An Overview about Cardiovascular manifestations of Inflammatory Bowel Disease

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Abstract

Background: Inflammatory Bowel Disease (IBD) defines a group of chronic inflammatory diseases that affect mainly the gastrointestinal tract , mainly presenting in two major forms: Crohn's Disease (CD) and Ulcerative Colitis (UC). The pathogenesis of IBD is not yet fully explained , but it is known to result from the interaction between four major components: an aberrant immune system, genetic factors, environmental triggors, and intestinal microbiota (so , the presence of only one component does not cause the onset of IBD). The main manifestations in IBD are intestinal (abdominal pain, mucoid or bloody stool, rectal bleeding, and tenesmus) and systemic (fever, fatigue, loss of appetite, and weight loss) . IBD can also exhibit a wide range of extraintestinal manifestations (IBD-associated disorders that affect organs that are distant to the digestive tract): hepatobiliary, genitourinary, musculoskeletal, respiratory, ophthalmic, cutaneous, and cardiovascular. Cardiovascular manifestations in IBD can be defined by IBD-associated disorders that affect the cardiovascular system . Cardiovascular manifestations in patients with IBD mostly occur as immune-related consequences and include the following: pericarditis, myocarditis, venous and arterial thromboembolism, left ventricle impairment, arrhythmias and conduction disorders, infective endocarditis, valvulopathy, and Takayasu arteritis.

Keywords: Cardiovascular manifestations, Inflammatory Bowel Disease

Introduction

IBD defines a group of chronic inflammatory diseases that affect mainly the gastrointestinal tract , mainly presenting in two major forms: Crohn's Disease (CD) and Ulcerative Colitis (UC). The pathogenesis of IBD is not yet fully explained , but it is known to result from the interaction between four major

components: an aberrant immune system, genetic factors, environmental triggors, and intestinal microbiota (so , the presence of only one component does not cause the onset of IBD). The inflammatory response is mediated by immune cells (T-helper 1 and T-helper 17 in CD and T-helper 2 in UC), cytokines (Tumor Necrosis Factor-α (TNF-α), transforming growth factor-β, and interleukins- (IL-) 12, IL-17, and IL23), chemokines, reactive oxygen species, neuropeptides, and nonimmune (myeloid, epithelial, mesenchymal, lymphoid, neurogenic, and endothelial) cells **(1).**

The primary immune response to one or more stimuli induces tissue destruction and proliferation of endothelial and mesenchymal cells, resulting in a secondary immune response that amplifies the already present inflammation and stimulates fibrosis, tissue remodeling, angiogenesis, and lymphangiogenesis . The

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nonresolving inflammation determines the installation of a vicious cycle of self-sustaining chronic inflammation and maintenance of angiogenesis, fibrosis, and tissue destruction processes. The main manifestations in IBD are intestinal (abdominal pain, mucoid or bloody stool, rectal bleeding, and tenesmus) and systemic (fever, fatigue, loss of appetite, and weight loss) . IBD can also exhibit a wide range of extraintestinal manifestations (IBD-associated disorders that affect organs that are distant to the digestive tract): hepatobiliary, genitourinary, musculoskeletal, respiratory, ophthalmic, cutaneous, and cardiovascular. Cardiovascular manifestations in IBD can be defined by IBD-associated disorders that affect the cardiovascular system . Cardiovascular manifestations in patients with IBD mostly occur as immune-related consequences and include the following: pericarditis, myocarditis, venous and arterial thromboembolism, left ventricle impairment, arrhythmias and conduction disorders, infective endocarditis, valvulopathy, and Takayasu arteritis **(2).**

Cardiovascular manifestations	*Possible pathogenic mechanisms*
Pericarditis and myocarditis	(i) Immune-mediated myocarditis in IBD as a result of exposure to autoantigens (ii) Cardiotoxicity as an adverse effect of the treatment with 5-ASA and its derivatives
Venous thromboembolism	(i) Hypercoagulability induced by the systemic inflammation (ii) Platelet abnormalities (iii) Endothelial dysfunction induced by mechanical and systemic factors (iv) Venous stasis (v) Acquired risk factors (prolonged hospitalization, surgical interventions, central venous catheters, prolonged immobilization and bed rest, glucocorticoids, smoking, oral contraceptives, vitamin deficiencies, dehydration, hormone replacement therapy, and hyperhomocysteinemia) (vi) Genetic risk factors (dysfibrinogenemias, prothrombin gene mutation, factor V Leiden thrombophilia, and deficiency of proteins C, S, and antithrombin)
Arterial thromboembolism	(i) Structural and functional vascular alterations induced by chronic systemic inflammation (ii) Accelerated development of atherosclerosis and highly unstable atherosclerotic plaques (iii) Endothelial dysfunction induced by microbial lipopolysaccharides (iv) Altered gut microbiota (v) Adipokines

