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The Risk of Cardiovascular Complications in Patients with Inflammatory Bowel Disease

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Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis (UC), is a chronic, relapsing-remitting inflammatory condition of the gastrointestinal tract. Beyond intestinal involvement, IBD commonly affects diverse organ systems in the body, making it a 'systemic disease with intestinal predominance'.

While extraintestinal manifestations are primarily due to immune-mediated involvement of organ systems, IBD also exerts systemic effects on the cardiovascular system. Emerging data suggests an association between IBD and myocardial infarction (MI), ischemic heart disease, cerebrovascular accidents, and other major adverse cardiovascular events (MACE).[1] As a result, the pathophysiological basis of cardiovascular complications in IBD has been a subject of growing investigation.

Pathophysiological Basis of Cardiovascular Risk in IBD

The inherent risk of cardiovascular complications in IBD stems from the effects of chronic systemic inflammation on the endothelium and coagulation pathways (**Figure 1**).

Endothelial Dysfunction

The chronic inflammatory state characteristic of IBD leads to persistently increased levels of proinflammatory cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β. These mediators induce endothelial activation and increased vascular permeability, thereby contributing to the development and progression of atherosclerotic plaque. In parallel, elevated reactive oxygen species levels lead to the formation of oxidated lipoproteins, upregulation of metallic metalloproteinases, and foam cell formation, collectively accelerating atherogenesis and impaired plaque stability.[2]

Hypercoagulable and Prothrombotic State

Elevated levels of proinflammatory cytokines upregulate procoagulant factors, such as fibrinogen, coagulation factors V, VIII and IX, while downregulating anticoagulant proteins (antithrombin-III, protein-S), leading to an increased risk of venous thrombotic events. Endothelial injury and dysfunction promote platelet activation and aggregation, resulting in the formation of microthrombi. Additionally, cytokine-mediated inhibition of the enzyme arginase inhibit leads to a decrease in production of endothelial nitric oxide (NO). Given NO's protective role in inhibiting platelet aggregation and leukocyte adhesion, this decrease corresponds to a worsening prothrombotic state.[3]

Gut Barrier Dysfunction

Chronic inflammation in IBD leads to a decrease in beneficial gut bacterial groups such as *Firmicutes, Bacteroidetes*, and *Bifidobacterium*, alongside an increase in detrimental groups, such as *Enterobacteriaceae, Bacteroides fragilis*, and *Escherichia coli*. This imbalance results in gut barrier dysfunction and facilitates translocation of bacterial lipopolysaccharides and trimethylamine N-oxide, which promote atherosclerosis and worsen cardiac health. Genetic susceptibility may further potentiate these effects. Mutations in *NOD2*, an intracellular sensor of bacterial peptidoglycan, can lead to impaired mucosal integrity and promote gut barrier dysfunction.[4]

A meta-analysis revealed that patients with IBD have a higher risk of developing cardiovascular

