Digestive and Liver Disease 57 (2025) 997–1005

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Vascular complications in hospitalized patients with inflammatory bowel disease and acute gastroenteritis and colitis: A propensity score-matched study

Alfredo Papa[a,b], Lucrezia Laterza[a,b,*], Valerio Papa[b,c], Loris Riccardo Lopetuso[a,d,e], Stefania Colantuono[a], Gaetano Coppola[a], Benedetta Simeoni[f], Franco Scaldaferri[a,b], Francesco Franceschi[b,f], Antonio Gasbarrini[a,b], Marcello Covino[b,f]

[a] Centre for Digestive Diseases (CEMAD) and Gastroenterology Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
[b] Università Cattolica del S. Cuore, Rome, Italy
[c] Digestive Surgery, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
[d] Department of Medicine and Ageing Sciences, G. D'Annunzio University of Chieti-Pescara, Chieti, Italy
[e] Center for Advanced Studies and Technology (CAST), G. D'Annunzio University of Chieti-Pescara, Chieti, Italy
[f] Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

ARTICLE INFO

Article history:
Received 23 December 2024
Accepted 23 January 2025
Available online 10 February 2025

Keywords:
Inflammatory bowel disease
Atherosclerotic cardiovascular disease
Ischemic heart disease
Venous thromboembolism

ABSTRACT

Objectives: Atherosclerotic cardiovascular disease (ASCVD) and venous thromboembolism (VTE) are severe complications of inflammatory bowel disease (IBD). Risk factors for ASCVD and VTE in IBD are not entirely elucidated. This study investigated the incidence and risk factors for ASCVD and VTE in IBD compared to acute infective gastroenteritis and colitis (AGC).

Methods: We reviewed the clinical records of inpatients with IBD and AGC over 6 years. Each group's propensity score-matched (PS) subpopulation consisted of 831 patients, ensuring a balanced comparison. Additionally, the effect of IBD on ASCVD and VTE was assessed.

Results: The PS cohorts indicated a significantly higher number of ASCVD events in IBD than controls (10.1 % vs. 5.5 %, $p = 0.001$) and an increased prevalence of ischemic heart disease (IHD) (7.9 % vs. 3.6 %, $p < 0.001$). Conversely, the study groups demonstrated similar VTE incidence. IBD diagnosis, male sex, hypertension, diabetes, and the Charlson Index were independently associated with ASCVD. Age was significantly associated with VTE.

Conclusions: Inpatients with IBD demonstrated an increased risk of ASCVD and IHD. IBD was an independent risk factor for ASCVD, and chronic inflammation was a significant enhancer factor for ASCVD. Aggressive control of inflammation is an essential target to reduce ASCVD risk.

1. Introduction

Inflammatory bowel diseases (IBD) are chronic disorders, including Crohn's disease (CD) and ulcerative colitis (UC), which primarily impact the intestine. The predominant onset of IBD is at a young age; hence, affected patients experience a long and intermittent lifetime exposure to inflammatory mediators that may exhibit systemic relevance [1,2]. Among the extraintestinal complications of IBD, atherosclerotic cardiovascular disease (ASCVD) and venous thromboembolism (VTE) represent a considerable burden, causing significant morbidity and not negligible mortality, particularly among inpatients [3–15]. Patients with IBD exhibit a well-recognized twofold to threefold increased risk of VTE than healthy controls [3,5,7–10,13]. VTEs are principally represented by deep vein thrombosis and pulmonary embolism (PE), and, to a lesser extent, affect abdominal and cerebral veins [4,15,16]. Considering patients with IBD, a 2.5-fold higher odds of mortality associated with VTE-related hospitalizations rather than non-VTE-related hospitalizations confirms the burden of these events [17]. International

* Correspondence author at: Fondazione Policlinico Universitario A. Gemelli, IRCCS, Internal Medicine and Gastroenterology Department, Università Cattolica del S. Cuore- L.go A. Gemelli, 8; 00168 Rome, Italy.
E-mail address: lucrezia.laterza@policlinicogemelli.it (L. Laterza).

