.

33. Tsai M-S, Lin C-L, Chen H-P, Lee P-H, Sung F-C, Kao C-H. Long-term risk of acute coronary syndrome in patients with inflammatory bowel disease: a 13-year nationwide cohort study in an Asian population. *Inflamm Bowel Dis.* 2014;20(3):502-507.

34. Alayo QA, Loftus EV Jr, Yarur A, et al. Inflammatory bowel disease is associated with an increased risk of incident acute arterial events: analysis of the United Kingdom Biobank. *Clin Gastroenterol Hepatol.* 2023;21(3):761-770.e13.

35. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Prognosis after first-time myocardial infarction in patients with inflammatory bowel disease according to disease activity: nationwide cohort study. *Circ Cardiovasc Qual Outcomes.* 2014;7(6):857-862.

36. Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. *Clin Gastroenterol Hepatol.* 2008;6(1):41-45.

37. Hansson GK. Inflammation and atherosclerosis: the end of a controversy. *Circulation.* 2017;136(20):1875-1877.

38. Ruparelia N, Chai JT, Fisher EA, Choudhury RP. Inflammatory processes in cardiovascular disease: a route to targeted therapies. *Nat Rev Cardiol.* 2017;14(3):133-144.

39. Gravina AG, Dallio M, Masarone M, et al. Vascular endothelial dysfunction in inflammatory bowel diseases: pharmacological and nonpharmacological targets. *Oxid Med Cell Longev.* 2018;2018:2568569.

40. Galluzzo S, Patti G, Dicuonzo G, et al. Association between NOD2/CARD15 polymorphisms and coronary artery disease: a case-control study. *Hum Immunol.* 2011;72(8):636-640.

41. Morton AC, Rothman AM, Greenwood JP, et al. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *Eur Heart J.* 2015;36(6):377-384.

42. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* 2017;377(12):1119-1131.

43. Ridker PM, Libby P, MacFadyen JG, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J.* 2018;39(38):3499-3507.

44. Kristensen SL, Lindhardsen J, Ahlehoff O, et al. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace.* 2014;16(4):477-484.

45. Deepak P, Paul D, Lobo F, et al. S103 Prevalence of cardiac conduction disorders of interest among adults with moderately-to-severely active ulcerative colitis in the US: a real-world analysis. *Am J Gastroenterol.* 2022;117:S27.

46. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation.* 2003;108(24):3006-3010.

47. Gawałko M, Balsam P, Lodziński P, et al. Cardiac arrhythmias in autoimmune diseases. *Circ J.* 2020;84(5):685-694.

48. Can G, Ekmen N, Can H, et al. Is there any link between atrial arrhythmias and inflammatory bowel disease? *Saudi J Gastroenterol.* 2021;27(5):289-295.

49. Bornaun HA, Yılmaz N, Kutluk G, et al. Prolonged P-wave and QT dispersion in children with inflammatory bowel disease in remission. *BioMed Res Int.* 2017;2017:6960810.

50. Efe TH, Cimen T, Ertem AG, et al. Atrial electromechanical properties in inflammatory bowel disease. *Echocardiography.* 2016;33(9):1309-1316.

51. Yorulmaz E, Sezgin A, Yorulmaz H, Adali G, Ciftci H. Prolonged QT dispersion in inflammatory bowel disease. *World J Gastroenterol.* 2013;19(1):65-71.

52. Dogan Y, Soylu A, Eren GA, et al. Evaluation of QT and P wave dispersion and mean platelet volume among inflammatory bowel disease patients. *Int J Med Sci.* 2011;8(7):540-546.

53. Abid MA, Gitlin N. Pericarditis—an extraintestinal complication of inflammatory bowel disease. *West J Med.* 1990;153(3):314-315.

54. Molnár T, Hõgye M, Nagy F, Lonovics J. Pericarditis associated with inflammatory bowel disease: case report. *Am J Gastroenterol.* 1999;94(4):1099-1100.

55. García-Morán S, Sáez-Royuela F, Pérez-Alvarez JC, Gento E, Téllez J. Myopericarditis and mitral insufficiency associated with ulcerative colitis treated with mesalazine. *Inflamm Bowel Dis.* 2006;12(4):334-335.

56. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. *Gastroenterology.* 2005;129(3):827-836.

57. Jackson JF, Sitaraman SV. Pericarditis as the presenting sign of Crohn's disease. *Inflamm Bowel Dis.* 2005;11(1):81-82.

58. Stasinopoulou P, Kaziani A, Mantzaris G, Roussos A, Skoutelis A. Parallel manifestation of Crohn's disease and acute pericarditis: a report of two cases. *Int J Colorectal Dis.* 2007;22(9):1123-1125.