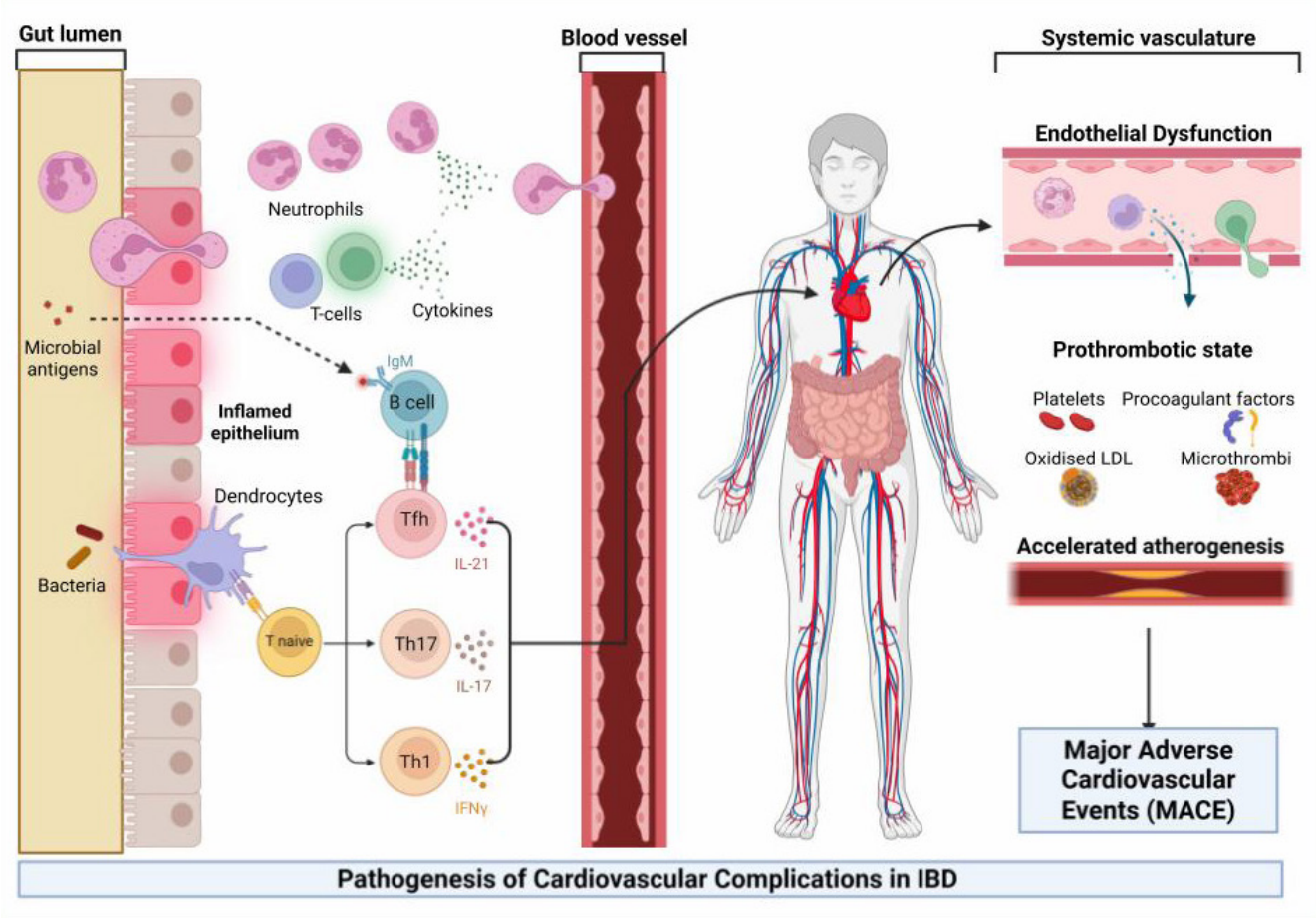

Figure 1. Pathogenesis of Cardiovascular Complications in IBD; *created in BioRender*.

disease despite a lower prevalence of traditional risk factors such as diabetes and hypertension, suggesting that IBD is, in itself, an inherent risk factor for cardiovascular disease.[5]

Cardiovascular Risk in Treatment Modalities

Given that chronic inflammation appears to be central to cardiovascular disease in IBD, effective suppression of disease activity may reduce cardiovascular risk. However, the varied mechanisms of action across different treatment classes necessitates a closer examination of the effects of specific treatment modalities on cardiovascular health (**Figure 2**).

Corticosteroids

Corticosteroids are primarily used to induce clinical remission during acute IBD flares, and guidelines recommend minimizing their use for maintenance therapy.[6] Corticosteroid exposure has shown a clear dose-dependent increase in the risk of cardiovascular disease. A longitudinal study on immune-mediated diseases including IBD revealed an increase in cumulative risk from 1.5% to 3.8% over one year among individuals receiving a daily prednisolone-equivalent dose of <5 mg, which increased to 9.1% with doses of >25 mg/day.[7] A meta-analysis revealed a two-fold increase in the rate of venous thromboembolism with corticosteroid use, especially during IBD flares, due to underlying inflammation.[8] Corticosteroids are well-recognized for contributing to hypertension, insulin resistance, and dyslipidemia, which potentiate the inherent risk of endothelial dysfunction and atherosclerosis in IBD. In addition, the relative risk of heart failure and acute MI are increased among IBD patients receiving corticosteroids, warranting the need for careful use in patients with cardiovascular comorbidities.[9]