https://doi.org/10.1016/j.dld.2025.01.195

guidelines on managing patients with IBD have been implemented to address this issue and recommend pharmacological prophylaxis for VTE among inpatients [18–20]. Additionally, consistent evidence reports that IBD is related to a higher risk of ASCVD when compared to the general population, considering ischemic heart disease (IHD), stroke, and mesenteric and peripheral arterial disease [4,6,11–14,21–24]. IBD "per se" has been hypothesized to represent an independent risk factor alongside the traditional risk factors for ASCVD and VTE [25]. Disease activity, with its intrinsic "inflammatory burden", plays a crucial role in the pathogenesis of thrombotic events among many other prothrombotic factors [26,27]; additionally, chronic inflammation is a major factor in the genesis and progression of atherogenic phenomena [28]. Confirming these results, C-reactive protein (CRP), frequently increasing during IBD flares, has been independently associated with IHD of the traditional cardiovascular risk factors [29]. Therefore, the present study primarily aimed to compare the ASCVD and VTE prevalence rates between patients with IBD and those with acute infective gastroenteritis and colitis (AGC). In the second place, we evaluated the risk factors for ASCVD and VTE in the two cohorts of patients to identify the association between IBD and thrombotic arterial or venous vascular disease.

2. Materials and methods

2.1. Study population

This retrospective, case-control, single-center study included all consecutive patients with IBD, aged ≥18 years, admitted to the ED of an academic hospital from January 1, 2014, to December 31, 2019, with a definitive IBD diagnosis (CD and UC). We extracted the clinical records of patients with a discharge diagnosis of IBD among the first three primary diagnoses following the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM), codes 555 and 556, and their subcategories (cases). The control groups included patients with a discharge diagnosis of AGC, including those caused by *Salmonella* (ICD-9-CM: 003.0), *Shigella* spp. (ICD-9-CM: 004.0 004.1, 004.2, and 004.3), and other bacterial colitis and enteritis (ICD-9-CM: 008 and subcategories and 009 and subcategories) among the first three primary diagnoses. We excluded pregnant women and patients diagnosed with colon or rectal cancer (ICD-9-CM: 153.0–153.9, and 197.5).

2.2. Outcomes

The study's primary outcome includes the prevalence of ASCVD and VTE in the IBD cohort compared to controls with AGC. In particular, we considered the following discharge diagnosis as VTE: pulmonary embolism (ICD-9-CM: 415 and subcategories), phlebitis, and thrombo-phlebitis (ICD-9-CM: 451 and subcategories), portal vein thrombosis (ICD-9-CM: 452), and other types of venous thrombosis (ICD-9-CM: 453 and subcategories). We considered cerebrovascular disease, including stroke (ICD: 433, 434, 435, 436, and 437 and their subcategories), IHD, such as acute myocardial infarction (ICD: 410, 411, 413, and 414 and their subcategories), and peripheral artery disease, including mesenteric artery disease and atherosclerotic disease (ICD 440, 443, 444 and their subcategories), as ASCVD. All the arterial and venous vascular events included were reported as new onset among discharge diagnoses. The secondary outcome consists of the prevalence of the traditional risk factors for ASCVD and VTE in the two study groups and, mainly, the association of IBD diagnosis with the risk of ASCVD and VTE.

2.3. Covariates

The following ASCCV and VTE risk factors were evaluated by reviewing hospital records at admission: hypertension (defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or use of antihypertensive agents), dyslipidemia (defined as a total cholesterol level of ≥200 mg/dl and/or triglycerides of ≥150 mg/dl mmol/L, previous diagnosis, and/or the use of lipid-lowering agents), diabetes mellitus (defined as fasting glucose of ≥126 mg/dl, non-fasting glucose of ≥200 mg/dl, previous diagnosis, or use of hypoglycemics agents), chronic kidney disease, severe obesity (for patients with a body mass index (BMI) of ≥40), and smoking (defined as being an active smoker or having stopped smoking for <6 months). Other comorbidities relevant to the study's outcomes are the history of IHD, congestive heart failure, cerebrovascular disease, atrial fibrillation, dementia, chronic obstructive pulmonary disease (COPD), and the Charlson Comorbidity Index. Additionally, data collected included the most predominantly administered medications to treat moderate to severe IBD, such as steroids (both systemic and intestinal-releasing steroids) and biologics (anti-tumor necrosis factor [TNF]-α agents, vedolizumab, and ustekinumab). Moreover, medications that could affect the course of arterial or venous atherothrombotic vascular disease, such as oral contraceptives, aspirin, and oral anticoagulants, have been documented.

