Inflammatory bowel disease and cardiovascular diseases: a concise review

Hao Wu [1,2], Tingzi Hu[1], Hong Hao[1], Michael A. Hill[3], Canxia Xu[2], and Zhenguo Liu[1],*

[1]Center for Precision Medicine and Division of Cardiovascular Medicine, Department of Medicine, University of Missouri School of Medicine, One Hospital Drive, Columbia, MO 65212, USA; [2]Department of Gastroenterology, The Third Xiangya Hospital, Central South University, 138 Tongzipo Road, Changsha 410013, China; and [3]Dalton Cardiovascular Research Center, University of Missouri, 134 Research Park Drive, Columbia, MO 65211, USA
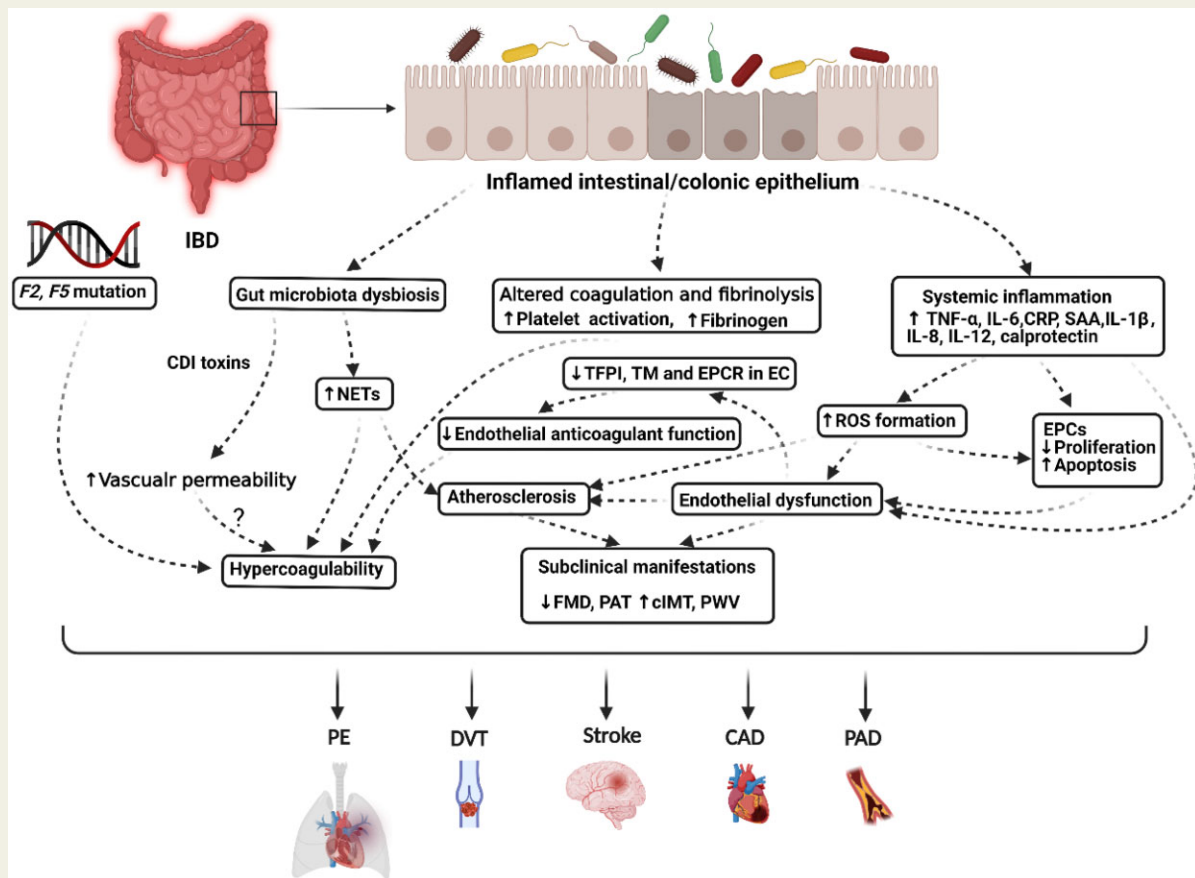
Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality despite aggressive treatment of traditional risk factors. Chronic inflammation plays an important role in the initiation and progression of CVDs. Inflammatory bowel disease (IBD) is a systemic state of inflammation exhibiting increased levels of pro-inflammatory cytokines including tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6. Importantly, IBD is associated with increased risk for CVDs especially in women and young adults, including coronary artery disease, stroke, thromboembolic diseases, and arrhythmias. Potential mechanisms underlying the increased risk for CVDs in IBD patients include increased levels of inflammatory cytokines and oxidative stress, altered platelet function, hypercoagulability, decreased numbers of circulating endothelial progenitor cells, endothelial dysfunction, and possible interruption of gut microbiota. Although IBD does not appear to exacerbate the traditional risk factors for CVDs, including hypertension, hyperlipidaemia, diabetes mellitus, and obesity, aggressive risk stratifications are important for primary and secondary prevention of CVDs for IBD patients. Compared to 5-aminosalicylates and corticosteroids, anti-TNF-α therapy in IBD patients was consistently associated with decreasing cardiovascular events. In the absence of contraindications, low-dose aspirin and statins appear to be beneficial for IBD patients. Low-molecular-weight heparin is also recommended for patients who are hospitalized with acute IBD flares without major bleeding risk. A multidisciplinary team approach should be considered for the management of IBD patients.

Graphical Abstract

Introduction

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC) and represents a significant health problem. Inflammatory bowel disease is characterized by chronic and recurrent intestinal inflammation and is associated with significant extraintestinal manifestations (EIMs) including non-infectious systemic inflammation and hypercoagulability. Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity globally. Systemic inflammation and endothelial dysfunction are critically involved in the development and progression of CVDs. Patients with chronic inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, have an increased risk of arterial and venous thrombo-embolic events.[1] Endothelium-dependent flow-mediated vaso-dilation (FMD) is significantly decreased in patients with IBD.[2,3] Recent studies have suggested that IBD patients might also have an increased risk for CVDs including coronary artery disease (CAD) and arterial and venous thromboembolism.[4,5] This review thus focuses on (i) IBD and systemic inflammation, (ii) IBD and CVDs, (iii) IBD and endothelial dysfunction, (iv) IBD and gut microbiota, (v) IBD and traditional cardiovascular risk factors, (vi) impact of IBD medications on CVDs, and (vii) considerations of cardiovascular medications in patients with IBD.