59. Simpson CD. Azathioprine-induced pericarditis in a patient with ulcerative colitis. *Can J Gastroenterol.* 1997;11(3):217-219.

60. Sentongo TA, Piccoli DA. Recurrent pericarditis due to mesalamine hypersensitivity: a pediatric case report and review of the literature. *J Pediatr Gastroenterol Nutr.* 1998;27(3):344-347.

61. Brown G. 5-aminosalicylic acid-associated myocarditis and pericarditis: a narrative review. *Can J Hosp Pharm.* 2016;69(6):466-472.

62. Burke JP, Kelleher B, Ramadan S, Quinlan M, Sugrue D, O'Donovan MA. Pericarditis as a complication of infliximab therapy in Crohn's disease. *Inflamm Bowel Dis.* 2008;14(3):428-429.

63. Devasahayam J, Pillai U, Lacasse A. A rare case of pericarditis, complication of infliximab treatment for Crohn's disease. *J Crohns Colitis.* 2012;6(6):730-731.

64. Bracamonte-Baran W, Čiháková D. Cardiac autoimmunity: myocarditis. *Adv Exp Med Biol.* 2017;1003:187-221.

65. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Inflammatory bowel disease is associated with an increased risk of hospitalization for heart failure: a Danish Nationwide Cohort study. *Circ Heart Fail.* 2014;7(5):717-722.

66. Kumar A, Lukin DJ. Incident heart failure is a predictor of adverse outcomes in inflammatory bowel disease. *Eur J Gastroenterol Hepatol.* 2020;32(2):205-215.

67. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75(11):1324-1340.

68. Sandek A, Bjarnason I, Volk HD, et al. Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. *Int J Cardiol.* 2012;157(1):80-85.

69. Kummen M, Mayerhofer CCK, Vestad B, et al. Gut microbiota signature in heart failure defined from profiling of 2 independent cohorts. *J Am Coll Cardiol.* 2018;71(10):1184-1186.

70. Mayerhofer CCK, Awoyemi AO, Moscavitch SD, et al. Design of the Gut-

Heart-targeting gut microbiota to treat heart failure-trial: a phase II, randomized clinical trial. *ESC Heart Fail.* 2018;5(5):977-984.

71. Ciccone MM, Principi M, Ierardi E, et al. Inflammatory bowel disease, liver diseases and endothelial function: is there a linkage? *J Cardiovasc Med (Hagerstown).* 2015;16(1):11-21.

72. Hatoum OA, Binion DG, Otterson MF, Gutterman DD. Acquired microvascular dysfunction in inflammatory bowel disease: loss of nitric oxide-mediated vasodilation. *Gastroenterology.* 2003;125(1):58-69.

73. Principi M, Mastrolonardo M, Scicchitano P, et al. Endothelial function and cardiovascular risk in active inflammatory bowel diseases. *J Crohns Colitis.* 2013;7(10):e427-e433.

74. Crowson CS, Matteson EL, Roger VL, Therneau TM, Gabriel SE. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. *Am J Cardiol.* 2012;110(3):420-424.

75. Kawai VK, Chung CP, Solus JF, Oeser A, Raggi P, Stein CM. The ability of the 2013 American College of Cardiology/American Heart Association cardiovascular risk score to identify rheumatoid arthritis patients with high coronary artery calcification scores. *Arthritis Rheumatol.* 2015;67(2):381-385.

76. Yu Z, Yang N, Everett BM, et al. Impact of changes in inflammation on estimated ten-year cardiovascular risk in rheumatoid arthritis. *Arthritis Rheumatol.* 2018;70(9):1392-1398.

77. Ayoub M, Shah H, Nguyen BC, et al. Coronary artery plaque assessment by CT angiogram in inflammatory bowel disease. *Inflamm Bowel Dis.* 2023;29(6):e22-e24.

78. Kaiser MG, During MJ. Combining laser Doppler flowmetry with microdialysis: a novel approach to investigate the coupling of regional cerebral blood flow to neuronal activity. *J Neurosci Methods.* 1995;60(1-2):165-173.

79. Emanuel G, Charlton J, Ashworth M, Gulliford MC, Dregan A. Cardiovascular risk assessment and treatment in chronic inflammatory disorders in primary care. *Heart.* 2016;102(24):1957-1962.

80. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;74(10):1376-1414.

81. Knuuti J, Wijns W, Saraste A, et al; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020;41(3):407-477.

82. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78(6):736-745.

83. Graham IM, Di Angelantonio E, Huculeci R; European Society of Cardiology's Cardiovascular Risk Collaboration (CRC). New way to "SCORE" risk: updates on the ESC scoring system and incorporation into ESC cardiovascular prevention guidelines. *Curr Cardiol Rep.* 2022;24(11):1679-1684.