2.4. Ethical statement

The Local Ethics Committee approved the study, conducted under the Declaration of Helsinki, for the use of the data stemming from standard clinical practice since no additional interventions were planned (observational study). All patients provided informed consent for study participation.

2.5. Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. Categorical variables are indicated in numbers (percentages) and compared using the Chi-squared test or Fisher's exact test as appropriate.

2.6. Propensity score-matched analysis

Significant differences were found between the patients with IBD and those with AGC in baseline clinical variables; thus, further analysis of differences in the prevalence rates of ASCVD and VTE between the two groups was conducted in a subpopulation of patients matched in a 1:1 ratio. Propensity score matching (PS) was generated using a logistic regression model on the baseline covariates potentially affecting the thrombotic risk. Variables for PS included age, gender, Charlson Index, dyslipidemia, hypertension, diabetes mellitus, smoking, obesity, estrogen-progestin therapy, anticoagulation therapy, and statin therapy. Patients were matched on these propensity scores by the nearest neighbor method with a 1:1 ratio. An optimal matching with a 0.2 caliper size avoided poor matches. Supplementary Table 1 and Supplementary Figure 1 describe PS analysis and distribution before and after the match.

The study variables significantly associated with ASCVD and VTE in univariate analysis were entered into a multivariate logistic regression model to determine independent predictors of vascular complications, considering the PS-matched cohort. IBD diagnosis was considered a factor in all multivariate models. Logistic regression results are presented as odds ratios (ORs) with 95 % confidence intervals (CIs). A two-sided p-value of ≤0.05 indicated

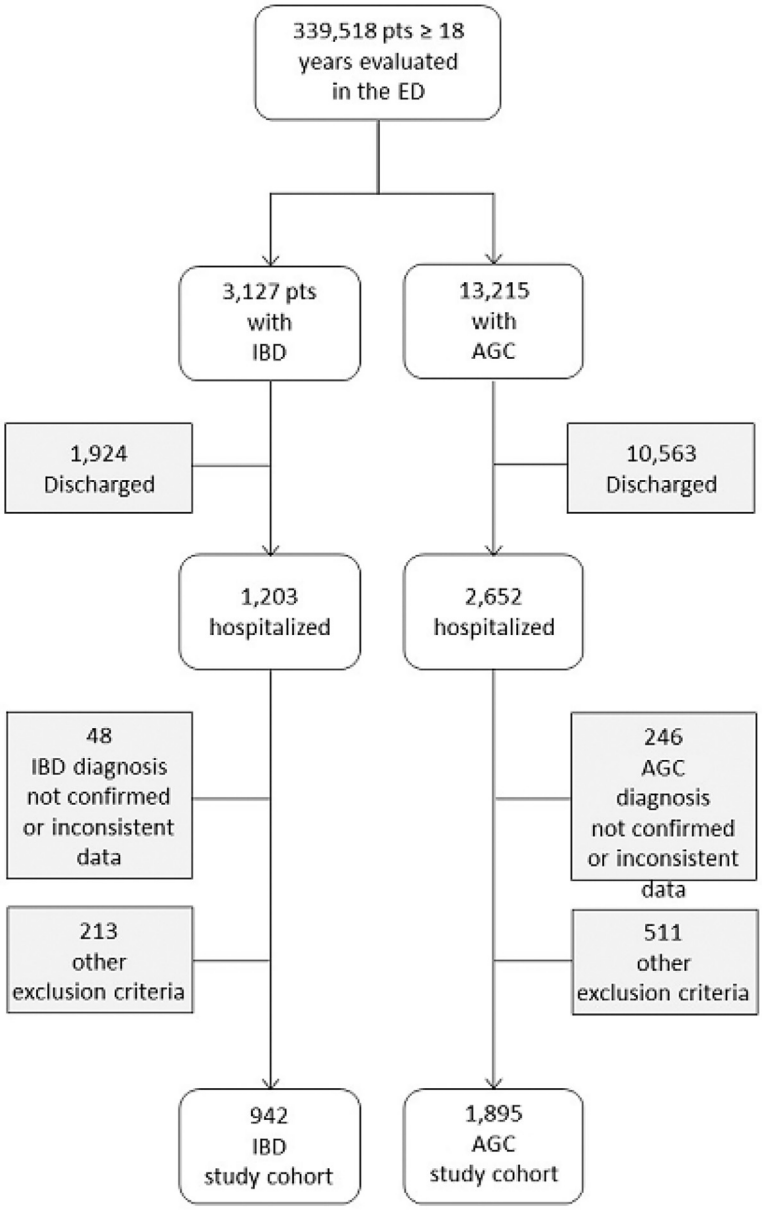

Fig. 1. Flowchart of the study.

significance. Statistical Package for the Social Sciences version 25® (IBM, Armonk, NY, USA) was used for all data analyses.