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	(vi) Calprotectin (vii) NOD2/CARD15 gene polymorphism (viii) Dyslipidemia
Heart failure	(i) Myocardial fibrosis secondary to altered collagen metabolism, impaired nitric oxide-mediated vasodilation, and deficiencies of vitamins and essential trace elements (ii) Heart muscle atrophy due to prolonged use of corticosteroids, total parenteral nutrition, and chronic inflammatory status (iii) Myocarditis, endocarditis, and valvulopathy
Arrhythmias and conduction disorders	(i) Interstitial fibrosis and structural and functional cardiac remodeling (ii) Impaired autonomic nervous system: increased sympathetic and decreased parasympathetic activity
Endocarditis	(i) Bacteremia due to increased transmucosal permeability (ii) Predisposing risk factors: immunosuppression, preexistent valvular heart disease, and central venous catheters
Valvulopathies	(i) Myxomatous degeneration (ii) Ascending aorta changes due to chronic systemic inflammation
Takayasu arteritis	Genetic risk factors: HLA-A∗24:02, HLA-B∗52:01, and HLA-DRB-1∗15:02

Table(1): Cardiovascular manifestations in IBD **(2).**

Epidemiology of Cardiovascular extraintestinal manifestations:

Frequencies of EIM in IBD range from 6% to 47%, and multiple EIM may concomitantly occur. Moreover, EIM may occur prior to the diagnosis of IBD in up to 25% of cases . The cardiovascular disease incidence among IBD patients is modestly higher than that in the general population and its incidence should not be ignored, considering the serious impact of the consequences if untreated **(3)**

Pericarditis represents the most frequent cardiovascular EIM in IBD patients (70% of the total number of cardiovascular complications) . Its prevalence is 0.19% among the CD patients and 0.23% among the UC patients . A review of 68 patients with IBD showed that pericarditis occurs more frequently in male patients with UC **(4).**

Patients with IBD may present with both venous and arterial thromboembolic complications. They present a 1.7-5.5-fold greater risk for venous thromboembolism than the general population , this has been reported in both adult and pediatric populations **(4).**

The incidence of atrial fibrillation is 11.3% in patients with IBD versus 0.9% in the general population . A Danish cohort study found a 2 times higher risk of atrial fibrillation in IBD during flares and episodes of persistent activity . It is important to acknowledge the increased risk of atrial fibrillation in IBD patients since this arrhythmia is associated with an increased risk of thromboembolism, heart failure, and mortality, it affects the quality of life and exercise capacity, and it increases the hospitalization risk. Recent studies involving pediatric population had showed considerable prolongation of the duration of P-wave and QT interval dispersion which occur earlier in life and may predispose patients to the development of serious

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atrial and ventricular arrhythmias in the long term. Therefore, it is advisable to perform frequent ECG examinations with accurate measurement parameters of the P-wave and QT variability in all paediatric IBD patients even if they have had no past CV diseases and are free of cardiac involvement **(5).**

Myocarditis and Pericarditis

Pericarditis represents the most common cardiovascular complication in IBD. Myocarditis can be defined as an inflammation of the myocytes and the interstitial tissue. Occasionally, the pericardium may also be involved, in which case it is called myopericarditis **(3)**

Patients with IBD have a higher risk for developing myopericarditis than the general population. This can be explained by two mechanisms: autoimmune mediation generated by exposure to autoantigens and drug toxicity following an administration of 5-aminosalicylic acid (5-ASA) or its derivativesExposure to autoantigens in an acute episode may cause direct cytotoxicity on myocytes, causing the release of inflammatory mediators and activation of the immune system. This sequence of events can lead to acute myocarditis. If myocarditis is not detected in the acute or subacute phase and the inflammation is not counteracted, myocardial destruction will continue and patients will develop chronic myocarditis. Remodeling processes that are characteristic of chronic inflammation may cause dilation of the cardiac cavities (resulting in systolic dysfunction, anomalies of parietal kinetics, and decreased ejection fraction), valvular regurgitation (by rupture of papillary muscles), or arrhythmias (due to the fibrosis of the conduction system, occurrence of reentry phenomena, and excessive adrenergic stimulation) **(6).**

The clinical picture for myopericarditis is nonspecific. Patients may present with symptoms similar to those of the acute coronary syndrome, heart failure (new onset or decompensated heart failure), arrhythmias, cardiogenic shock, or sudden death . The occurrence of such clinical picture within the first 28 days since the initiation of the treatment with 5-ASA or its derivatives raises the suspicion of drug toxicity **(6).**

The 12-lead electrocardiogram may be normal, or it may reveal an ST segment elevation or depression, a negative T wave or rhythm, or conduction disorders.Blood tests may indicate elevated levels of biomarkers of cardiac injury (troponin, creatine kinase, creatine kinase-MB, alanine aminotransferase, and aspartate aminotransferase), as well as B-type natriuretic peptide and N-terminal probrain natriuretic peptide in patients with associated heart failure. Leukocytosis and increased levels of acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein, and fibrinogen) may also be present **(6).**