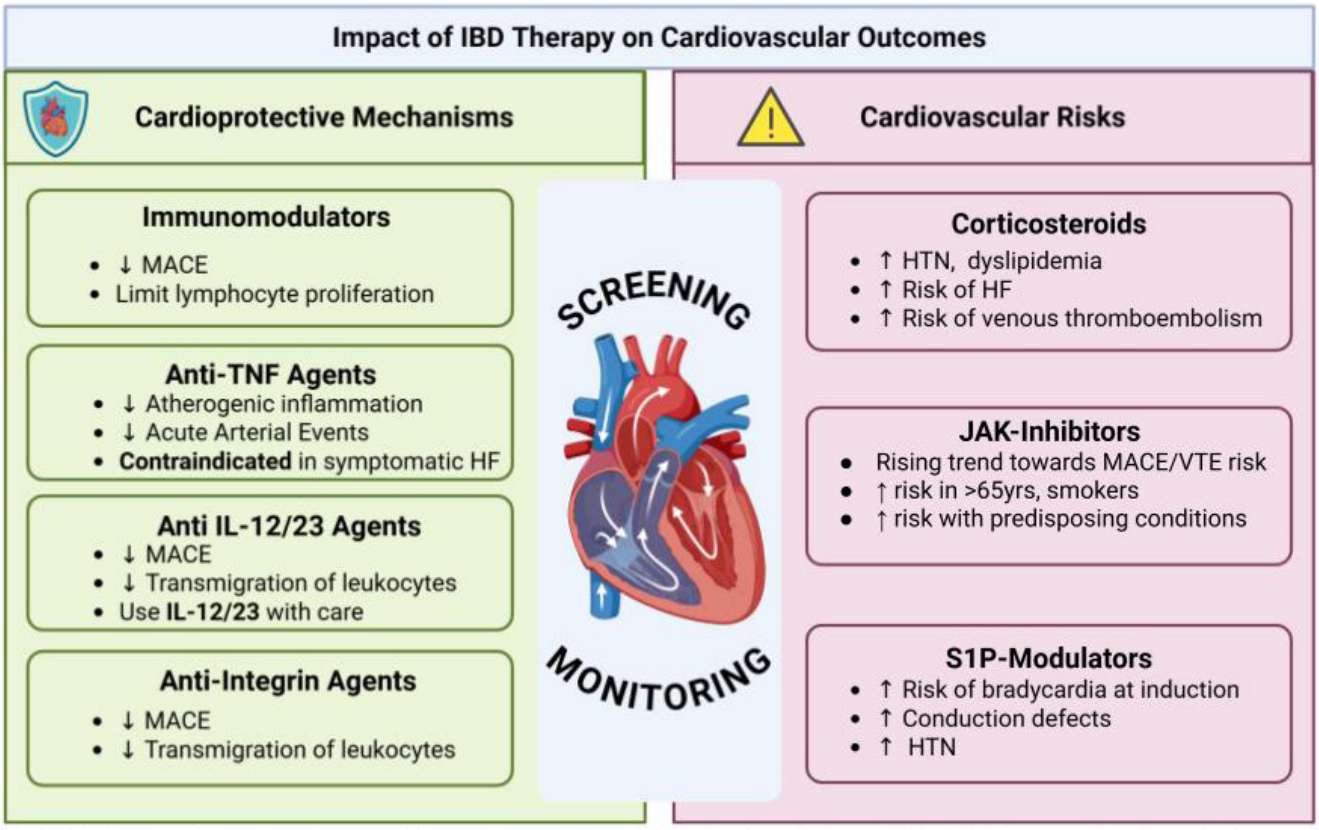

Figure 2. Impact of IBD Therapy on Cardiovascular Outcomes; *created in BioRender*.

TNF-α Inhibitors

TNF-α inhibitors or anti-TNF agents act by binding to TNF-α, a key proinflammatory cytokine that is overexpressed in the intestinal mucosa and promotes leukocyte recruitment and activation, increases epithelial permeability, and contributes to barrier disruption. Large nationwide cohort studies indicate that anti-TNF agents reduce the risk of acute arterial events by reducing atherogenic chronic inflammation in the body.[10,11] Another study reports that anti-TNF agents confer a greater reduction in the risk of MACE than other conventional non-biologic therapies.[12]

Despite these benefits, anti-TNF agents carry a U.S. Food and Drug Administration (FDA) label warning for cardiovascular side effects. The use of infliximab >5 mg/kg is contraindicated in moderate-to-severe symptomatic heart failure (HF) of (New York Heart Association [NYHA] class III/IV), based on the findings of the Anti-TNF Alpha Therapy Against Congestive Heart Failure (ATTACH) trial, which evaluated patients with reduced ejection fraction (EF) of <35%.[13] A case report described an IBD patient with cardiovascular risk factors and probable structural heart disease who developed decompensated HF following exposure to high-dose infliximab.[15] In a nationwide study, IBD patients receiving anti-TNF agents showed a higher risk of atrial fibrillation,[15] while a separate study in patients with ankylosing spondylitis demonstrated a reduction in QT interval with infliximab, indicating the lack of consensus on this matter.[16] Overall, the use of anti-TNF agents is associated with a reduced risk of MACE events, but should be used with caution in patients with moderate-to-severe HF (EF ≤40%).

