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# INFLAMMATORY BOWEL DISEASES AND THE RISK OF CARDIOVASCULAR EVENTS — A LITERATURE REVIEW

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## ABSTRACT

Inflammatory bowel disease (IBD) — ulcerative colitis (UC) and Crohn's disease (CD) — comprises chronic, immune-mediated disorders of the gastrointestinal tract whose pathophysiological impact extends beyond the intestinal mucosa. A growing body of epidemiological evidence, including large-scale meta-analyses, indicates that patients with IBD carry an elevated risk of cardiovascular events, including coronary artery disease, stroke, heart failure (HF), venous thromboembolism (VTE), and atrial fibrillation (AF), despite a relatively lower prevalence of classical atherosclerotic risk factors in this population. This risk is particularly pronounced during periods of active, uncontrolled intestinal inflammation and in younger patients, in whom the contribution of the inflammatory process to overall cardiovascular risk is proportionally greatest. This review summarizes current evidence on the epidemiology of this association and the pathophysiological mechanisms linking chronic intestinal inflammation to vascular injury, including endothelial dysfunction, a prothrombotic state, gut microbiota dysbiosis and its metabolites — notably trimethylamine N-oxide (TMAO) — and inflammatory biomarkers. The differential impact of IBD pharmacotherapy on cardiovascular risk is also addressed, with particular emphasis on Janus kinase (JAK) inhibitors, associated with an elevated risk of thromboembolic complications, in contrast to biologic agents, which in several observational studies have demonstrated a potentially cardioprotective effect. The risk profile of TNF- $\alpha$  inhibitors in patients with coexisting heart failure is discussed separately. Finally, recommendations for cardiovascular risk stratification and prophylaxis in this population are presented, incorporating recent dedicated expert position statements from scientific societies, alongside directions for future investigation.

**Methods and Materials** A systematic review of the scientific literature concerning the risk of cardiovascular events in patients with a diagnosed inflammatory bowel disease was conducted. Randomized controlled trials, meta-analyses, and [observational] studies were analyzed...

**Conclusions** Particular attention should be paid to the assessment of cardiovascular event risk in patients with inflammatory bowel disease, especially in those who have had the disease for many years. Patients with inflammatory bowel disease [have an] increased risk of cardiovascular events, which is primarily attributable to chronic inflammation acting on the vascular wall through endothelial dysfunction, activation of coagulation, and disturbances of the gut microbiota, with the risk correlating more strongly with disease activity than with the diagnosis itself.

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## KEYWORDS

Inflammatory Bowel Diseases, Cardiovascular Risk, Atherosclerosis, Venous Thromboembolism, Endothelial Dysfunction

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## 1. Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), are chronic, multifactorially determined inflammatory diseases of the gastrointestinal tract, underlain by an abnormal immune response of the intestinal mucosa to environmental factors in genetically predisposed individuals, occurring alongside alterations in the composition of the gut microbiota. The incidence of IBD is steadily increasing worldwide, making these diseases a significant public health problem [1]. Their essence lies in a persistent, though temporally variable, inflammatory process of the gastrointestinal mucosa which — as data from the past decade increasingly indicate — does not leave distant organs unaffected, including the cardiovascular system.

Chronic immune-mediated inflammatory diseases — rheumatoid arthritis, systemic lupus erythematosus, psoriasis, or vasculitides — have long been known to be associated with an increased cardiovascular risk, independent of traditional atherosclerotic risk factors. This fact is reflected in the European Society of Cardiology (ESC) guidelines on cardiovascular disease prevention, in which chronic inflammatory conditions — including inflammatory bowel disease — are listed as factors modifying the estimated cardiovascular risk, although this association has to date been best documented for rheumatoid arthritis [22].

The place of IBD in this context remains the subject of intensive research. On one hand, patients with IBD more often present features of malabsorption syndrome, have a lower body mass index (BMI), lower cholesterol and glucose levels, and are less frequently diagnosed with arterial hypertension, which traditionally would suggest classifying them into a lower cardiovascular risk group as estimated by standard risk scores [11]. On the other hand, a growing number of cohort studies and meta-analyses indicate that, despite a more favorable profile of classical risk factors, patients with IBD more frequently experience coronary events, strokes, and thromboembolic complications than individuals without this disease — a phenomenon referred to in the literature as the "cardiovascular risk paradox" in IBD [10, 11]. Explanations for this paradox are sought in the direct, systemic effect of chronic inflammation on the vessel wall — through endothelial dysfunction, accelerated atherogenesis, activation of the coagulation system, and disturbances of the gut microbiota [4, 20]. An additional element is the effect of IBD treatment itself on cardiovascular risk — both potentially unfavorable (glucocorticosteroids, Janus kinase inhibitors) and potentially protective (biologic agents, particularly TNF- $\alpha$  inhibitors) [12, 23].