Transthoracic echocardiography should be performed in all patients with clinical presentation suggestive for myopericarditis. The presence of left ventricular dysfunction, anomalies of parietal kinetics, low ejection fraction, or pericardial effusion should raise the suspicion of myopericarditis. Coronary angiography should be done in all patients with the clinical picture suggestive for acute coronary syndrome, since the absence of hemodynamically significant angiographic lesions of the coronary arteries excludes the diagnosis of myocardial infarction (**7).**

Cardiovascular magnetic resonance (CMR) offers noninvasive characterization of the myocardial tissue, and it can provide the necessary information for the diagnosis of myocarditis. CMR diagnostic

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criteria for myocarditis include myocardial (regional or global) oedema, myocardial hyperaemia, and focal fibrosis or necrosis with noncoronary artery distribution . If patients are hemodynamically stable , then it is recommended to perform CMR before endomyocardial biopsy. Endomyocardial biopsy should be performed in life-threatening conditions, when CMR is not indicated. Endomyocardial biopsy remains the gold standard for diagnosing and establishing the cause of myocarditis. IBD-associated myocarditis can frequently present under two histopathological forms: acute/chronic lymphocytic myocarditis and giant cell myocarditis (the latter form has a poor prognosis). Supportive therapy depends on the patients' hemodynamic stability. Hemodynamically unstable patients should be redirected to intensive care units that can provide advanced cardiopulmonary support such as mechanical ventilation and extracorporeal membrane oxygenation . Hemodynamically stable patients should be monitored in a hospital setting and treated according to the current recommendations for heart failure with beta-blockers and/or inhibitors of the renin-angiotensin-aldosterone system *(8).*

Nonsteroidal anti-inflammatory drugs can be used in patients with pericardial involvement . However nonsteroidal anti-inflammatory drugs which selectively inhibit the cyclooxygenase-2 should be recommended Considering the high possibility of gastrointestinal toxicity. Colchicine, another drug usually used for treatment of pericarditis, may cause diarrhea as a side effect and, therefore, it can potentially complicate the evolution of IBD. Immunosuppressive therapy may be associated with the supportive therapy after exclusion of infectious etiology. The most widely used immunosuppressive agents are immunoglobulin, corticosteroids, azathioprine, and cyclosporine, and the duration of administration usually ranges from 3 to 6 months . Management of myocarditis also involves restriction of physical activity during the acute phase and for the following 6 months. Recovery signs include improvement of ejection fraction and parietal kinetics *(9).*

4. Venous Thromboembolism

Deep vein thrombosis and pulmonary thromboembolism constitute the most frequent venous thromboembolic events. But venous thromboembolic events can also occur in the cerebral, portal, mesenteric, or retinal sites. Recent studies investigating the incidence of venous thromboembolism in children with inflammatory bowel disease revealed that the overall incidence of VTE in children with IBD was significantly higher than previously described. a large Canadian population-based matched cohort conducted in five provinces, including 3593 children with IBD and 16 284 matched controls. Patients were identified using validated algorithms from health administrative data and compared with age- and gender-matched children without IBD. Data regarding hospitalisations for VTE within 5 years from IBD diagnosis were collected. Not surprisingly, the results showed that the incidence of VTE was significantly higher in the IBD group than in the controls [from 12- to 45-fold higher], and the risk of VTE in ulcerative colitis [UC] was nearly double that seen in Crohn's disease [CD]. Only a quarter of VTE events were associated with IBD surgery **(10).**

Venous thromboembolism can be triggered by genetic or acquired factors. Long-term hospitalization, surgical interventions, central venous catheters, prolonged bed rest and immobilization, corticosteroid therapy, vitamin deficiency, dehydration, hormone replacement therapy, and hyperhomocysteinemia are among the most frequent acquired risk factors for venous thromboembolism . Genetic risk factors such as dysfibrinogenemia, prothrombin gene mutations   , factor V Leiden, antithrombin, and protein C or S deficiency should be evaluated in children with IBD with recurrent thromboembolic venous events.