2.7. Sample size estimation

The logistic regression models for arterial and venous thrombotic events involve 12 and 2 variables; thus, 120 arterial thrombotic events and 20 venous thrombotic events would have been required for correct parameter estimation. The PS study cohort is sufficient for both analyses.

3. Results

3.1. Demographic and clinical characteristics of patients with IBD and controls

During the study period, 3127 patients with IBD were evaluated in our ED. Of them, 1203 were inpatients, and 261 were excluded due to unconfirmed diagnoses, inconsistent clinical data, or other exclusion criteria (Fig. 1). Finally, the study analyzed 942 patients with IBD, including 453 (48.1 %) with CD and 489 (51.9 %) with UC. The control group consisted of 1895 inpatients among 13,215 who were evaluated in our ED. Table 1 shows the demographic and clinical characteristics of patients with IBD and controls. All cardiovascular risk factors and comorbidities were significantly more prevalent in patients included in the control group than in those with IBD, except for smoking. There was no difference in aspirin and statin use between the two studied groups, whereas oral anticoagulant use was more frequent in controls. As expected, steroids and biologics use were significantly higher in patients with IBD than in controls (8.9 % vs. 2.3 %, $p < 0.001$ and 7.5 % vs. 0.4 %, $p < 0.001$, respectively).

3.2. VTE and ASCVD prevalence rates in the original cohort

Table 2 presents ASCVD and VTE prevalence rates in patients with IBD and controls. In detail, the rates of IHD (including myocardial infarction) and peripheral artery disease did not differ be-

Table 1
Demographics and clinical characteristics of patients with inflammatory bowel disease (IBD) and with acute infective gastroenteritis and colitis (AGC) in the original cohorts.

Variable	Crohn's Disease $n = 453$	Ulcerative colitis $n = 489$	Overall IBD $n = 942$	AGC n. 1895	p
Age[§]	54 [38–70]	58 [39–73]	56 [38–71]	74 [60–83]	<0.001
Age ≥ 65 years	146 (32.2 %)	191 (39.1 %)	337 (35.8 %)	1260 (66.5 %)	<0.001
Sex (Male)	242 (53.4 %)	262 (53.6 %)	504 (53.5 %)	836 (44.1 %)	<0.001
Cardiovascular risk factors					
Hypertension	64 (14.1 %)	104 (21.3 %)	168 (17.8 %)	585 (30.9 %)	<0.001
CKD	37 (8.2 %)	35 (7.2 %)	72 (7.6 %)	322 (17.0 %)	<0.001
Diabetes	27 (6.0 %)	44 (9.0 %)	71 (7.5 %)	317 (16.7 %)	0.002
Dyslipidemia	20 (4.4 %)	16 (3.3 %)	36 (3.8 %)	114 (6.0 %)	0.014
Smokers	60 (12.7 %)	68 (14.4 %)	128 (13.6 %)	202 (10.7 %)	0.022
Severe obesity	0	2 (0.4 %)	2 (0.2 %)	27 (1.4 %)	0.002
Other Comorbidities					
Charlson Index[§]	1 [0–4]	2 [0–4]	2 [0–4]	4 [2–6]	<0.001
History of IHD	36 (7.9 %)	52 (10.6 %)	88 (9.3 %)	252 (13.3 %)	0.002
Congestive heart failure	15 (3.3 %)	22 (4.5 %)	37 (3.9 %)	241 (12.7 %)	<0.001
Cerebrovascular disease	14 (3.1 %)	18 (3.7 %)	32 (3.4 %)	118 (6.2 %)	0.002
History of atrial fibrillation	19 (4.2 %)	31 (6.3 %)	50 (5.3 %)	180 (9.5 %)	0.001
Dementia	5 (1.1 %)	6 (1.2 %)	11 (1.2 %)	96 (5.1 %)	0.001
COPD	17 (3.8 %)	25 (5.1 %)	42 (4.5 %)	182 (9.6 %)	0.001
Pharmacological therapy					
Cardioaspirin	51 (11.3 %)	87 (17.8 %)	138 (14.6 %)	266 (14.0 %)	0.660
Steroids	26 (5.7 %)	58 (11.9 %)	84 (8.9 %)	44 (2.3 %)	<0.001
Biological therapy	33 (7.3 %)	38 (7.8 %)	71 (7.5 %)	8 (0.4 %)	<0.001
Statins	17 (3.8 %)	14 (2.9 %)	31 (3.3 %)	86 (4.5 %)	0.116
Estrogen-progestin therapy	3 (0.7 %)	1 (0.2 %)	4 (0.4 %)	2 (0.1 %)	0.081
Oral anticoagulants	25 (5.5 %)	29 (5.9 %)	54 (5.7 %)	162 (8.5 %)	0.008