Inflammatory bowel disease and systemic inflammation

Inflammatory bowel disease is a chronic disease condition with significant local and systemic non-infectious inflammation. Several inflammatory biomarkers, including C-reactive protein (CRP), serum amyloid A (SAA), tumour necrosis factor-α (TNF-α), inter-leukin (IL)-1β, IL-6, IL-8, IL-12, and calprotectin, are significantly

Table 1 Inflammatory biomarkers in IBD and CVDs

Inflammatory markers	Cardiovascular effects
CRP	Increased risk of CAD
SAA	Increased all-cause and cardiovascular mortality
TNF-α	Increased risk for CVDs
IL-1β	Increased risk of atherosclerosis and CAD
IL-6	Increased risk for CVDs
IL-8	Poor clinical outcome in patients with MI
IL-12	Enhancing the development of atherosclerosis
	Increased risk of CAD
Calprotectin	Increased risk of amputation in PAD

See Supplementary material online for references.
CAD, coronary artery disease; CRP, C-reactive protein; CVD, cardiovascular disease; IL, interleukin; MI, myocardial infarction; PAD, peripheral artery disease; SAA, serum amyloid A; TNF-α, tumour necrosis factor-α.

increased in patients with IBD. These biomarkers are also associated with CVDs (Table 1). A study with over 100 000 subjects showed a significant increase in serum CRP level in IBD patients with an increased risk for CAD.[6,7] The levels of SAA have been shown to predict all-cause and cardiovascular mortality and are associated with the atherogenic process. Tumour necrosis factor-α and IL-6 are important cell signalling molecules and involved in inflammation, endothelial dysfunction, and CVDs. Interleukin-1β, IL-8, and IL-12 are potent pro-inflammatory cytokines and are associated with increased risk of atherosclerosis and CAD or impaired cardiac recovery in patients with myocardial infarction (MI). Calprotectin is associated with atherosclerosis development and prognosis of peripheral artery disease (PAD). Collectively, these examples highlight the relationship between IBD and CVDs.

Relationship between inflammatory bowel disease and cardiovascular diseases

Chronic inflammation plays important roles in the initiation and progression of CVDs, thus, IBD and CVDs may share similar mechanisms important to their pathophysiology. However, data relating to the risk for CVDs in IBD patients has been inconsistent and sometimes controversial. Accumulating evidence has demonstrated an increased risk for CVDs including CAD, PAD, stroke, arrhythmias, and venous thromboembolism in IBD patients as detailed below.

Coronary and peripheral arterial diseases

Studies have shown that IBD patients have an increased risk for atherosclerosis and related CAD and PAD compared with the subjects without IBD. Inflammatory bowel disease patients have an increased incidence of CAD over controls and increased risk of MI.[7,8] While another study has demonstrated that there was no increased risk for MI or transient ischaemic attack in IBD patients over controls, there was
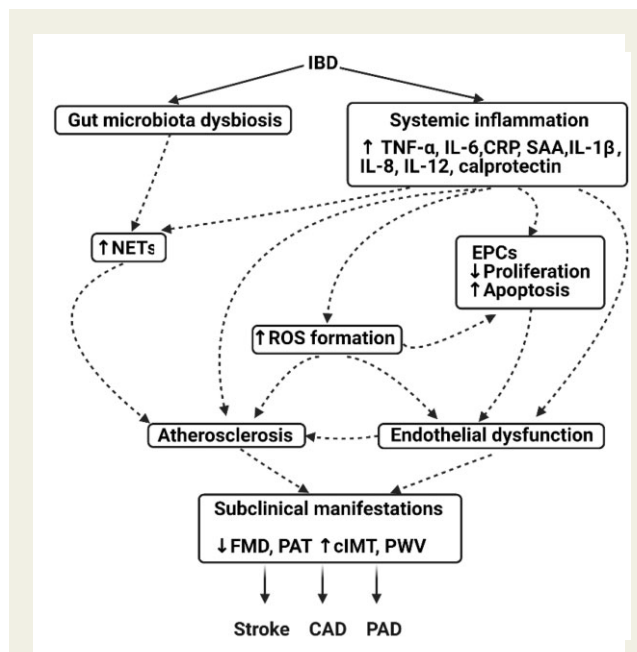

Figure 1 Schematic diagram showing the relationship between inflammatory bowel disease and increased risk of arterial diseases together with potential mechanisms. A variety of pro-inflammatory cytokines including tumour necrosis factor-α, interleukin-6, interleukin-1β, interleukin-8, interleukin-12, and Calprotectin are produced in inflammatory bowel disease patients. Patients with inflammatory bowel disease also exhibit a decrease in the number of circulating endothelial progenitor cells, endothelial dysfunction, and possible interruption of gut microbiota, as well as increase in neutrophil extracellular traps, leading to atherosclerosis and related diseases including stroke, coronary artery disease, and peripheral artery disease. CAD, coronary artery disease; cIMT, carotid intima-media thickness; CRP, C-reactive protein; EPC, endothelial progenitor cell; FMD, brachial artery flow-mediated dilation; IBD, inflammatory bowel disease; IL, interleukin; NETs, neutrophil extracellular traps; PAD, peripheral artery disease; PAT, pulse arterial tonometry indices; PWV, pulse wave velocity; ROS, reactive oxygen species; SAA, serum amyloid A; TNF-α, tumour necrosis factor-α.

an increased risk for acute mesenteric ischaemia.[9] A UK study demonstrated an increased risk of ischaemic stroke in younger patients (<50 years) with CD.[10] It was further reported that women with IBD below 40 years of age had a significantly higher risk of stroke than those aged over 40, or males,[9,11] and associated with increased risk of CAD and acute arterial thrombotic events,[4,8] without association with PAD[11] (Figure 1).