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Virchow's triad, known to be associated with venous thromboembolism, describes three conditions that predispose to thrombosis: hypercoagulability, endothelial dysfunction, and venous stasis **(11).**

Hypercoagulability states is mediated by the inflammatory process that initiates clotting and interferes with the fibrinolytic system, decreasing the anticoagulant activity . The inflammation in IBD levels can be illustrated by increased levels of C-reactive protein and cytokines (the most frequently observed cytokines are TNF-α, vascular endothelial growth factor, and IL-6). The reduction in anticoagulant activity not only increases thrombosis risk but also helps sustain the inflammatory status by stimulation of thrombin to produce TNF-α, IL-6, and IL-10 **(4).**

In addition, the following hemostatic diseases have been observed during flares: elevated levels of coagulation factors (V, VIII, von Willebrand, and fibrinogen) and products of thrombin and fibrin formation, increased markers of vascular endothelial activation, and acquired deficiencies or dysfunction of natural anticoagulants (protein C, protein S, and antithrombin) **(11).** Platelet abnormalities (reactive thrombocytosis, reduced mean platelet volume, and increased granular content) also contribute to the hypercoagulability. The enhanced activation state of platelets is mediated by the CD40-CD40 ligand pathway **(12).**

Endothelial dysfunction in children with IBD (procoagulant surface of the vascular bed) is a result of mechanical damage (e.g., intravenous catheters) or activation of the vascular endothelial cells by inflammatory mediators. Inflammation determines the occurrence of the thrombophilic effect of the vascular endothelium, and it accentuates the adhesion between the endothelial surface and leukocytes or platelets **(13).**

The last condition described by Virchow's triad is represented by a disturbance of the blood flow, as in patients with prolonged immobilization (a common situation encountered during flares in IBD), dehydration, or central vein catheters **(11).**

The clinical manifestations of venous thromboembolism depend on the site of the thrombus, and it can range from asymptomatic to severely symptomatic, but thevenous thromboembolic event is suspected when the patient has an unexplained episode of dyspnea, hypoxia or unilateral leg pain, and swelling **(4).**

The diagnosis of venous thromboembolic events is based on appropriate imaging investigations such as compression ultrasound or venography for deep vein thrombosis, ventilation/perfusion lung scanning or spiral computed tomography for pulmonary emboli, and computed tomography for other affected sites. Existing guidelines on primary prevention of thromboembolism in children with IBD provide conflicting recommendations. The current ECCO/ESPGHAN guideline only recommends prophylaxis for hospitalised children with acute severe colitis with at least one additional risk factor for VTE.The Canadian Association of Gastroenterology recommend against prophylaxis even in children hospitalised because of severe recurrence of their IBD **(14).**

Adult and paediatric gastroenterologists are cautious about prescribing thromboprophylaxis due to the presumed bleeding risk, but it has been shown to be safe in adults with IBD, even in those presenting with rectal bleeding. Interestingly, a recent RAND consensus on the treatment of paediatric acute severe colitis during the COVID-19 pandemic recommended all patients should receive prophylaxis.In addition to conflicting recommendations for ulcerative colitis, no guideline exists for thromboprophylaxis in paediatric Crohn's disease **(14).**

Treatment of acute venous thromboembolism in patients with IBD is similar to that in patients without IBD. The use of anticoagulants (unfractionated heparin and low-molecular-weight heparin) is

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recommended for mild and moderate venous thrombosis, whereas local or systemic thrombolysis is recommended for massive vein thrombosis**.** The secondary prevention of venous thromboembolism (anticoagulation) must be individualized according to each patient's hemorrhagic and thromboembolic risks.Long-term anticoagulation using low-molecular-weight heparin, vitamin K antagonists, or novel direct oral anticoagulants is indicated in case of initial unprovoked venous thromboembolic event (in the absence of disease activity or temporary/transient risk factors) . Short-term anticoagulation (3-6 months) is indicated in case of provoked thromboembolic event, and prophylaxis of disease exacerbations can also be added. The placement of inferior vena cava filters is recommended to patients with high thromboembolic risk **(15).**

5. Arterial Thromboembolism

It is a well-known chronic inflammation and abnormalities of endothelial function play an important role in atherogenesis, one of the most important factors involved in arterial thromboembolism. C-reactive protein, TNF-α, vascular endothelial growth factor, and IL-6 represent molecules involved in both atherogenesis and IBD, and their increased serum levels among the IBD patients confirm that atherogenesis is accelerated among this class of patients **(16).**

There are multiple mechanisms involved in maintenance of the chronic inflammation. IBD patients are also characterized by a disrupted intestinal barrier which facilitates the passage of microbial products (lipopolysaccharides and other endotoxins) to bloodstream. Lipopolysaccharides are known to increase the expression of proinflammatory cytokines, to affect the oxidation of low-density cholesterol, and to activate the macrophages, all of which contributing to endothelial dysfunction, foam cell formation, and atherosclerosis **(16).**

Obesity (when present) also augments the inflammatory status. The adipose tissue is known for producing adipokines: leptin, resistin, and adiponectin (proinflammatory cytokines). Mesenteric fat also produces proinflammatory cytokines, such as TNF-α and IL-6 **(27).**