[§] Values are expressed as Median [Interquartile range];*CKD: Chronic kidney disease; COPD: chronic obstructive pulmonary disease; IHD: ischemic heart disease.

Table 2
Prevalence rates of ATEs and VTEs in patients with inflammatory bowel disease (IBD) and with acute infective gastroenteritis and colitis (AGC) in the original cohorts.

Variable	Crohn's disease $n = 453$	Ulcerative colitis n489	Overall IBD $n = 942$	AGC $n = 1895$	p
ATEs					
Ischemic heart disease	29 (6.4 %)	37 (7.6 %)	66 (7.0 %)	149 (7.9 %)	0.417
Peripheral artery disease	8 (1.8 %)	15 (3.1 %)	23 (2.4 %)	56 (3.0 %)	0.434
Cerebrovascular disease	2 (0.4 %)	12 (2.5 %)	23 (1.5 %)	56 (3.7 %)	0.001
Overall vascular arterial	33 (7.3 %)	52 (10.6 %)	85 (9.0 %)	236 (12.5 %)	0.007
VTEs					
Deep venous thrombosis	3 (0.6 %)	8 (1.7 %)	11 (1.2 %)	29 (1.5 %)	0.440
Pulmonary embolism	2 (0.4 %)	10 (2.0 %)	12 (1.3 %)	21 (1.1 %)	0.698
Other venous thrombosis	1 (0.2 %)	5 (1.1 %)	6 (0.6 %)	18 (0.9 %)	0.391
Overall venous thrombosis	5 (1.1 %)	19 (4.0 %)	24 (2.5 %)	63 (3.3 %)	0.258
Outcomes					
Death	6 (1.3 %)	20 (4.1 %)	26 (2.8 %)	179 (9.4 %)	<0.001
Minor Surgery	41 (9.1 %)	47 (9.6 %)	88 (9.3 %)	124 (6.5 %)	0.020
Major surgery	62 (13.7 %)	33 (6.7 %)	95 (10.1 %)	178 (9.4 %)	
Mechanical Ventilation	5 (1.1 %)	9 (1.8 %)	14 (1.5 %)	68 (3.6 %)	0.002
LOS[§,#]	8.4 [5.4–13.5]	9.2 [6.0–13.5]	8.6 [5.6–13.5]	9.5 [5.7–18.3]	<0.001

[§] Values are expressed as Median [Interquartile range].
[#] Length of hospital stay (LOS) was calculated from emergency department admission to hospital discharge/death. ATEs: arterial thromboembolic events; VTEs: venous thromboembolic events.

tween IBD and controls ($p = 0.417$ and $p = 0.434$, respectively). Likewise, cerebrovascular disease (including stroke) rate and the number of patients with at least one ASCVD event were significantly higher in controls than in patients with IBD ($p < 0.05$ and $p = 0.007$, respectively). Supplementary Figure 2 shows the prevalence of ASCVD events in patients with CD and UC. No difference was found considering the prevalence of VTE between patients with IBD and controls. Supplementary Figure 3 shows the VTE rate based on IBD type. We observed that patients with UC had a significantly increased PE prevalence than controls ($p < 0.05$). Interestingly, we observed that ASCVD events were significantly more prevalent in the subgroup of patients with IBD aged 50–64 years than controls when patients with IBD and controls were stratified by age in four groups (<50 years, 50–64 years, 65–79 years, and ≥80 years) ($p < 0.05$); no difference was found for the other age groups. Considering VTE prevalence, we observed a significantly increased incidence of VTE in patients with UC aged 65–79. Supplementary Figures 4 and 5 summarize these data.