The aim of this review is to systematize current knowledge regarding the epidemiology and mechanisms of elevated cardiovascular risk in patients with inflammatory bowel disease, to discuss the impact of individual drug classes used in IBD therapy on this risk, and to present practical implications for cardiovascular risk assessment and prophylaxis in this population, based on the most recent publications in the PubMed and Google Scholar databases.

## 2. Epidemiology of Cardiovascular Risk in Inflammatory Bowel Disease

Epidemiological data concerning the association between IBD and cardiovascular disease derive primarily from large, population-based cohort studies drawing on national registries, as well as from meta-analyses pooling the results of such studies. A meta-analysis and meta-regression published in 2025 in PLOS One, comprising 19 primary studies, showed that the overall population of patients with IBD has an increased risk of developing cardiovascular disease compared with individuals without this condition, with a relative risk (RR) of 1.52 (95% CI: 1.28–1.80), whereas a separate analysis of 12 studies in the Crohn's disease subgroup showed an RR of 1.46 (95% CI: 1.21–1.76) [1]. The authors noted, however, that the certainty of the evidence for individual endpoints, as assessed by the GRADE method, was very low, owing to substantial heterogeneity between studies ( $I^2 = 94\%$  for the overall IBD population), which in the meta-regression analysis was largely explained by the methodological quality of the primary studies as assessed by the Newcastle-Ottawa Scale;

the currently available data do not yet justify the implementation of primary pharmacological prevention targeted solely at an IBD diagnosis — randomized controlled trials are needed to fill this gap [1].

A considerably larger and more recent body of evidence is provided by an extensive meta-analysis published in late 2025, encompassing 53 studies and a total of over 1.4 million patients with IBD, which demonstrated statistically significantly elevated, adjusted relative risks (aHR) across the entire spectrum of cardiovascular complications: coronary artery disease (aHR 1.25), myocardial infarction (aHR 1.25), acute coronary syndrome (aHR 1.43), heart failure (aHR 1.24), atrial fibrillation (aHR 1.20), and stroke (aHR 1.13) [51]. The same analysis also demonstrated an elevated risk of peripheral artery disease (aHR 1.41) and diabetes (aHR 1.40), and, with regard to venous complications — a significantly increased risk of venous thromboembolism (aHR 1.98), deep vein thrombosis (aHR 2.85), and pulmonary embolism (aHR 1.98) [51]. Comparable relative risk values for individual disease entities — venous thromboembolism (RR 2.5), atherosclerotic cardiovascular disease (RR 1.2), and heart failure (RR 2.0) compared with the general population — are presented in an earlier systematic review devoted to thromboembolic and atherosclerotic mechanisms in IBD, which emphasized that this risk is particularly high in patients under 40 years of age [52]. A separate literature review, drawing on earlier meta-analyses, reports in turn that the risk of coronary artery disease in IBD is elevated by an RR of 1.24, the risk of heart failure by an HR of 2.03, and the risk of atrial fibrillation by an HR of 2.26 compared with the population without IBD, while the risk of premature atherosclerotic cardiovascular disease (diagnosed before age 40) was elevated by as much as an odds ratio (OR) of 1.61 [53].

A Swedish cohort study drawing on data from the entire national population demonstrated an increased risk of acute coronary syndrome among patients with IBD compared with a matched control group from the general population [2]. Similar conclusions were reached in an analysis of the UK Biobank, in which an IBD diagnosis was associated with an elevated risk of incident acute arterial events [3]. In turn, the French national BERENICE cohort study demonstrated that the risk of acute arterial events is particularly pronounced in younger patients and during periods of severe disease activity, suggesting that it is the degree of control of the inflammatory process, rather than the mere presence of an IBD diagnosis, that may be the key modifiable determinant of risk [6]. Direct confirmation of this relationship comes from a Danish cohort study encompassing over 20,000 patients with newly diagnosed IBD, followed for a mean of 6 years, in which the risk of myocardial infarction, stroke, and cardiovascular death was significantly elevated exclusively during periods of flare and sustained disease activity, and did not increase during periods of remission — with patients with Crohn's disease exhibiting a higher risk of stroke and cardiovascular death than patients with UC [54]. A separate historical cohort study demonstrated that the association between IBD and the risk of coronary artery disease is significantly modified by sex and age at diagnosis, arguing for a universal, yet heterogeneous, character of this phenomenon within the IBD population itself [45].