The gut microbiota in IBD is characterized by an abnormal composition of microbial environment (loss of microbial diversity) that can induce immunoregulatory pathways and can mitigate the chronic inflammation. The gut microbiota is also involved in the atherosclerosis process and increased platelet activation via decreased levels of trimethylamine N-oxide and the induction of expression of Toll-like receptors 2 and 4. Microorganisms can also affect the blood pressure in IBD. Calprotectin is an acute-phase reactant that has been associated with the disease activity in IBD and higher risk for cardiovascular complications. Calprotectin binds to Toll-like receptor 4, a receptor that amplifies inflammation and atherosclerosis. Also, calprotectin binds to the receptors for advanced glycation end products (RAGE) which mediate myocardial dysfunction**(18).**

The chronic inflammatory process induces structural and functional arterial changes. Smooth muscle cell hyperplasia can be demonstrated by measurement of carotid intima-media thickness (a subclinical marker of atherosclerosis). Vascular fibrosis and degradation of elastic fibers that occur in the walls of large blood vessels determine vascular stiffness (another subclinical marker of atherosclerosis). Vascular stiffness is not associated with the cardiovascular risk factors, but with the duration of the episodes of disease activity.IBD patients are also characterized by abnormal lipid profiles (low levels of total and high-density cholesterol and high levels of low-density cholesterol), known risk factors for atherosclerosis. The exact mechanism is not clear , but it may be due to either chronic inflammation or malabsorption **(19).**The clinical picture depends on the location of the thrombus, and it can vary from asymptomatic to intensely symptomatic (e.g., chest pain or heart failure symptoms in myocardial infarction and pale, cold, and painful

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extremities   in   acute limb ischemia). Arterial thromboembolism is suspected when the patients complain of chest pain or motor deficits. Primary preventive strategies of arterial thromboembolism involve maintenance of remission, strict control of cardiovascular risk factors, avoiding consumption of oral contraceptives or hormonal replacement therapy, and administration of vitamin B6, B12, and folic acid supplements in case of hyperhomocysteinemia . Acute management and secondary prevention of arterial thromboembolism are not different from those in non-IBD patients **(20).**

6. Heart Failure

Acute heart failure can be caused by acute myocardial infarction, myocarditis, pericarditis complicated by tamponade, or endocarditis. Chronic heart failure is caused by valvulopathies, untreated/undiagnosed myocarditis, heart muscle atrophy due to prolonged use of corticosteroids or total parenteral nutrition, and chronic inflammatory status **(21).**

A chronic inflammatory status associated with IBD affects collagen metabolism, causing an inadequate collagen deposit in both affected and distant target organs (demonstrated by elevated serum levels of procollagen III peptides). This, together with secondary microvascular endothelial dysfunction, alteration of nitric oxide-mediated vasodilation, and vitamins and essential elements deficiencies, contributes to myocardial fibrosis **(21).**

Myocardial fibrosis causes left ventricle (LV) impairment: both systolic and diastolic. Transthoracic echocardiography represents the modality of choice to diagnose heart failure and evaluate both systolic and diastolic LV functions . LV ejection fraction reflects the systolic function of the LV, but there are new deformation imaging techniques (strain and strain rate) that can detect subtle abnormalities in the systolic function of the LV even from the preclinical stage. Thus, one can see a low LV global longitudinal strain that can moreover be correlated with the indexes for IBD activity [87–89]. In addition, LV longitudinal strain rates are also reduced, suggesting delayed LV peak contractility . Another sign of LV systolic dysfunction is the detection of abnormalities of wall kinetics (myocarditis and arterial involvement should be taken into consideration) **(22).**

Diastolic dysfunction can be clarified in the early stages by measuring the ratio between early mitral inflow velocity and early mitral annular diastolic velocity (one of the most used echocardiographic parameters, a ratio that reflects the LV filling pressures), which will be increased (>14) in patients with IBD with subclinical LV diastolic impairment **(22).**

7. Arrhythmias and Conduction Disorders

Patients with IBD present a predisposition for atrial and ventricular arrhythmias and conduction disturbances. The chronic inflammatory condition found in IBD is the key element in the pathogenesis of arrhythmias. The chronic inflammatory process mediated by proinflammatory cytokines (C-reactive protein, IL-6, and TNF-α) causes, through ischemia and oxidative stress, myocardial destruction that, in time, causes interstitial fibrosis and impairs the intracellular calcium current resulting in structural and electrical remodeling, known determinants of arrhythmias. During the active periods of the disease, the enhanced inflammatory status will probably trigger the arrhythmia **(23).**

Chronic inflammation also leads to the occurrence of autonomic dysregulation (increased sympathetic tone and decreased parasympathetic tone), resulting in reduced heart rate variability and prolonged QT interval, factors that contribute to the development of arrhythmias . Heart rate variability in patients with IBD correlates with periods of activity, duration of illness, and inflammatory markers **(24).**

Patients with IBD experienced increased values for corrected QT interval and corrected QT dispersion. These parameters reflect the ventricular depolarization/repolarization time and conduction