Arterial and venous thromboembolism

Inflammatory bowel disease is associated with hypercoagulability and an increased risk of arterial and venous thromboembolism (VTE). Population studies have shown an increased risk of acute arterial thrombotic events in IBD patients. A French study with 210 162 IBD patients revealed that, after adjusting for hypertension (HTN), hyperlipidaemia, diabetes mellitus (DM), obesity,

tobacco, and alcohol usage, the incidence of acute arterial thrombotic events was 19% higher in IBD patients than in subjects without IBD.[4] A sex- and age-matched study with 13 756 IBD patients and 71 672 control subjects demonstrated that IBD significantly increased the risk of VTE.[5] A Danish study with 49 799 IBD patients and 477 504 control subjects showed that the risk for VTE including deep venous thromboembolism (DVT) and pulmonary embolism (PE) was significantly increased in those with IBD, especially in young patients of ≤20 years old.[12] Another study further showed that the risk of developing DVT and PE was higher in women with IBD than men.[13]

The mechanisms for increased risk of arterial VTE in IBD patients appear to be multifactorial (*Figure 2*). Genetically, Factor V Leiden and prothrombin G20210A mutations are associated with increased thromboembolic events among IBD patients, although there was no difference in the frequency of these mutations between 8984 IBD cases and 2600 controls.[14] Inflammation could create a hypercoagulable state, and trigger thromboembolism in IBD patients with IBD. Indeed, significant abnormalities in coagulation and fibrinolysis are observed in IBD patients (*Table 2*). Elevated levels of thrombin–antithrombin complexes and prothrombin fragments 1 and 2 were reported in patients with active CD and UC, while it was unclear if these changes were present in the inactive state of IBD. Some studies reported increased levels of fibrinogen and D-dimer in IBD, and others only in active IBD. There are also significant changes in the number, morphology, and function of platelets in IBD patients. Increased platelet number and aggregation, and decreased mean platelet volume have been described in IBD patients.[15]

Neutrophil extracellular traps (NETs) are extracellular and web-like structures composed of cytosolic and granule proteins on a scaffold of decondensed chromatin. Neutrophil extracellular traps play an essential role in infection control by promoting neutrophil homing to the sites of infection and attacking pathogens. Excessive production of NETs could increase inflammation levels and trigger autoimmunity and inappropriate thrombosis. Studies have shown that IBD patients have elevated levels of plasma NETs.[16] Neutrophil extracellular traps may also be involved in atherosclerotic plaque formation and arterial thrombosis.[17]

Heart failure

Data relating to the risk for heart failure (HF) in IBD patients has been inconsistent. A Danish study showed that IBD patients had a 37% increased risk of hospitalization for HF compared with the controls and this risk was strongly correlated with disease activity.[18] A study of 50 patients with CD and 50 healthy control subjects demonstrated a significant impairment in left ventricular function in patients with CD,[19]
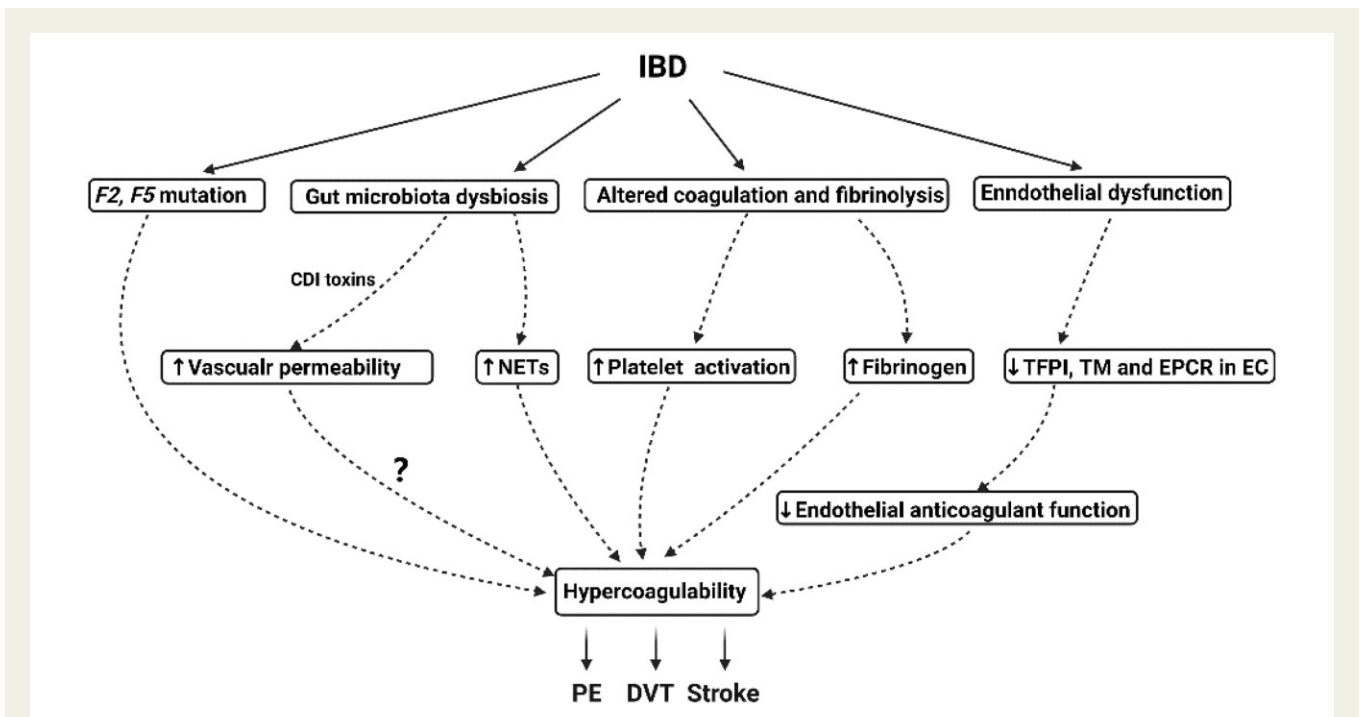
Figure 2 Schematic diagram showing the relationship between inflammatory bowel disease and increased risk of venous thromboembolic events and potential mechanisms. In inflammatory bowel disease patients, significant platelet alterations, hypercoagulability, endothelial dysfunction, increase in neutrophil extracellular traps, and possible interruption of gut microbiota could increase the risk of venous thromboembolic events and pulmonary embolism. CDI, *Clostridium difficile* infection; DVT, deep venous thromboembolism; EC, endothelial cell; EPCR, endothelial protein C receptor; F2, prothrombin G20210A; F5, Factor V Leiden; IBD, inflammatory bowel disease; NETs, neutrophil extracellular traps; PE, pulmonary embolism; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin.