IL-12/23 and IL-23 Inhibitors

The IL-12/23 pathway contributes to the proinflammatory state by promoting differentiation and maintenance of inflammatory T-cells. Medications such as ustekinumab act on the p-40 subunit of IL-12 and IL-23. In contrast, other therapeutics such as risankizumab, guselkumab, and mirikizumab specifically inhibit the p19 subunit of IL-23. Compared with anti-TNF therapies, these biologics have fewer systemic side effects and

are increasingly finding utility for IBD patients who have not responded to conventional therapy.

Cardiovascular side effects data from IBD cohorts are generally reassuring for therapeutic modalities targeting the IL-12/23 pathway. Clinical trials and real-world cohort studies have not reported cases of HF among IBD patients using these agents. Moreover, an analysis of a TriNetX IBD cohort showed a lower risk of atherosclerotic disease with IL-12/23 inhibitors than with other biologics.[17] On the other hand, a meta-analysis examining the risk of MACE across immune-mediated inflammatory disorders reported an increased risk with IL-12/23 inhibitors compared with placebo, but not with IL-23 specific inhibitors.[18] A study comparing biologic therapies in psoriasis noted an increased risk of MACE with IL-12/23 inhibitors compared with TNF inhibitors.[19] Additionally analyses of U.S. FDA adverse effects reporting data have identified a statistically significant signal for atrial fibrillation and coronary artery disease associated with risankizumab, a finding not observed with guselkumab.[20] Thus, while IL-12/23 inhibitors may reduce the risk of adverse cardiovascular outcomes in IBD patients, monitoring for any new onset MACE or atrial fibrillation is suggested.

Anti-integrin Agents

Anti-integrin monoclonal antibodies, such as vedolizumab and natalizumab, bind to adhesion molecules on the vascular endothelium, and exert their effects by blocking the transmigration of leukocytes from the bloodstream into bowel tissue. This targeted blockade reduces immune-mediated inflammation while avoiding broad immunosuppression.

Analysis of a TriNetX IBD cohort showed a reduction in the risk of MACE among patients treated with anti-integrin agents.[17] Data from the GEMINI trials and the real-world ENEIDA registry have not indicated increased risks of HF, acute coronary syndrome, or arrhythmias associated with these therapies.[21] Meta-analyses that examined the comparative risk of MACE with anti-integrin agents have similarly reported no increased risk of MACE with these therapies versus placebo. However, data from one study noted more instances of MACE with vedolizumab versus anti-TNF agents, a finding that may reflect differences in disease control.[22]

Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors such as tofacitinib, upadacitinib, and filgotinib, act on the intracellular JAK-signal transducers and activators of transcription (STAT) signalling pathway by blocking kinase activity and preventing STAT phosphorylation.

Cardiovascular safety concerns with oral JAK inhibitor surveillance have been most clearly identified in older, high-risk populations, particularly from the Oral Rheumatoid Arthritis (ORAL) Surveillance trial. This randomized trial evaluated MACE in patients with rheumatoid arthritis who were 50 years of age or older with at least one cardiovascular risk factor (approximately half were ever-smokers),comparing tofacitinib 10 mg and 5 mg twice daily with TNF inhibitors. Tofacitinib failed to demonstrate non-inferiority for the composite cardiovascular endpoint, indicating an increased risk of MACE relative to TNF inhibitors. Subgroup analysis revealed a higher incidence of MACE among patients aged 65 years or older compared to younger patients.[23] As a result, JAK-inhibitors (tofacitinib, and upadacitinib) carry a U.S. FDA black-box warning for MACE and thrombotic events.