A Dutch study comparing cardiovascular risk profiles of patients with IBD with a matched control group from the general population confirmed the paradoxical nature of this phenomenon — despite a more favorable profile of classical risk factors (lower BMI, less frequent hypertension, a more favorable lipid profile), patients with IBD exhibited features of subclinical vascular damage, including increased arterial stiffness [5, 24]. This phenomenon, previously described as increased aortofemoral pulse wave velocity in patients with IBD, is explained by impaired vascular endothelial function, reduced nitric oxide bioavailability, and elevated levels of the vasoconstrictor endothelin-1, which over the longer term leads to structural remodeling of the vessel wall [24]. A more recent review devoted to mapping cardiometabolic risk in IBD emphasizes that patients with IBD develop coronary artery disease and atherosclerosis more frequently than would be expected based on the prevalence of classical risk factors alone, such as obesity or smoking, and that the course of cardiovascular disease in this population tends to be earlier than in the general population [55].

A systematic review and meta-analysis on cardiac function in patients with IBD, published in 2024, confirmed that although overt clinical involvement of the myocardium in the course of IBD is rarely reported, the available data indicate an increased risk of cardiovascular events in this population, independent of the lower prevalence of classical risk factors [4]. Moreover, a meta-analysis of atrial fibrillation, based on an analysis of 25 studies, showed that the pooled estimated prevalence of this arrhythmia among patients with IBD is approximately 6%, and that the cumulative risk of its development is significantly higher than in the general population [7, 32]. It should be emphasized that this risk is not constant over time — a Danish registry-based study encompassing over 24,000 newly diagnosed patients with IBD demonstrated that the increased incidence of atrial fibrillation and ischemic stroke is concentrated almost exclusively during periods of flare and sustained disease activity, whereas during periods of complete clinical remission the risk of these

complications approaches values observed in the general population, further confirming the key role of inflammation control in limiting cardiovascular risk [33]. Concordant results, indicating an elevated risk of ischemic stroke in patients with IBD, were also reported in a more recent systematic review devoted to the mutual associations between IBD and cerebrovascular disease [34].

An analysis of mortality trends in the United States between 1999 and 2023, based on the CDC WONDER database, confirmed a persistent association between IBD and an increased risk of death from cardiovascular causes, including coronary artery disease, cerebrovascular disease, and myocardial infarction, while simultaneously indicating substantial differences in this regard depending on sex and region [8].

### **2.1. Heart Failure**

A separate, increasingly well-documented component of elevated cardiovascular risk in IBD is heart failure. A large, population-based Danish cohort study demonstrated that the relative risk of acute myocardial infarction is significantly increased in both patients with Crohn's disease and those with ulcerative colitis, with this risk being further heightened among patients using systemic glucocorticosteroids [26]. In the same study, the risk of heart failure was significantly increased in patients with UC, but did not reach statistical significance in the CD group, with the greatest increase in risk again observed among patients treated with steroids [26]. The authors emphasized that this phenomenon occurred despite a lower prevalence of classical risk factors for these complications in the IBD population compared with the control group.

These findings were confirmed by a Swedish nationwide cohort study, encompassing over 80,000 patients with IBD diagnosed over the course of half a century, in which a higher incidence of heart failure was found compared with both a matched general-population control group and unaffected siblings of the patients [27] — which is methodologically significant, as comparison with siblings allows the influence of shared familial and genetic factors on the observed association to be partly excluded. A separate analysis of US hospital data further demonstrated that the presence of IBD in patients hospitalized for congestive heart failure is associated with a distinct in-hospital course, which the authors attribute to the systemic effects of elevated levels of C-reactive protein, TNF- $\alpha$ , vascular endothelial growth factor, and interleukin-6 — typical of active intestinal inflammation — on myocardial function and remodeling [28].

### **2.2. Disease Activity, Histologic Changes, and the Risk of Major Adverse Cardiovascular Events**

Increasing attention is being devoted to the question of whether clinical or, rather, microscopic (histologic) inflammatory activity of the bowel correlates more strongly with cardiovascular risk. A large Swedish cohort study, encompassing a total of over 150,000 patients with both histologic and clinical assessment of disease activity, demonstrated that the presence of histologic inflammation is associated with an elevated risk of coronary artery disease, myocardial infarction, ischemic stroke, and heart failure, whereas no such association was found with hemorrhagic stroke [29]. Of particular clinical significance, clinically active disease was associated with an approximately 1.5-fold higher risk of the composite endpoint of major adverse cardiovascular events (MACE), and even among patients in clinical remission, persistent histologically active inflammation of the mucosa remained independently associated with an elevated risk of myocardial infarction and heart failure [29]. This observation suggests that achieving deep, histologic disease remission — rather than clinical or endoscopic remission alone — may be relevant not only to intestinal prognosis but also to the reduction of cardiovascular risk.