Table 2 Coagulation and fibrinolysis markers in IBD

Marker	Conditions	Changes
Coagulation		
Activated partial thromboplastin time	IBD	↑ in IBD men
	UC	No change
Prothrombin time	IBD	↑ in CD women
		↑ in active IBD
Thrombin-antithrombin complex	IBD	↑ with disease activity
		↑↑ in UC, ↑ in CD
	UC	↑ in active UC
Fragment 1 + 2	IBD	↑ in IBD
		↑ with disease activity
	UC	↑ in active UC
Fibrinolysis		
Fibrinogen	IBD	↑↑ in active IBD, ↑ in inactive IBD
		↑ in active IBD
Plasminogen	IBD	↑ in CD
		No change
Tissue plasminogen activator	IBD	↑ in IBD
		↓ in IBD
Plasminogen activator inhibitor-1	IBD	↑in IBD
		↑ in IBD
D-dimer	IBD	↑↑ in UC, ↑ in CD
		↑ in active IBD
	UC	↑↑ in active UC, ↑ in inactive UC

See Supplementary material online for references.
↑↑, markedly increased; ↑, increased; ↓, decreased; CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

while another study showed no association between IBD and incident of HF.[20]

Arrhythmias

Increased levels of inflammation may predispose IBD patients to develop arrhythmias. A study with 847 235 IBD patients and 84 757 349 non-IBD cohorts showed that the prevalence of atrial fibrillation (AF), atrial flutter, ventricular tachycardia, and ventricular fibrillation was higher in IBD patients than that in control subjects.[21] Another study demonstrated that increased risk of AF was observed in patients with IBD flares and persistent activity, not in the remission periods.[22]

Sex differences in cardiovascular diseases in inflammatory bowel disease patients

There are significant sex differences in the prevalence, clinical manifestations, disease progression, EIMs, and responses to therapies in IBD. Epidemiological studies have shown a higher prevalence and greater severity of CD in women than in men, while exactly the opposite in the prevalence and severity for UC. Several population studies have clearly demonstrated that women with IBD are at higher risk for acute arterial thrombotic events compared to men.[4,7,8] However, data on the risk of VTE in male and female IBD patients are inconsistent. One study showed that the risk of VTE was similar for men and women,[12] while another suggested that men with IBD could be at a higher risk for VTE compared to women.[13] The mechanisms for sex differences in CVDs remains largely unknown in IBD patients.

Inflammatory bowel disease and endothelial dysfunction

Endothelial dysfunction is critically involved in the development of atherosclerosis-related vascular diseases. Microvascular endothelial function can be measured using pulse arterial tonometry (PAT), whereas macrovascular endothelial dysfunction can be evaluated using brachial artery FMD. Inflammatory bowel disease patients exhibit both microvascular and macrovascular endothelial dysfunction with decreased PAT indices and FMD levels.[2,3] Increased aortic stiffness is a well-established indicator for vascular endothelial dysfunction and an independent predictor of cardiovascular events. Pulse wave velocity (PWV) is a validated quantitative measurement for arterial stiffness. It was reported that PWV is significantly increased in adults with IBD compared with age-matched controls.[8] Circulating endothelial progenitor cells (EPCs) are essential for endothelial repair and vascular function. Circulating EPCs levels have been suggested to predict the occurrence of adverse cardiovascular events and cardiovascular mortality. In relation to this, the numbers of EPCs were found to be significantly decreased in IBD patients compared to healthy controls, together with increased apoptosis and impaired proliferation.[23]

The endothelium has anticoagulant properties which manifest in the synthesis of tissue factor pathway inhibitor (TFPI) and proteins enabling protein C (PC) activation such as thrombomodulin (TM) and endothelial PC receptor (EPCR). Endothelial dysfunction triggered by inflammation leads to TFPI dislocation from endothelial surface to circulation. Thus, in IBD patients, circulating TFPI is increased and correlates with disease activity.[24] However, plasma from IBD patients displays hyposensitivity to the anticoagulant activity of exogenous TFPI,[25] suggesting that circulating TFPI may have reduced anticoagulant properties compared to TFPI in endothelial cells in IBD. Plasma TM is elevated in UC patients, while TM expression in inflamed bowel tissue and expressions of TM and EPCR in microvasculature of colonic mucosa are decreased in IBD patients.[26] Thus, endothelial anticoagulant function is impaired in IBD patients, increasing the risk for arterial and venous thrombosis.

Inflammatory bowel disease and gut microbiota

Inflammatory bowel disease is a gastrointestinal disease associated with gut microbiota dysbiosis. Alterations in gut microbiota are also associated with CVDs including atherosclerosis and CAD. Thus, knowledge of the impact of IBD on gut microbiota may aid in

understanding the increased risk of CVD in IBD patients. Indeed, a study showed that the rate of VTE was significantly higher in IBD patients with *Clostridium difficile* infection (CDI) compared to those without CDI,[27] and it is reported that *C. difficile* toxins increase colonic vascular permeability.[28] Colonization with gut microbiota has been shown to restore the production of von Willebrand factor in hepatic endothelial cells and prevent platelet aggregate formation in Toll-like receptor-2 (*Tlr2*)-deficient mice, thus correcting plasma vWF levels and thrombus growth in *Tlr2*-deficient mice.[29] Gut microbiota also suppresses the reactivity of neutrophils towards the formation of NETs,[30] which is known to be critically involved in atherosclerotic plaque formation and arterial thrombosis.[17] In addition to alterations in gut microbiota populations, the metabolic potential of gut microbes has been regarded as an essential factor to the development of CVDs. Trimethylamine *N*-oxide (TMAO) is a gut microbiota-derived metabolite that promotes platelet responsiveness and in vivo thrombosis in animal models. Clinical studies suggest that plasma TMAO levels could predict the risk for CVDs and mortality. A study with 479 subjects (106 IBD and 373 non-IBD controls) showed decreased levels of TMAO in IBD patients compared to controls.[31]