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heterogeneity at this level. This demonstrates the increased risk of ventricular arrhythmias in patients with IBD. Obesity, iron deficiency anemia and electrolyte disturbances (hypokalemia, hypocalcaemia, and hypomagnesaemia), and selenium deficiency among\IBD patients are additional risk factors for ventricular arrhythmias **(5).**

P-wave dispersion measured by electrocardiogram reflects the conduction of the sinus electrical stimulus at the atrial level. Increased values are found in IBD patients, and it indicates the heterogeneity of intra-atrial and interatrial conduction as well as discontinuous propagation of electrical impulses, which leads to atrial fibrillation **(5).**

Intra-atrial and interatrial conduction can also be assessed by the Doppler echocardiography, and IBD patients present an increase in atrial electromechanical delay and a reduction in left atrial mechanical function, changes that correlate with\the disease duration (patients with active disease have significantly higher values than patients in remission, but both patients with active disease and in remission have higher values than the general population) **.**Chronic inflammation also affects the success rate of cardioversion and maintenance of the sinus rhythm in patients with IBD and atrial fibrillation **(23).**

Atrioventricular conduction disturbances (complete atrioventricular block, second-degree or first-degree atrioventricular block) have been reported in patients with IBD and may occur due to the administration of infliximab, ischemia in the conduction system secondary to inflammation, vasculitis, or microvascular endothelial dysfunction**.** Careful ECG monitoring (including 24 h Holter ECG), regular measurements of serum electrolyte levels, and maintenance of remission for as long as possible are additional measures that need to be taken into consideration during management of IBD **(23).**

8. Endocarditis

Cases of infectious endocarditis are reported in the literature in patients with IBD. Predisposing risk factors include immunosuppressive medication, the presence of central venous catheters, and significant preexisting valvulopathies. In addition, IBD patients have an increased risk of secondary bacteremia due to increased transmucosal permeability and secondary immunosuppression due to the corticosteroids or other immunosuppressants **(25).**

Microbial agents described in the literature as being involved in the etiopathogenesis of infectious endocarditis are Enterococcus faecalis, Enterococcus faecium, Peptostreptococcus, Streptococcus bovis, Candida albicans, and Bacteroides fragilis **(25).**

Symptoms and signs that suggest the possibility of endocarditis are fever, heart murmurs, or embolic phenomena. Treatment of infectious endocarditis in patients with IBD does not differ from that in patients without IBD **(26).**

The Advisory Group of the British Cardiac Society Clinical Practice Committee and Royal College of Physicians Clinical Effectiveness and Evaluation Unit consider the IBD patients as a high-risk group. Antibiotic prophylaxis should be mandatory in the case of invasive procedures or central venous catheters, especially if the patient has a preexistent valvulopathy. Furthermore, the use of immunosuppressive therapy and corticosteroids should be also minimized **(25).**

9. valvulopathies:

The most common IBD-related valvulopathies are aortic and mitral regurgitation . In IBD, inflammation contributes to mitral and aortic valvulopathies (where blood pressures are high), and excess TNF-α causes the thickening and shortening of the leaflets leading to regurgitation. Another possible

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explanation is the myxomatous degeneration (collagen deposition on the valve) resulting in a benign valve leaflets prolapse or even mild regurgitation **(27).**

Other changes that may be secondary to the chronic inflammatory process involve aortic aneurysm or ectasia, coronary ostial stenosis, and atrioventricular conduction abnormalities . Early detection of these valvular changes could help in prevention of flares in IBD or prograssion of the valvulopathies **(2).**

10. Takayasu Arteritis:

Takayasu arteritis is an autoimmune disorder usually affecting large vessel components. The degree of inflammation of the vessels determines fibrosis, stenosis, and thrombosis. Takayasu arteritis and IBD (especially UC) have several common types of HLA: class I (HLA-A∗24:02 and HLA-B∗52:01) and class II (HLA-DRB-1∗15:02), which could explain their coexistence in some patients with IBD . In patients with IBD and Takayasu arteritis, IBD symptoms are the first to appear. At the same time, in these patients, Takayasu arteritis manifestations appear more quickly when compared to patients with only Takayasu arteritis, without IBD **(28)**

The clinical picture involves fever, fatigue, and focal symptoms (depending on the site and size of the affected vessel): cervical, maxillary, brachial, humeroscapular, or chest pain, whether or not accompanied by unilateral or bilateral paraesthesia . In patients with IBD and Takayasu arteritis, the clinical picture is formed more frequently by constitutional symptoms, headache, vertigo, and gastrointestinal symptoms **(29).**