84. Corrales A, González-Juanatey C, Peiró ME, Blanco R, Llorca J, González-Gay MA. Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. *Ann Rheum Dis.* 2014;73(4):722-727.

85. Harbord M, Annese V, Vavricka SR, et al; European Crohn's and Colitis Organisation. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis.* 2016;10(3):239-254.

86. Shehab M, Alrashed F, Alkazemi A, Lakatos PL, Bessissow T. Impact of biologic therapies and small molecules on the risk of major adverse cardiovascular events in patients with inflammatory bowel diseases: systematic review and meta-analysis of randomized controlled trials. *Expert Rev Gastroenterol Hepatol.* 2023;17(5):469-477.

87. Olivera PA, Lasa JS, Peretto G, Zuily S, Danese S, Peyrin-Biroulet L. Review article: risk of cardiovascular events in patients with inflammatory bowel disease receiving small molecule drugs. *Aliment Pharmacol Ther.* 2023;57(11):1231-1248.

88. Nussinovitch U, de Carvalho JF, Pereira RM, Shoenfeld Y. Glucocorticoids and the cardiovascular system: state of the art. *Curr Pharm Des.* 2010;16(32):3574-3585.

89. Roubille C, Richer V, Starnino T, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis.* 2015;74(3):480-489.

90. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. *Ann Rheum Dis.* 2009;68(12):1833-1838.

91. Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther.* 2002;96(1):23-43.

92. Lewis JD, Scott FI, Brensinger CM, et al. Increased mortality rates with prolonged corticosteroid therapy when compared with antitumor necrosis factor-α-directed therapy for inflammatory bowel disease. *Am J Gastroenterol.* 2018;113(3):405-417.

93. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation.* 2004;109(13):1594-1602.

94. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT; Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation.* 2003;107(25):3133-3140.

95. Solomon DH, Rassen JA, Kuriya B, et al. Heart failure risk among patients with rheumatoid arthritis starting a TNF antagonist. *Ann Rheum Dis.* 2013;72(11):1813-1818.

96. Ljung L, Rantapää-Dahlqvist S, Jacobsson LT, Askling J. Response to biological treatment and subsequent risk of coronary events in rheumatoid arthritis. *Ann Rheum Dis.* 2016;75(12):2087-2094.

97. Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register Control Centre Consortium; British Society for Rheumatology Biologics Register. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 2007;56(9):2905-2912.

98. Kirchgesner J, Nyboe Andersen N, Carrat F, Jess T, Beaugerie L; BERENICE study group. Risk of acute arterial events associated with treatment of inflammatory bowel diseases: nationwide French cohort study. *Gut.* 2020;69(5):852-858.

99. Singh S, Fumery M, Singh AG, et al. Comparative risk of cardiovascular events with biologic and synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken).* 2020;72(4):561-576.

100. Zanoli L, Inserra G, Cappello M, Ozturk K, Castellino P. Aortic stiffness in patients with inflammatory bowel disease reduced after anti-tumor necrosis factor therapy. *J Am Coll Cardiol.* 2019;73(8):981-982.

101. Gabay C, McInnes IB, Kavanaugh A, et al. Comparison of lipid and lipid-associated cardiovascular risk marker changes after treatment with tocilizumab or adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2016;75(10):1806-1812.

102. Hauer AD, Uyttenhove C, de Vos P, et al. Blockade of interleukin-12 function by protein vaccination attenuates atherosclerosis. *Circulation.* 2005;112(7):1054-1062.

103. Hugh J, Van Voorhees AS, Nijhawan RI, et al. From the Medical Board of the National Psoriasis Foundation: the risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. *J Am Acad Dermatol.* 2014;70(1):168-177.

104. Sandborn WJ, Rutgeerts P, Gasink C, et al. Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. *Aliment Pharmacol Ther.* 2018;48(1):65-77.

105. Papp KA, Griffiths CE, Gordon K, et al; PHOENIX 1 Investigators; PHOENIX 2 Investigators; ACCEPT Investigators. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Dermatol.* 2013;168(4):844-854.

106. Ikonomidis I, Papadavid E, Makavos G, et al. Lowering interleukin-12 activity improves myocardial and vascular function compared with tumor necrosis factor-a antagonism or cyclosporine in psoriasis. *Circ Cardiovasc Imaging.* 2017;10(9):e006283.

107. Ferrante M, Feagan BG, Panés J, et al. Long-term safety and efficacy of risankizumab treatment in patients with Crohn's disease: results from the phase 2 open-label extension study. *J Crohns Colitis.* 2021;15(12):2001-2010.

108. Ytterberg SR, Bhatt DL, Mikuls TR, et al; ORAL Surveillance Investigators. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med.* 2022;386(4):316-326.