Inflammatory bowel disease and traditional risk factors for cardiovascular diseases

Two population studies have reported a higher prevalence of DM and HTN in IBD patients.[13,32] However, another study showed that the prevalences of obesity, HTN and hyperlipidaemia were lower in IBD patients than their controls; but the proportion of smokers was higher in the patients with CD than those with UC and controls.[33] In apparent contrast, a Danish study showed that the prevalence

estimates of HTN and DM were not significantly different between IBD patients and control population.[18] A study has suggested that IBD patients have elevated levels of LDL cholesterol and decreased levels of HDL cholesterol compared to the general population.[34] In contrast, other studies have reported decreased levels of total and LDL cholesterol in IBD patients.[22] The inconsistency of study results relating to lipid levels and body weight could reflect differences in the status of nutrition and absorption, as well as disease activity in IBD patients. Thus, the current data appear inadequate to suggest that a significant modification of the traditional cardiovascular risk factors is associated with increased risk for endothelial dysfunction and CVDs in IBD patients.

Impact of inflammatory bowel disease medications on cardiovascular diseases

It is reasonable to think that medications that decrease inflammatory burden in IBD patients would lead to decreased risk for CVDs. Currently and commonly used medications in the treatment of IBD patients are briefly discussed in the following section with emphasis on their effect on CVDs as summarized in *Table 3*.

5-aminosalicylates

Data on the potential effect of 5-aminosalicylates (5-ASA) on CVDs are inconsistent, although limited. For example, a Danish study showed that the risk of CAD was lower in IBD patients using 5-ASA than the non-users.[7] In contrast, analysis of a UK cohort revealed contrasting results with a higher risk of CVDs in IBD patients receiving 5-ASA.[36] In a multicentre longitudinal study, treatment with

Table 3   **Impacts of IBD and cardiovascular medications on cardiovascular and gastroenterological systems**

Medications	CV system	GI system
IBD medications		
5-ASA	Myocarditis and pericarditis[35]	Inducing and maintain IBD remission
	Inconclusive data for risk of CVDs[13,36]	
Corticosteroids	Increase risk of CVDs[36,37]	Inducing remission
Anti-TNF-α	Decrease risk of CVDs[37,38]	Inducing and maintain remission
	Reduce baseline procoagulant imbalance[39]	
Cardiovascular medications		
Aspirin	Primary and secondary prevention of CVDs in high-risk patients	Reduce the risk of colorectal adenoma and cancer
		Dose-related oesophagitis, peptic ulcers, and GI bleeding
		Potential increase in risk of CD[40]
Ridogrel	Anti-platelet therapy	Reduce mucosal thromboxane B2 concentration[41]
LMWH	Reduce risk of VTE	Attenuating IBD progression[42]
Statins	Lower cholesterol level	Reduce inflammation in CD[43]
		Reduce the use of oral steroids in IBD[44]
		Reduce risk of colorectal cancer in IBD[45]
		Reduce the risk of IBD[46]

5ASA, 5-aminosalicylates; CD, Crohn's disease; CV, cardiovascular; CVDs, cardiovascular diseases; ED, erectile dysfunction; GI, gastrointestinal; IBD, inflammatory bowel disease; LMWH, low-molecular-weight heparin; MI, myocardial infarction; VTE, venous thromboembolism.

salicylates increased aortic stiffness in IBD patients.[47] Additionally, 5-ASA use may be associated with myocarditis and pericarditis.[35]

Corticosteroids

Systemic use of corticosteroids may interrupt physiological metabolic processes with increases in blood glucose, water retention, and blood pressure, leading to exacerbation of DM, HTN, and HF. Studies indicate that IBD patients receiving corticosteroids exhibit a higher risk for cardiometabolic abnormalities and CVD than do control subjects.[6,36] A study examining a cohort of hospitalized IBD patients demonstrated that corticosteroid use is associated with an increased risk of thromboembolism.[37] Thus, while systemic use of corticosteroids may be beneficial in the short-term control of acute inflammatory flare in IBD patients, prolonged use could be detrimental with increased risk of CVDs and associated metabolic abnormalities.

Anti-tumour necrosis factor-α medications

Tumour necrosis factor-α is recognized as an important pro-inflammatory cytokine in IBD and anti-TNF-α approaches have been used in IBD patients. Studies have shown that anti-TNF-α therapy is associated with decreased incidence of cardiovascular events for patients with CD compared with prolonged corticosteroid treatment and could reduce aortic stiffness.[38,47] Anti-TNF-α 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.[37,39] Compared to 5-ASA and corticosteroids, anti-TNF-α therapy substantially reduces disease activity in IBD patients and is consistently associated with decreased cardiovascular events.

Considerations of cardiovascular medications in patients with inflammatory bowel disease

As similar pathophysiology appears to exist in both IBD and CVDs, and IBD patients have increased risk for CVDs, some medications commonly used in the treatment of CVDs are briefly discussed. Emphasis is placed on the additional benefits these cardiovascular medications may have for patients with IBD (*Table 3*).

Anti-platelet agents

Aspirin (ASA) has been widely used for primary and secondary prevention of CVDs in high-risk patients. One of the main concerns for IBD patients is the increased risk for colorectal malignancies. Aspirin has been shown to reduce the risk of colorectal adenoma and cancer. On the other hand, ASA is known to induce esophagitis, peptic ulcers, and gastrointestinal bleeding. Aspirin use was reported to increase the risk of developing CD, but not UC.[40] In contrast, other studies showed that aspirin use was not associated with an increased incidence of IBD or IBD flare.[48] Considering an increased risk for thromboembolic events in IBD patients, the benefits of using low-dose aspirin (i.e. its cardiovascular benefits and protective effect on colorectal cancer) might outweigh its risks (i.e. its dose-related

gastrointestinal complications) and potential impact on increased risk of CD. Current data suggest that it might be beneficial to use low-dose aspirin for primary and secondary prevention in IBD patients, but further data are needed.