### **2.3. Venous Thromboembolism**

A separate, well-documented component of cardiovascular risk in IBD is venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism. A systematic review from 2024 emphasizes that the complex, proinflammatory and prothrombotic pathophysiology of IBD makes VTE a frequent complication associated with substantial morbidity and mortality, with the activity of the underlying disease remaining the principal risk factor [9, 12]. The relative risk of VTE in patients with IBD is estimated in most studies to be two- to three-fold higher than in the general population, with this risk being markedly higher during periods of disease flare than during remission, further underscoring the close relationship between the intensity of the inflammatory process and activation of the coagulation system in this population [12].

The most recent, extensive meta-analysis of risk factors for VTE in IBD, encompassing 123 studies and over 23.5 million patients, identified 48 variables assessed for their association with VTE, of which 27 showed a statistically significant association [11]. The strongest risk factors were: a prior episode of VTE (OR 4.44;

95% CI: 2.63–7.49), surgical complications (OR 3.06; 95% CI: 2.48–3.77), urgent (non-elective) surgery (OR 2.33; 95% CI: 1.62–3.35), blood transfusions (OR 2.68; 95% CI: 1.17–6.12), hypoalbuminemia (OR 2.25; 95% CI: 1.93–2.62), and parenteral nutrition (OR 2.21; 95% CI: 1.85–2.64); the use of glucocorticosteroids was likewise associated with an elevated risk (OR 1.60; 95% CI: 1.46–1.76), whereas treatment with TNF- $\alpha$  inhibitors — in contrast to steroids — did not increase the risk of VTE, and in fact showed a trend toward a protective association (OR 0.66; 95% CI: 0.46–0.97) [11]. The authors noted that the strength of individual risk factors differs depending on the phase of care the patient is in — hospitalization, the perioperative period, the post-discharge period, or outpatient care — which has important implications for the planning of thromboprophylaxis [11]. The risk of VTE is further increased during pregnancy, and despite growing knowledge of the pathogenesis of this complication, clear guidelines regarding thromboprophylaxis following hospital discharge are still lacking, notwithstanding the persistently elevated risk during this period [10]. Of practical clinical relevance, VTE in the course of IBD affects a substantial proportion of relatively young individuals lacking classical thrombotic risk factors, such as obesity, immobilization from other causes, or inherited thrombophilia, which can contribute to delayed recognition of this complication in clinical practice.

### **3. Pathomechanisms Linking Inflammatory Bowel Disease to Cardiovascular Damage**

The association between IBD and cardiovascular disease is multifactorial and results from the overlap of several, partly independent mechanisms: systemic chronic inflammation, vascular endothelial dysfunction, a prothrombotic state, and disturbances in the composition and function of the gut microbiota [20]. These individual mechanisms do not act in isolation but rather reinforce one another, creating a self-perpetuating vicious cycle of inflammation and vascular damage [40].

#### **3.1. Chronic Inflammation and Endothelial Dysfunction**

Atherosclerosis is now widely recognized as a chronic inflammatory disease of the vasculature, in which endothelial dysfunction constitutes a key, initiating step in pathogenesis [19]. In patients with IBD, circulating proinflammatory cytokines, including TNF- $\alpha$  and interleukins 1 and 6, act systemically on vascular endothelial cells, leading to increased expression of adhesion molecules (VCAM-1, ICAM-1), impaired nitric oxide bioavailability, and increased oxidative stress [20]. This state promotes monocyte adhesion to the vessel wall, foam cell formation, and accelerated progression of atherosclerotic lesions, and is clinically reflected in an increase in arterial stiffness detectable by non-invasive testing already in the early stages of disease, even in patients without classical risk factors [20, 24].

#### **3.2. Prothrombotic State**

Inflammatory bowel disease is characterized by complex disturbances of hemostasis, encompassing simultaneous activation of the coagulation system, impairment of anticoagulant mechanisms, and disturbances of fibrinolysis. Chronic inflammation leads to increased expression of tissue factor and activation of the coagulation cascade mediated by proinflammatory cytokines, together with reactive thrombocytosis and platelet hyperreactivity, which intensify during periods of disease flare [9, 17]. An additional factor heightening thrombotic risk in hospitalized patients is immobilization, dehydration related to diarrhea, and the use of glucocorticosteroids [10]. This mechanism explains why the risk of venous thromboembolism in IBD correlates closely with disease activity rather than solely with the diagnosis itself.