Risk factors for CVD in IBD

Multiple factors contribute to the pathogenesis of atherosclerosis, which comprises traditional and nontraditional risk factors. The traditional risk factors for CVD are age , male gender, family history of coronary artery disease (CAD), obesity (BMI >30), HTN, HLD, DM,smoking, alcohol use, and chronic kidney disease. It has been noted that patients with IBD do not have a higher incidence of HLD, obesity, or HTN and yet have a higher risk for CVD, denoting that nontraditional risk factors such as disease activity and chronic inflammation play an important role in the development and progression of CVD **(3)**

Role of chronic inflammation

The role of pro-inflammatory cytokines in the pathogenesis of CVD is well documented. Many studies proved that several inflammatory markers—such as CRP, TNF-α, interleukin (IL)-6, IL-1β—play an essential role in the atherosclerotic process and increased odds of CV event. Chronic inflammation—characteristic for IBD and associated with increased levels of pro-inflammatory cytokines—is an essential factor associated with the severity of IBD. TNF-α–pro-atherothrombotic cytokine, is increased in both UC and CD and augments the expression of VCAM-1 (vascular cell adhesion protein-1), which in turn contributes to the interaction of leukocytes with endothelium **(30)**

It should be remembered that endothelial dysfunction is also involved in the pathogenesis of IBD. Moreover, It was observed that the use of infliximab, blocking the TNF-α, also decreases the expression of VCAM-1 from the intestinal mucosa from intestinal micro veins, which further inhibits their inflammation and interaction with the T-cells. Further, one of the results of chronic inflammation among IBD patients is aortic stiffening; however, as Zanoli et al. have shown, long-term anti-TNFα therapy reduces aortic pulse-wave velocity in IBD population, which suggests that inflammation therapy may reduce CV risk in IBD patients**.** Vascular endothelial growth factor (VEGF)—mediating angiogenesis—is another cytokine which increases inflammation in the intestines . Interestingly, it is a proatherogenic factor at the same time. However, its protective effect, associated with the stimulation of new veins of the collateral circulation, may also be found in the literature. CRP is the most frequently used inflammatory biomarker both in the clinical practice and in the literature. It has been established that its concentration increases during active phase of IBD, thus proving the presence of inflammation. Furthermore, the cardiovascular

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risk is higher when CRP concentrations are increased. Nevertheless, according to the new studies, the longer the exposure, the higher the risk, which in turn could suggest that the duration of increased CRP concentrations is more critical than the CRP levels. This observation may be particularly essential in the IBD population presenting with chronic inflammation **(31).**

Drugs Used in IBD and CV Risk

It is intuitive to think that decreasing inflammatory burden with medications can lead to decrease in long-term CV risks in patients with IBD. Treating underlying chronic inflammation, especially early in the disease process, has been shown to improve CV outcomes in CID. The most frequently used drugs in IBD are 5-aminosalicylates, glucocorticoids (GCs), immunomodulatory drugs, and biological drugs **(32).**

Corticosteroids

Steroids have been historically used to reduce inflammation. However, detrimental effects such as edema, worsening HF, electrolyte imbalance, increase in blood glucose, and blood pressure need close monitoring with high-dose steroids.In addition, metabolic effects of long-term steroid use such as HTN, obesity, HLD, and insulin resistance have been associated with increased CV risk in the general population and CID. Corticosteroids have been shown to increase CAD risk in IBD patients, but data are inconsistent. Close and colleagues reported that patients with ulcerative colitis (UC) had a higher incidence of IHD and MI with steroid use but A retrospective single-center case control study did not show this association**.(33).**

The side effects of prolonged steroid use (defined by >3 gm or equivalent dose over a 12-month period) in IBD patients was studied by Lewis and colleagues in the cohort of Medicaid and Medicare patients. Crohn's disease (CD) patients had increased mortality with prolonged steroid use as compared with anti-TNF use that was mainly related to major cardiovascular events and hip fractures **.** It is hard to decipher whether the increase in CV events during this time period is due to direct effect of steroids or uncontrolled disease activity. Overall, corticosteroids might have a beneficial anti-inflammatory action in the short term, but there is overarching evidence of long-term side effects of corticosteroids, which include CVD and mortality.for these reasons, the latest guidelines for RA and other CID recommend tapering glucocorticoids as soon as disease activity allows and transitioning to combination therapy. Specific guidelines for use of corticosteroids in IBD patients with respect to CVD are lacking **(34)**.