Ridogrel is a combined thromboxane synthase inhibitor and receptor antagonist, which has been used for the prevention of systemic thromboembolism and as an adjunctive agent for thrombolytic therapy in MI. A clinical study in patients with active left-sided UC showed that ridogrel enemas could reduce mucosal thromboxane B2 concentration; however, it did not appear to improve disease progression.[41] In contrast, small clinical trials suggest that oral ridogrel might not have therapeutic benefit on inducing clinical remission of IBD compared to placebo.[49]

Heparin

Heparin has anticoagulant and anti-inflammatory properties, and thus, could be beneficial for IBD patients. A meta-analysis in patients with UC suggested that high-dose low-molecular-weight heparin (LMWH) administered via enemas was beneficial over placebo as assessed by clinical remission and endoscopic examination.[42] In 2014, the Canadian Association of Gastroenterology published a consensus statement on risk, prevention and treatment of VTE in IBD patients, and recommended anticoagulant thromboprophylaxis for IBD patients hospitalized with IBD flares without active bleeding. Thus, LMWH may be beneficial for IBD patients by reducing the risk of VTE and attenuating IBD progression if no bleeding risk.

Statins

Statins are known to have potent anti-inflammatory effects and to reduce the risk of cardiovascular morbidity and mortality. Studies have suggested that atorvastatin therapy could reduce inflammation (as measured by plasma cytokines and faecal calprotectin) in patients with CD.[43] A study with 1986 statin-treated and 9871 control subjects showed that statin use was associated with a significant reduction in the use of oral steroids in IBD patients.[44] Another large study with 11 001 subjects showed that statin use was associated with a significantly reduced risk of colorectal cancer in IBD patients.[45] A case–control study with 9617 patients and 46 665 controls demonstrated that any statin exposure was associated with a significantly reduced risk of IBD, CD, and UC.[46] Clearly, statins appear safe and beneficial as adjunctive therapies in IBD.

Conclusions

Inflammatory bowel disease is a systemic inflammatory disease and is associated with increased risk for CVDs especially in women and young adults, including CAD, stroke, thromboembolic diseases, and arrhythmias. The potential mechanisms for increased risk for CVDs in IBD patients include increased levels of inflammatory cytokines and oxidative stress, hypercoagulability, decreased circulating EPCs, endothelial dysfunction, and possible interruption of gut microbiota. Compared to 5-ASA and corticosteroids, anti-TNF-α therapy in IBD patients is consistently associated with decreased cardiovascular events. Although IBD does not appear to exacerbate the traditional risk factors for CVDs, aggressive risk stratifications are important for primary and secondary prevention of CVDs for IBD patients.

Low-dose aspirin and statins appear to be beneficial for IBD patients if there are no contraindications. Low-molecular-weight heparin is recommended for IBD patients who are hospitalized with IBD flares without risk of major bleeding. Considering the gastrointestinal and EIMs in IBD patients, a multidisciplinary team approach including cardiology should be considered for IBD management.

Lead author biography
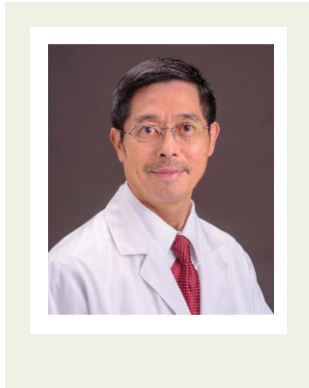
Zhenguo Liu, MD, PhD, obtained his medical education in Hunan Medical College in China in 1984, and PhD in cardiovascular pharmacology at Queen's University in Kingston, Canada, in 1995. After research fellowship in vascular biology, residency in internal medicine, and fellowships in cardiovascular diseases and clinical cardiac electrophysiology, Dr. Liu started his career as a physician-scientist and independent investigator in vascular biology and oxidative stress. He is currently a Professor of Medicine and Medical Pharmacology, Margaret Proctor Mulligan Endowed Professor in Cardiovascular Research, and Director of Cardiovascular Medicine, University of Missouri School of Medicine in Columbia, Missouri, USA.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Conflict of interest: none declared.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