109. Charles-Schoeman C, Buch MH, Dougados M, et al. Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL Surveillance. *Ann Rheum Dis.* 2023;82(1):119-129.

110. Sandborn WJ, D'Haens GR, Sands BE, et al. Tofacitinib for the treatment of ulcerative colitis: an integrated summary of up to 7.8 years of safety data from the Global Clinical Programme. *J Crohns Colitis.* 2023;17(3):338-351.

111. Sands BE, Colombel JF, Ha C, et al. Lipid profiles in patients with ulcerative colitis receiving tofacitinib-implications for cardiovascular risk and patient management. *Inflamm Bowel Dis.* 2021;27(6):797-808.

112. Schreiber S, Rubin D, Ng S, et al. S775 Major cardiovascular adverse events by baseline cardiovascular risk stratification in patients with ulcerative colitis treated with tofacitinib: data from the OCTAVE clinical program. *Am J Gastroenterol.* 2022;117(10S):e551-e552.

113. Cohen SB, Tanaka Y, Mariette X, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. *RMD Open.* 2020;6(3):e001395.

114. Deepak P, Alayo QA, Khatiwada A, et al. Safety of tofacitinib in a real-world cohort of patients with ulcerative colitis. *Clin Gastroenterol Hepatol.* 2021;19(8):1592-1601.e3.

115. Kochar BD, Cheng D, Cai T, Ananthakrishnan AN. Comparative risk of thrombotic and cardiovascular events with tofacitinib and anti-TNF agents in patients with inflammatory bowel diseases. *Dig Dis Sci.* 2022;67(11):5206-5212.

116. Danese S, Vermeire S, Zhou W, et al. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. *Lancet.* 2022;399(10341):2113-2128.

117. D'Haens G, Panés J, Louis E, et al. Upadacitinib was efficacious and well-tolerated over 30 months in patients with Crohn's disease in the CELEST Extension Study. *Clin Gastroenterol Hepatol.* 2022;20(10):2337-2346.e3.

118. Feagan BG, Danese S, Loftus EV Jr, et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *Lancet.* 2021;397(10292):2372-2384.

119. Cohen SB, van Vollenhoven RF, Winthrop KL, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann Rheum Dis.* 2021;80(3):304-311.

120. Burmester GR, Winthrop K, Blanco R, et al. Safety profile of upadacitinib up to 3 years in psoriatic arthritis: an integrated analysis of two pivotal phase 3 trials. *Rheumatol Ther.* 2022;9(2):521-539.

121. Guttman-Yassky E, Thyssen JP, Silverberg JI, et al. Safety of upadacitinib in moderate-to-severe atopic dermatitis: an integrated analysis of phase 3 studies. *J Allergy Clin Immunol.* 2023;151(1):172-181.

122. Winthrop KL, Tanaka Y, Takeuchi T, et al. Integrated safety analysis of filgotinib in patients with moderately to severely active rheumatoid arthritis receiving treatment over a median of 1.6 years. *Ann Rheum Dis.* 2022;81(2):184-192.

123. Namour F, Anderson K, Nelson C, Tasset C. Filgotinib: a clinical pharmacology review. *Clin Pharmacokinet.* 2022;61(6):819-832.

124. Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroulet L. Safety of Janus kinase inhibitors in patients with inflammatory bowel diseases or other immune-mediated diseases: a systematic review and meta-analysis. *Gastroenterology.* 2020;158(6):1554-1573.e12.

125. Xie W, Xiao S, Huang Y, Sun X, Zhang Z. Effect of tofacitinib on cardiovascular events and all-cause mortality in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis of randomized controlled trials. *Ther Adv Musculoskelet Dis.* 2019;11:1759720X19895492.

126. Charles-Schoeman C, DeMasi R, Valdez H, et al. Risk factors for major adverse cardiovascular events in phase III and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. *Arthritis Rheumatol.* 2019;71(9):1450-1459.

127. European Medicines Agency. EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders. https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki. Published October 2023. Accessed March 2024.

128. US Food and Drug Administration. FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR). https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and. Published July 26, 2019. Accessed March 2024.

129. Brinkmann V, Cyster JG, Hla T. FTY720: sphingosine 1-phosphate receptor-1 in the control of lymphocyte egress and endothelial barrier function. *Am J Transplant.* 2004;4(7):1019-1025.

130. Paik J. Ozanimod: a review in ulcerative colitis. *Drugs.* 2022;82(12):1303-1313.

131. Long M, Cross R, Calkwood J, et al. P038 Ozanimod first-dose cardiac effects in patients with moderately to severely active ulcerative colitis and relapsing multiple sclerosis. *Am J Gastroenterol.* 2021;116(suppl 1):S9-S10.