5-aminosalicylates

5-aminosalicylate (5-ASA) medications have been found to be associated with a decrease in CV events; however, data are inconsistent. In a Danish cohort study, 5-ASA use was associated with decrease in IHD , and the effect was more pronounced in long-term users.Analysis of a UK cohort did not find the association between 5-ASA use and CV events statistically significant. On the other hand, 5-ASA medications have been associated with side effects such as myocarditis and pericarditis and Sinus bradycardia has been reported with mesalamine use in UC patients. Zanoli and colleagues reported in their longitudinal case control study of IBD patients that salicylate use (n = 107) was associated with increase in arterial stiffness, as measured by carotid femoral PWV.34 Whether this effect is due to ineffective control of inflammation or actual mechanism of action of the drug is unclear. With current knowledge, it is debatable whether 5-ASA medications can be used as a treatment modality to decrease CV risk in IBD patients **.(35).**

Anti-tumour necrosis factor-a medications

Tumour necrosis factor-a is recognized as an important proinflammatory cytokine in IBD and anti-TNF-a approaches have been used in IBD patients. Studies have shown that anti-TNF-a therapy is

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associated with decreased incidence of cardiovascular events for patients with CD compared with prolonged corticosteroid treatment and could reduce aortic stiffness **.(35).**

Anti-TNF-a therapy has been shown to be associated with a reduced risk of thromboembolism and reduces baseline pro-coagulant imbalance of IBD patients with decreased levels of fibrinogen and CRP.Compared to 5- ASA and corticosteroids, anti-TNF-a therapy substantially reduces disease activity in IBD patients and is consistently associated with decreased cardiovascular events **(36).**

Janus Kinase Inhibitors Tofacitinib is a first-generation pan JAK inhibitor and the first oral small molecule to be approved for use in UC in United States. In 2019, Food and Drug Administration (FDA) issued a warning about increased risk of venous thromboembolism (VTE) and death with tofacitinib changing its indication for use in UC only as a second-line agent with recommendation for early dose reduction to 5 mg twice a day**.** Even though , mortality and VTE risks were not significantly increased with use of JAK inhibitors in IBD and other CID patients even with higher doses**.** JAK inhibitors have been associated with alteration in lipid profile, and hyperlipidemia is a known risk factor for CVD. However, the mechanism of lipid disorder, especially with a higher dose of 10 mg twice a day, is not clearly understood and has been shown to improve with dose de-escalation. Moreover, the implication of short-term dyslipidemia on CV events such as MI and stroke is unclear due to lack of long-term data in IBD patients **(37) .**

There is a lack of long-term data on CV adverse events with tofacitinib in IBD patients, and it is still to be deciphered whether the risk of VTE is related to the disease or the drug.

Interleukin 12/23 Inhibitors

Interleukin-12 is implicated in the pathogenesis of atherosclerosis, and inhibition of IL-12 in murine models may prevent atherosclerosis.Ustekinumab has been used for treatment of plaque psoriasis and PsA and is now available for treatment of CD and UC . Studies with briakinumab, another IL-12/23 inhibitor reported increased major cardiovascular events, which led to discontinuation of trials in 2011. Ustekinumab may be an effective and safe treatment option for pediatric and adolescent Crohn's disease and Crohn's disease-like inflammatory bowel disease patients having nonresponse or adverse reactions to anti-tumor necrosis factor agents and Two-year follow-up data from CD and UC trials did not indicate an increase or decrease in risk of CV events. Long-term data are awaited in the IBD population **(38)**

Anti-integrins

Vedolizumab is a humanised immunoglobulin G1 monoclonal antibody acting against α4β7 integrin which modulates lymphocyte trafficking specifically to the gut. Results from the GEMINI 1 and GEMINI 2 trials demonstrated effectiveness of vedolizumab in induction and maintenance of remission in both ulcerative colitis [UC] and Crohn's disease [CD], respectively, but the clinical benefit seems slightly superior in UC also vedolizumab is safe and effective in paediatric UC, and to a lesser extent also in CD **(39).**

Vedolizumab is a novel drug for IBD and does not have data from long-term studies in other CID. Randomized controlled trials and real-world observational studies have not reported an increased risk of CV events in IBD patients**.** However, postmarketing data from US FDA database of self-reported adverse events showed an increase in cerebrovascular events such as stroke and cerebral hemorrhage in patients treated with vedolizumab as compared with anti-TNF. When interpreting these data, confounding factors such as selfreporting and lack of information on CV risk factors and disease activity have to be considered **(40) .**

Medication	CV Effects	CVD in IBD

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Aminosalicylic acid	Myocarditis Pericarditis Arrythmia	Inconsistent data
Corticosteroid	Edema Heart failure Electrolyte disbalance Hypertension Obesity Hyperlipidemia Insulin resistance	Worsen CV outcomes
Immunomodulators	Pericarditis Arrythmia	Inconsistent data
Anti TNF	Heart failure Hypertriglyceridemia Arrythmia	May improve CV outcomes
Anti-Integrins (Vedolizumab)	Cerebral hemorrhagea Stroke	Limited data
Anti IL12/IL23 inhibitor (Ustekinumab)	Dyslipidemia	May improve CV outcomes
JAK1/3 inhibitors (Tofacitinib)	Dyslipidemia Increase venous thromboembolism	No increase in adverse CV outcomes Limited long-term data

Table (2): IBD medications and their effects on cardiovascular disease **(40) .**

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