References

1. Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. *Eur Heart J* 2015;**36**:482–489c.
2. Roifman I, Sun YC, Fedwick JP, Panaccione R, Buret AG, Liu H, Rostom A, Anderson TJ, Beck PL. Evidence of endothelial dysfunction in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2009;**7**:175–182.
3. Ozturk K, Guler AK, Cakir M, Ozen A, Demirci H, Turker T, Demirbas S, Uygun A, Gulsen M, Bagci S. Pulse wave velocity, intima media thickness, and flow-mediated dilatation in patients with normotensive normoglycemic inflammatory bowel disease. *Inflamm Bowel Dis* 2015;**21**:1314–1320.
4. Kirchgesner J, Beaugerie L, Carrat F, Andersen NN, Jess T, Schwarzinger M; BERENICE study group. Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study. *Gut* 2018;**67**:1261–1268.
5. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010;**375**:657–663.
6. Aarestrup J, Jess T, Kobylecki CJ, Nordestgaard BG, Allin KH. Cardiovascular risk profile among patients with inflammatory bowel disease: a population-based study of more than 100 000 individuals. *J Crohns Colitis* 2019;**13**:319–323.
7. Rungoe C, Basit S, Ranthe MF, Wohlfahrt J, Langholz E, Jess T. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. *Gut* 2013;**62**:689–694.
8. Choi YJ, Lee DH, Shin DW, Han K-D, Yoon H, Shin CM, Park YS, Kim N. Patients with inflammatory bowel disease have an increased risk of myocardial infarction: a nationwide study. *Aliment Pharmacol Ther* 2019;**50**:769–779.
9. Ha C, Magowan S, Accortt NA, Chen J, Stone CD. Risk of arterial thrombotic events in inflammatory bowel disease. *Am J Gastroenterol* 2009;**104**:1445–1451.
10. Andersohn F, Waring M, Garbe E. Risk of ischemic stroke in patients with Crohn's disease: a population-based nested case-control study. *Inflamm Bowel Dis* 2010;**16**:1387–1392.
11. Singh S, Singh H, Loftus EV, Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014;**12**:382–393.
12. Kappelman MD, Horvath-Puho E, Sandler RS, Rubin DT, Ullman TA, Pedersen L, Baron JA, Sørensen HT. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. *Gut* 2011;**60**:937–943.
13. Chung W-S, Lin C-L, Hsu W-H, Kao C-H. Inflammatory bowel disease increases the risks of deep vein thrombosis and pulmonary embolism in the hospitalized patients: a nationwide cohort study. *Thromb Res* 2015;**135**:492–496.
14. Naito T, Botwin GJ, Haritunians T, Li D, Yang S, Khrom M, Braun J, Abbou L, Mengesha E, Stevens C, Masamune A, Daly M, McGovern DPB; NIDDK IBD Genetics Consortium. Prevalence and effect of genetic risk of thromboembolic disease in inflammatory bowel disease. *Gastroenterology* 2021;**160**:771–780.e4.
15. Shen J, Ran ZH, Zhang Y, Cai Q, Yin HM, Zhou XT, Xiao SD. Biomarkers of altered coagulation and fibrinolysis as measures of disease activity in active inflammatory bowel disease: a gender-stratified, cohort analysis. *Thromb Res* 2009;**123**:604–611.
16. Li T, Wang C, Liu Y, Li B, Zhang W, Wang L, Yu M, Zhao X, Du J, Zhang J, Dong Z, Jiang T, Xie R, Ma R, Fang S, Zhou J, Shi J. Neutrophil extracellular traps induce intestinal damage and thrombotic tendency in inflammatory bowel disease. *J Crohns Colitis* 2020;**14**:240–253.
17. Döring Y, Soehnlein O, Weber C. Neutrophil extracellular traps in atherosclerosis and atherothrombosis. *Circ Res* 2017;**120**:736–743.
18. Kristensen SL, Ahlehoff O, Lindhardsen J, Erichsen R, Lamberts M, Khalid U, Nielsen OH, Torp-Pedersen C, Gislason GH, Hansen PR. Inflammatory bowel disease is associated with an increased risk of hospitalization for heart failure: a Danish Nationwide Cohort study. *Circ Heart Fail* 2014;**7**:717–722.
19. Kivrak T, Sunbul M, Cincin A, Kani T, Durmus E, Banzragch M, Bozbay M, Aydin Y, Imeryuz N, Sari I, Akin H, Basaran Y. Two-dimensional speckle tracking echocardiography is useful in early detection of left ventricular impairment in patients with Crohn's disease. *Eur Rev Med Pharmacol Sci* 2016;**20**:3249–3254.
20. Prasada S, Rivera A, Nishtala A, Pawlowski AE, Sinha A, Bundy JD, Chadha SA, Ahmad FS, Khan SS, Achenbach C, Palella FJ, Ramsey-Goldman R, Lee YC, Silverberg JI, Taiwo BO, Shah SJ, Lloyd-Jones DM, Feinstein MJ. Differential associations of chronic inflammatory diseases with incident heart failure. *JACC Heart Fail* 2020;**8**:489–498.
21. Mubasher M, Syed T, Hanafi A, Yu Z, Yusuf I, Abdullah AS, Mohamed MF, Alweis R, Rao M, Hoefen R, Danjuma MI. An investigation into the association between inflammatory bowel disease and cardiac arrhythmias: an examination of the United States national inpatient sample database. *Clin Med Insights Cardiol* 2020;**14**:1179546820955179.
22. Kristensen SL, Lindhardsen J, Ahlehoff O, Erichsen R, Lamberts M, Khalid U, Torp-Pedersen C, Nielsen OH, Gislason GH, Hansen PR. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace* 2014;**16**:477–484.
23. Garolla A, D'Incà R, Checchin D, Biagioli A, De Toni L, Nicoletti V, Scarpa M, Bolzonello E, Sturniolo GC, Foresta C. Reduced endothelial progenitor cell number and function in inflammatory bowel disease: a possible link to the pathogenesis. *Am J Gastroenterol* 2009;**104**:2500–2507.
24. Cibor D, Szczeklik K, Mach T, Owczarek D. Levels of tissue factor pathway inhibitor in patients with inflammatory bowel disease. *Pol Arch Intern Med* 2019;**129**:253–258.
25. Schlagenhauf A, Haidl H, Sina P, Jörg J, Muntean W, Siegfried G. Children with inflammatory bowel disease exhibit insensitivity to tissue factor pathway inhibitor. *Blood* 2018;**132**:2504.
26. Scaldaferri F, Sans M, Vetrano S, Graziani C, De Cristofaro R, Gerlitz B, Repici A, Arena V, Malesci A, Panes J, Grinnell BW, Danese S. Crucial role of the protein C pathway in governing microvascular inflammation in inflammatory bowel disease. *J Clin Invest* 2007;**117**:1951–1960.
27. Bhandari S, Mohammed Abdul MK, Dhakal B, Kreuziger LB, Saeian K, Stein D. Increased rate of venous thromboembolism in hospitalized inflammatory bowel disease patients with *Clostridium difficile* infection. *Inflamm Bowel Dis* 2017;**23**:1847–1852.

28. Huang J, Kelly CP, Bakirtzi K, Villafuerte Gálvez JA, Lyras D, Mileto SJ, Larcombe S, Xu H, Yang X, Shields KS, Zhu W, Zhang Y, Goldsmith JD, Patel IJ, Hansen J, Huang M, Yla-Herttuala S, Moss AC, Paredes-Sabja D, Pothoulakis C, Shah YM, Wang J, Chen X. Clostridium difficile toxins induce VEGF-A and vascular permeability to promote disease pathogenesis. Nat Microbiol 2019;4: 269–279.