#### **3.3. Gut Microbiota and Bacterial Metabolites**

In the course of IBD, dysbiosis occurs, along with damage to the intestinal barrier and the so-called gut-vascular barrier, which promotes microbial translocation into the systemic circulation and intensifies immune-mediated activation of the vascular endothelium [20]. Particular attention is being devoted to the role of trimethylamine N-oxide (TMAO) — a metabolite generated from the conversion of choline and carnitine by gut bacteria [18]. In one publication it was demonstrated that gut microbial metabolism of phosphatidylcholine promotes the development of atherosclerosis [18]. Elevated TMAO levels are associated with endothelial dysfunction, platelet hyperreactivity, and enhanced thrombin generation mediated via the NF- $\kappa$ B pathway [21], although a direct link between the dysbiosis characteristic of IBD and TMAO levels requires further research directed specifically at this population.

### **3.4. The Role of Disease Activity and Inflammatory Biomarkers**

An observation recurring throughout most of the cited studies is a stronger association of cardiovascular risk with the activity of intestinal inflammation than with the diagnosis itself — risk is particularly elevated during periods of flare and diminishes during clinical remission [6, 9]. A concordant position is presented by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU), emphasizing that it is the cumulative exposure to active inflammation over the course of a patient's life that should be regarded as the principal, modifiable target of intervention [38]. C-reactive protein, routinely used as a marker of IBD activity [30], is at the same time a recognized, independent predictor of cardiovascular risk in the general population [31], which lends it a potentially dual clinical significance — although dedicated predictive tools incorporating this parameter specifically for patients with IBD have not yet been developed.

## **4. Impact of Inflammatory Bowel Disease Treatment on Cardiovascular Risk**

The assessment of the impact of IBD pharmacotherapy on cardiovascular risk has become a distinct area of research. Individual drugs may modify this risk both directly (e.g., metabolic or prothrombotic effects) and indirectly — through their efficacy in controlling the inflammatory process, in line with the previously discussed relationship between disease activity and vascular risk.

### **4.1. Glucocorticosteroids**

Glucocorticosteroids, despite their efficacy in inducing remission, are associated with an unfavorable metabolic and prothrombotic profile — they increase levels of procoagulant factors while simultaneously reducing the activity of natural anticoagulants, translating into an increased risk of venous thromboembolism, particularly in hospitalized patients [10]. They also promote the development of hypertension, hyperglycemia, and dyslipidemia. In the previously cited cohort studies, exposure to glucocorticosteroids was a recurring, independent factor increasing the risk of both myocardial infarction and heart failure in patients with IBD, further strengthening the rationale for limiting the duration of their use in favor of targeted therapies.

### **4.2. Biologic Agents — TNF- $\alpha$ Inhibitors and Other Advanced Therapies**

In contrast to glucocorticosteroids, effective biologic treatment has been linked to a potential cardioprotective effect. An analysis of the French social insurance registry demonstrated an association between the use of TNF- $\alpha$  inhibitors and thiopurines and a reduction in cardiovascular risk among patients with IBD [23]. A more recent meta-analysis, encompassing both randomized controlled trials and observational studies, assessing the risk of MACE associated with the use of advanced therapies (anti-TNF, JAK inhibitors, anti-IL-23, integrin antagonists), showed a statistically non-significant trend toward a reduction in MACE risk relative to placebo — partly attributable to the low number of events in registration trials, which typically exclude patients with significant cardiac comorbidity [12]. A pooled analysis of data on ozanimod — a sphingosine-1-phosphate (S1P) receptor modulator approved for the treatment of UC — from the True North trial did not demonstrate an increased risk of clinically significant cardiovascular events, although this drug may induce transient bradycardia during the first days of therapy, warranting gradual dose up-titration [13].