A network meta-analysis assessing the risk of MACE, venous thromboembolism, and cardiovascular events reported no significant increase in risk associated with JAK-inhibitors overall, although a rising trend was noted for tofacitinib and upadacitinib.[24] Consistent with these findings, a recent study based on a real-world cohort compared the cardiovascular safety of JAK-inhibitors and anti-TNF agents reported no difference between the two treatment classes.[25,26] In contrast, a study based on an analysis of the U.S. FDA Adverse Event Reporting System (FAERS) data identified a potential association between JAK inhibitor use and cardiovascular adverse events in older patients (72% aged above 50 years and 39% aged above 65 years) and those with pre-existing cardiovascular risk factors.[27] Accordingly, cautious use of these drugs is recommended in patients ≥65 years of age with pre-existing risk factors for cardiovascular disease.

Sphingosine-1-phosphate Modulators

Sphingosine-1-phosphate (S1P)-receptor modulators such as ozanimod and etrasimod act by binding to the S1P-receptor and preventing

it from sensing S1P levels, thereby inhibiting lymphocyte egress from lymphoid tissue. These agents have the potential to cause cardiac conduction-related abnormalities in patients. Clinical trial data for ozanimod in patients with UC indicate a risk of bradycardia in the induction phase, with a subset of patients also developing mild atrioventricular conduction block.[28] Mild-to-moderate hypertension has also been noted as a treatment-emergent adverse effect in patients on etrasimod.[29] Given the consistent observation of bradycardia, hypertension, and conduction defects, it is advisable to perform a baseline electrocardiographic assessment and careful dose titration to help reduce the risk of cardiovascular adverse effects. S1P receptor modulators are contraindicated in patients with a history of MACE, unstable angina, transient ischemic attack, decompensated HF, or NYHA class III/IV HF within the preceding 6 months, as well as in those with advanced heart block or sick sinus syndrome unless a functioning pacemaker is present.

Immunomodulators

Traditional immunomodulators in IBD, which include azathioprine, 6-mercaptopurine and methotrexate are frequently used in combination with biologic therapies to enhance efficacy and reduce immunogenicity. In select cases, particularly in UC, they may be used as monotherapy for maintenance of remission. Studies of IBD cohorts have noted the cardioprotective effect of thiopurines, with associations to reduced incidence of HF, MI, and stroke. These benefits have been observed despite thiopurines often being introduced in patients with refractory disease and considerable underlying inflammation, indicating the strong immunomodulatory and antithrombotic effect of these therapies.[1,11] Although cardiovascular outcomes data from IBD cohorts are limited for methotrexate, data from other immune-mediated diseases has shown that methotrexate use is associated with reductions in MACE and cardiovascular mortality.[30]

5-Aminosalicylic Acid Agents

5-Aminosalicylic acid (5-ASA) agents exert their anti-inflammatory effects on the intestinal mucosa, by inhibiting cyclooxygenase and lipoxygenase pathways, reducing production of proinflammatory cytokines, and scavenging reactive oxygen species.

Evidence on the effect of 5-ASA agents on cardiovascular outcomes is inconclusive. While a Danish study reported coronary artery disease risk reduction, a study from the UK showed a higher risk of cardiovascular disease among treated patients. Other investigations have shown increased aortic stiffness with 5-ASA therapy, a finding that can contribute to hypertension and adverse cardiovascular outcomes. In addition, rare cases of myocarditis and pericarditis have also been observed in patients using 5-ASA, likely representing an idiosyncratic hypersensitivity reaction.[31] Taken together, the presence of conflicting data suggests that these agents should be used with caution in individuals with pre-existing cardiovascular disease.

Conclusion

Patients with IBD are at increased risk of cardiovascular morbidity, largely driven by chronic systemic inflammation. While many IBD therapies reduce inflammation and improve cardiovascular outcomes, the magnitude and consistency of these benefits vary across drug classes. Agents such as corticosteroids, anti-TNF therapies, anti-IL12/23 and anti-IL23 inhibitors, small molecule therapies, and 5-ASA, while generally beneficial, have the potential to produce class-specific cardiovascular adverse effects that must be considered when making decisions regarding treatment plans.

Additionally, clinicians should proactively screen for traditional risk factors such as hypertension, diabetes, dyslipidemia, obesity, and smoking, as these factors can predispose patients with IBD to cardiovascular events. Establishing a baseline cardiovascular assessment in patients prior to starting IBD therapy can help detect and possibly mitigate the risk of cardiovascular morbidity. Implementation of class-specific measures such as cardiovascular risk stratification and regular monitoring of lipid profiles for patients receiving JAK-inhibitors, as well as baseline electrocardiographic assessment for those treated with S1P-modulators, can meaningfully improve long-term cardiovascular outcomes in patients with IBD.

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