29. Jäckel S, Kiouptsi K, Lillich M, Hendrikx T, Khandagale A, Kollar B, Hörmann N, Reiss C, Subramaniam S, Wilms E, Ebner K, Brühl M-L. V, Rausch P, Baines JF, Haberichter S, Lämmle B, Binder CJ, Jurk K, Ruggeri ZM, Massberg S, Walter U, Ruf W, Reinhardt C. Gut microbiota regulate hepatic von Willebrand factor synthesis and arterial thrombus formation via Toll-like receptor-2. Blood 2017;130: 542–553.

30. Ascher S, Wilms E, Pontarollo G, Formes H, Bayer F, Müller M, Malinarich F, Grill A, Bosmann M, Saffarzadeh M, Brandão I, Groß K, Kiouptsi K, Kittner JM, Lackner KJ, Jurk K, Reinhardt C. Gut microbiota restricts NETosis in acute mesenteric ischemia-reperfusion injury. Arterioscler Thromb Vasc Biol 2020;40: 2279–2292.

31. Wilson A, Teft WA, Morse BL, Choi Y-H, Woolsey S, DeGorter MK, Hegele RA, Tirona RG, Kim RB. Trimethylamine-N-oxide: a novel biomarker for the identification of inflammatory bowel disease. Dig Dis Sci 2015;60: 3620–3630.

32. Kristensen SL, Ahlehoff O, Lindhardsen J, Erichsen R, Jensen GV, Torp-Pedersen C, Nielsen OH, Gislason GH, Hansen PR. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death—a Danish nationwide cohort study. PLoS One 2013;8:e56944.

33. Dregan A, Charlton J, Chowienczyk P, Gulliford MC. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. Circulation 2014;130:837–844.

34. Sappati Biyyani RS, Putka BS, Mullen KD. Dyslipidemia and lipoprotein profiles in patients with inflammatory bowel disease. J Clin Lipidol 2010;4:478–482.

35. Brown G. 5-aminosalicylic acid-associated myocarditis and pericarditis: a narrative review. Can J Hosp Pharm 2016;69:466–472.

36. Close H, Mason JM, Wilson DW, Hungin APS, Jones R, Rubin G. Risk of ischaemic heart disease in patients with inflammatory bowel disease: cohort study using the general practice research database. PLoS One 2015;10:e0139745.

37. deFonseka AM, Tuskey A, Conaway MR, Behm BW. Antitumor necrosis factor-α therapy is associated with reduced risk of thromboembolic events in hospitalized patients with inflammatory bowel disease. J Clin Gastroenterol 2016;50: 578–583.

38. Lewis JD, Scott FI, Brensinger CM, Roy JA, Osterman MT, Mamtani R, Bewtra M, Chen L, Yun H, Xie F, Curtis JR. Increased mortality rates with prolonged cor-ticosteroid therapy when compared with antitumor necrosis factor-α-directed therapy for inflammatory bowel disease. Am J Gastroenterol 2018;113:405–417.

39. Tripodi A, Spina L, Pisani LF, Padovan L, Cavallaro F, Chantarangkul V, Valsecchi C, Peyvandi F, Vecchi M. Anti-TNF-α treatment reduces the baseline procoagulant imbalance of patients with inflammatory bowel diseases. Inflamm Bowel Dis 2021;doi:10.1093/ibd/izaa351.

40. Chan SSM, Luben R, Bergmann MM, Boeing H, Olsen A, Tjonneland A, Overvad K, Kaaks R, Kennedy H, Khaw K-T, Riboli E, Hart AR. Aspirin in the aetiology of Crohn's disease and ulcerative colitis: a European prospective cohort study. Aliment Pharmacol Ther 2011;34:649–655.

41. Auwerda JJ, Zijlstra FJ, Tak CJ, van den Ingh HF, Wilson JH, Ouwendijk RJ. Ridogrel enemas in distal ulcerative colitis. Eur J Gastroenterol Hepatol 2001;13:397–400.

42. Chande N, MacDonald JK, Wang JJ, McDonald JWD. Unfractionated or low molecular weight heparin for induction of remission in ulcerative colitis: a Cochrane inflammatory bowel disease and functional bowel disorders systematic review of randomized trials. Inflamm Bowel Dis 2011;17:1979–1986.

43. Grip O, Janciauskiene S, Bredberg A. Use of atorvastatin as an anti-inflammatory treatment in Crohn's disease. Br J Pharmacol 2008;155:1085–1092.

44. Crockett SD, Hansen RA, Stürmer T, Schectman R, Darter J, Sandler RS, Kappelman MD. Statins are associated with reduced use of steroids in inflammatory bowel disease: a retrospective cohort study. Inflamm Bowel Dis 2012;18: 1048–1056.

45. Ananthakrishnan AN, Cagan A, Cai T, Gainer VS, Shaw SY, Churchill S, Karlson EW, Murphy SN, Liao KP, Kohane I. Statin use is associated with reduced risk of colorectal cancer in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2016;14:973–979.

46. Ungaro R, Chang HL, Côté-Daigneault J, Mehandru S, Atreja A, Colombel J-F. Statins associated with decreased risk of new onset inflammatory bowel disease. Am J Gastroenterol 2016;111:1416–1423.

47. Zanoli L, Ozturk K, Cappello M, Inserra G, Geraci G, Tuttolomondo A, Torres D, Pinto A, Duminuco A, Riguccio G, Aykan MB, Mulé G, Cottone S, Perna AF, Laurent S, Fatuzzo P, Castellino P, Boutouyrie P. Inflammation and aortic pulse wave velocity: a multicenter longitudinal study in patients with inflammatory bowel disease. J Am Heart Assoc 2019;8:e010942.

48. Ananthakrishnan AN, Higuchi LM, Huang ES, Khalili H, Richter JM, Fuchs CS, Chan AT. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. Ann Intern Med 2012;156: 350–359.

49. Tytgat GNJ, Van Nueten L, Van De Velde I, Joslyn A, Hanauer SB. Efficacy and safety of oral ridogrel in the treatment of ulcerative colitis: two multi-centre, randomized, double-blind studies. Aliment Pharmacol Ther 2002;16: 87–99.