### **4.3. Janus Kinase (JAK) Inhibitors**

JAK inhibitors — tofacitinib, filgotinib, and upadacitinib — constitute a drug class for which cardiovascular safety has been the subject of particularly intensive analysis. A turning point was the ORAL Surveillance trial in patients with rheumatoid arthritis burdened with cardiovascular risk factors, in which tofacitinib was associated with a higher risk of MACE and malignancy than TNF- $\alpha$  inhibitors [14, 25]. This led the Food and Drug Administration (FDA) to impose its highest-level safety alert for the entire JAK inhibitor class, along with a recommendation to use these agents primarily after failure of anti-TNF therapy, with caution in patients over 65 years of age or those burdened with risk factors [15, 16]. It should be emphasized that there is a limitation in extrapolating these findings to the IBD population — the ORAL Surveillance trial was conducted in an older, more cardiovascularly burdened rheumatologic population. Real-world data on tofacitinib in UC indicate that the increased risk of VTE primarily concerns patients with additional risk factors, and that the risk of pulmonary embolism is dose-dependent — higher with the induction dose of 10 mg twice daily than with the maintenance dose of 5 mg [16, 17]. Data on selective JAK1 inhibitors (filgotinib, upadacitinib) suggest a satisfactory safety profile, although the FDA regulatory warning was extended to the entire drug class on a precautionary basis, rather than on the basis of direct evidence for each individual molecule [15, 16].

#### **4.4. Other Biologic Agents — Vedolizumab, Ustekinumab, and Interleukin-23 Inhibitors**

Vedolizumab and ustekinumab have not to date been clearly linked to an increased cardiovascular risk, although the number of cardiovascular events analyzed in the studied populations remains small [12, 48]. A comprehensive review of the cardiovascular safety of biologic and small-molecule agents in IBD confirms a favorable safety profile for both drugs [46, 47]. With regard to inhibitors of the p19 subunit of IL-23 (risankizumab, guselkumab, mirikizumab), the same review indicates an overall low incidence of cardiovascular events, although isolated signals of an increased incidence of atrial fibrillation with risankizumab have emerged, requiring confirmation through post-marketing surveillance [46].

#### **4.5. Effect of TNF- $\alpha$ Inhibitors on Cardiac Function**

An issue well recognized for over two decades is the risk of exacerbation or new onset of heart failure in patients treated with infliximab. These concerns originated from the ATTACH trial, in which, among patients with moderate-to-severe heart failure, an infliximab dose exceeding 5 mg/kg was associated with adverse clinical outcomes, leading to a contraindication of this dose in patients with New York Heart Association (NYHA) class III–IV heart failure [50]. TNF- $\alpha$  plays a complex role in the regulation of myocardial function, and its complete blockade in patients with impaired left ventricular function may exacerbate cardiac dysfunction [49]. Guidelines from some scientific societies recommend contraindicating anti-TNF agents in patients with clinically overt heart failure, whereas the position of the European Crohn's and Colitis Organisation (ECCO) has not to date formulated unequivocal recommendations in this regard [49].

#### **4.6. Statins in the Population of Patients with Inflammatory Bowel Disease**

Statins exhibit pleiotropic effects extending beyond LDL cholesterol reduction — anti-inflammatory, antioxidant, and endothelial function-improving effects [37]. Case-control studies have shown that their use is associated with a significantly lower risk of newly diagnosed IBD [35]. More recent real-world data further suggest that, among patients with moderate-to-severe IBD, concomitant statin use was associated with a lower likelihood of surgical treatment, which the authors attribute to their anti-inflammatory effect within the intestinal mucosa [36]. These observations indicate that, in patients with IBD meeting standard cardiological indications for lipid-lowering therapy, statin therapy may confer benefit not only in terms of cardiovascular prevention but potentially also with regard to the course of the intestinal disease itself [35, 36, 37].

### **5. Special Populations**

#### **5.1. Young Adults**

One of the most concerning observations emerging from cohort studies is the fact that the relative increase in the risk of acute arterial events associated with IBD is particularly pronounced in younger patients, in whom classical, age-dependent cardiovascular risk is initially low, and thus the contribution of the inflammatory process itself to overall risk is proportionally greater [6]. This means that the classical cardiovascular risk scales used in clinical practice, calibrated primarily on the basis of age and classical risk factors, may substantially underestimate the true risk in young patients with IBD, particularly during periods of heightened disease activity. This phenomenon carries additional practical significance, as IBD is typically diagnosed in the second and third decades of life, meaning that a substantial proportion of patients are exposed to the cumulative effects of chronic inflammation on the vasculature from a young age, long before classical atherosclerotic risk factors begin to play a dominant role — pointing to the need to shift the perspective of cardiovascular risk assessment in this group away from an approach based solely on short- and medium-term risk toward an assessment of cumulative lifetime risk.

#### **5.2. The Perioperative Period and Hospitalization**

Hospitalization for IBD flare and the perioperative period, particularly following bowel resection surgery, are associated with a significantly increased risk of venous thromboembolism, as confirmed by both observational data and gastroenterological society guidelines recommending routine pharmacological VTE prophylaxis in hospitalized patients with IBD, regardless of the indication for hospitalization (medical or surgical) [9, 11]. This recommendation distinguishes the IBD patient population from certain other groups of patients hospitalized for non-surgical reasons, in whom the decision regarding pharmacological prophylaxis is contingent upon an additional risk score — in the case of IBD, hospitalization for disease flare alone is

generally considered a sufficient indication for the routine implementation of prophylaxis, provided there are no significant contraindications, such as active massive gastrointestinal bleeding. This risk remains elevated following hospital discharge as well, although — as the authors of the most recent reviews emphasize — clear, evidence-based guidelines regarding the optimal duration of pharmacological thromboprophylaxis during this period are still lacking [10], and the decision to extend it after discharge remains, in clinical practice, a matter of individual assessment, taking into account factors such as the patient's degree of mobility, the presence of additional risk factors, and the degree of resolution of inflammatory activity.

### **5.3. Pregnancy**

Pregnancy itself constitutes a state of physiologically increased blood coagulability, and in combination with the active inflammatory process typical of IBD flare, the risk of venous thromboembolism in pregnant patients with IBD is further heightened compared with pregnant women without this disease, necessitating individualization of prophylactic management, particularly during the peripartum period and in cases of active disease during pregnancy [10]. An additional argument in favor of striving for remission prior to planned conception is the fact that active disease at the time of conception increases not only the risk of thromboembolic complications but also the risk of adverse obstetric outcomes, making preconception optimization of IBD treatment an important element of care for women of reproductive age planning pregnancy.

### **5.4. Sex-Related Differences**

Sex appears to significantly modify the cardiovascular risk associated with IBD. A retrospective historical cohort study, encompassing nearly 15,000 patients with IBD matched by sex and date of birth to over 120,000 individuals from the general population, demonstrated a significantly increased risk of coronary artery disease among patients with IBD, with this association being clearly differentiated by sex and age at diagnosis [45]. A similar direction of association was observed in earlier reviews devoted to sex-related differences in the course of IBD, in which the increased risk of coronary artery disease associated with IBD proved to be relatively stronger in women than in men [43]. This phenomenon is consistent with the broader picture known from other chronic immune-mediated inflammatory diseases, in which it is precisely in women that the natural protective advantage against cardiovascular disease typically conferred by reproductive age is abolished. Female sex is furthermore associated with a distinct profile of extraintestinal IBD complications, including a significantly higher burden of cardiovascular disease compared with men, suggesting that it is warranted to account for sex as an element of individualized cardiovascular risk assessment in this population [44].

### **5.5. Rare, Direct Cardiac Complications**

Beyond the previously discussed risk of coronary artery disease, stroke, heart failure, and thromboembolic complications, the literature also describes rare cases of direct, immune-mediated cardiac involvement in the course of IBD, most commonly in the form of pericarditis or myocarditis, reported primarily as an extraintestinal manifestation of ulcerative colitis [41]. Isolated cases of myocardial infarction have also been reported in young, actively symptomatic patients with ulcerative colitis lacking classical atherosclerotic risk factors, in which the authors postulated the involvement of a localized prothrombotic and inflammatory process affecting the coronary vasculature [42]. Notwithstanding the rarity of these complications, their description underscores that, in patients with active IBD presenting with atypical cardiac symptoms, involvement of the heart in the course of the underlying disease should be considered in the differential diagnosis.

## **6. Cardiovascular Risk Assessment and Practical Implications**

The 2021 European Society of Cardiology guidelines on cardiovascular disease prevention include inflammatory bowel disease, alongside other chronic immune-mediated inflammatory diseases, as a condition that may modify the cardiovascular risk estimated using classical risk scores, although the level of evidence for this association remains lower than for rheumatoid arthritis, for which recommendations are best documented [22]. In practice, this means that, in patients with IBD, it may be worth considering the risk estimated using standard calculators as a potentially underestimated value, particularly during periods of active disease and in younger patients, in whom classical risk factors contribute less to the total absolute risk [6, 22].

This gap is partly addressed by newer, dedicated expert position statements developed specifically for the IBD patient population. The Spanish Working Group GETECCU, in collaboration with a consulting

cardiologist, published an interdisciplinary position statement on cardiovascular disease in patients with IBD, encompassing a discussion of classical and non-classical risk factors, the pathophysiology of atherosclerosis in this population, available methods for assessing subclinical atherosclerosis and endothelial dysfunction, as well as practical recommendations regarding the application of risk calculators in daily clinical practice and the mutual interactions between IBD treatment and standard cardiovascular pharmacotherapy [38]. Concordant conclusions are presented in a review published in 2025 devoted to the management of atherosclerotic cardiovascular risk in IBD, which proposed a multidisciplinary care framework, incorporating, among other elements, the assessment of lipoprotein(a) levels and LDL and HDL cholesterol fractions as components of individualized preventive management in these patients [39]. The emergence of this type of dedicated, multidisciplinary recommendations, developed jointly by gastroenterologists and cardiologists, should be regarded as an important step toward standardizing the approach to cardiovascular risk assessment and reduction in this population [38, 39, 40].

From a practical standpoint, based on the literature discussed, the following elements of an approach to cardiovascular risk assessment and reduction in patients with IBD can be formulated:

- Pursuing durable control of inflammatory disease activity as a fundamental element of the strategy for reducing cardiovascular risk, including limiting periods of uncontrolled, active inflammation, ideally with the goal of achieving histologic remission [6, 9, 29].
- Routine assessment of indications for pharmacological VTE prophylaxis in every patient hospitalized for IBD, regardless of the reason for hospitalization, taking into account individual risk factors [9, 11].
- Careful selection of patients for treatment with Janus kinase inhibitors, avoiding this drug class or exercising heightened vigilance in patients over 65 years of age, those with a prior history of VTE, obesity, smoking, or other significant cardiovascular risk factors, in accordance with current regulatory warnings [15, 16, 17].
- Limiting long-term use of systemic glucocorticosteroids in favor of targeted therapies enabling durable inflammation control [10, 26].
- Exercising caution when considering TNF- $\alpha$  inhibitor therapy in patients with clinically overt heart failure, particularly NYHA class III–IV, in accordance with data from the ATTACH trial [49, 50].
- Taking into account the IBD diagnosis itself, particularly when the disease is active, as a potential factor modifying decisions regarding cardiovascular risk assessment and intervention thresholds, with such decisions ideally made individually, in collaboration between the gastroenterologist and the primary care physician or cardiologist, in accordance with proposed multidisciplinary care models [22, 38].
- Monitoring the lipid profile and metabolic parameters in patients treated with JAK inhibitors, particularly during the first months of therapy [15].
- Considering the role of statins in patients with IBD who meet standard cardiological indications for lipid-lowering therapy, taking into account their potentially favorable effect on the course of the intestinal disease itself [35, 36, 37].

It should be emphasized at the same time that the currently available data do not justify the implementation of routine preventive pharmacotherapy (e.g., acetylsalicylic acid or statins) on the basis of an IBD diagnosis alone, in isolation from an individually assessed total cardiovascular risk — as the authors of the most recent meta-analysis emphasize, dedicated randomized controlled trials conducted specifically in the IBD population are needed to formulate such recommendations [1].

## 7. Summary and Directions for Further Research

The accumulated data consistently indicate that patients with inflammatory bowel disease carry an increased risk of cardiovascular events, encompassing both atherosclerotic complications and heart failure [26, 27], venous thromboembolism [9, 11], and atrial fibrillation [7, 32, 33], despite a relatively more favorable profile of classical risk factors in this population. This phenomenon is attributable primarily to the direct, systemic effect of chronic inflammation on the vessel wall — through endothelial dysfunction, activation of the coagulation system, and disturbances of the gut microbiota and its metabolites. A key, recurring theme throughout the literature discussed is that this risk correlates more strongly with disease activity than with the diagnosis itself [29, 33, 38], shifting the emphasis of clinical implications toward achieving deep, durable remission. An important element of this picture is the differential impact of individual drug classes — from the unfavorable effect of chronic steroid therapy [26] and the risk of thromboembolic complications associated

with JAK inhibitors [14, 16, 17], through the specific risk of heart failure associated with TNF- $\alpha$  inhibitors [49, 50], to the suggested cardioprotective effect of effective biologic therapy as a whole [23, 46].

Despite considerable advances in knowledge in recent years, the level of certainty of the scientific evidence for many of the associations discussed remains limited, primarily owing to the observational nature of most available studies and the relatively small number of cardiovascular events recorded in clinical trials of drugs used in IBD [1, 12]. Further research should focus on: prospective validation of risk assessment tools incorporating IBD activity and inflammatory biomarkers [29, 31]; dedicated randomized controlled trials evaluating the efficacy of primary pharmacological prevention, including the role of statins [1, 35]; long-term safety monitoring of newer advanced therapies [15, 46]; and further elucidation of the role of the gut microbiota as a therapeutic target [18, 21]. Until such data become available, practical management should be based on a combination of standard cardiovascular risk assessment and individualized clinical observation, in line with the direction set by the most recent, dedicated expert position statements [38, 39].

#### **Author's contribution:**

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