3.3. Demographic and clinical characteristics of the cohort in PS

For the PS, the study cohorts comprised 831 patients with IBD and 831 controls. Supplementary Table 2 presents the detailed characteristics of patients in the PS cohorts. Most of the study variables and risk factors for vascular thrombotic events were well-balanced between the two groups.

Table 3
Univariate and multivariate (logistic regression model) analyses of factors associated with ASCVD (any), performed on the propensity score-matched study cohorts.

Variable	Absence of ASCVD $n = 1532$	Any ASCVD $n = 130$	Univariate analysis *p-value*	Multivariate analysis Odds Ratio [95 % confidence interval]	Multivariate analysis *p*-value
IBD	747 (48.8 %)	85 (64.6 %)	**0.001**	2.21 [1.47–3.31]	**<0.001**
Age[§]	58 [45–71]	73 [63–80]	**<0.001**	1.02 [0.99–1.03]	**0.058**
Sex (Male)	779 (50.8 %)	80 (61.5 %)	**0.019**	1.66 [1.11–2.49]	**0.013**
Cardiovascular risk factors					
Hypertension	286 (18.7 %)	71 (54.6 %)	**<0.001**	3.12 [2.07–4.73]	**<0.001**
CKD	133 (8.7 %)	22 (16.9 %)	**0.002**	0.87 [0.48–1.57]	0.655
Diabetes	137 (8.9 %)	22 (25.4 %)	**<0.001**	1.68 [1.02–2.76]	**0.040**
Dyslipidemia	55 (3.6 %)	14 (10.8 %)	**<0.001**	1.74 [0.40–7.49]	0.457
Smoking	150 (9.8 %)	26 (20.0 %)	**0.043**	3.36 [0.70–16.01]	0.129
Severe obesity	13 (0.8 %)	0	0.616		
Other comorbidities					
Charlson Index[§]	2 [1–4]	5 [3–6]	**<0.001**	1.26 [1.13– 1.39]	**<0.001**
History of CAD	69 (4.5 %)	72 (55.4 %)	<0.001		
Congestive heart failure	56 (3.7 %)	20 (15.4 %)	<0.001		
Cerebrovascular disease	35 (2.3 %)	18 (13.8 %)	<0.001		
History of atrial fibrillation	70 (4.6 %)	17 (13.1 %)	<0.001		
Dementia	31 (2.0 %)	2 (1.5 %)	1.000		
COPD	73 (4.8 %)	13 (10.0 %)	0.010		
Therapy					
Cardioaspirin	176 (11.5 %)	32 (24.6 %)	**<0.001**	1.36 [0.85–2.28]	0.185
Steroids	82 (5.4 %)	4 (3.1 %)	0.406		
Biological therapy	56 (3.7 %)	4 (3.1 %)	0.734		
Statins	44 (2.9 %)	11 (8.5 %)	**0.001**	0.76 [0.14–3.92]	0.747
Estrogen-progestin therapy	4 (0.3 %)	0	1.000		
Oral anticoagulation	76 (5.0 %)	14 (10.8 %)	**0.005**	1.47 [0.76–2.84]	0.255

[§] Values are expressed as Median [Interquartile range]; CAD: coronary artery disease; CKD: Chronic kidney disease; COPD: chronic obstructive pulmonary disease; IBD: inflammatory bowel disease; IHD: ischemic heart disease.The logistic model had an overall accuracy of 92.2 %, (model Chi-square: 171.384; log-likelihood^{-2}: 740.7; Hosmer & Lemeshow test Chi^2: 9.83 $p = 0.277$; constant was included in the model).

3.4. Analysis of ASCVD events after PS

The PS cohorts indicated 130 (7.8 %) patients experienced at least one ASCVD event during the in-hospital stay. The number of patients with ASCVD was significantly greater in those with IBD than in controls (10.1 % vs. 5.5 %, $p = 0.001$), and the IHD prevalence was higher in patients with IBD than in controls (7.9 % vs. 3.6 %, $p < 0.001$) (Supplementary Table 3). The ASCVD was more predominant in males and older patients (Table 3). Similarly, most of the well-known risk factors for ASCVD were related to an arterial event. Interestingly, IBD diagnosis was significantly associated with ASCVD occurrence. IBD diagnosis, male sex, hypertension, diabetes mellitus, and the Charlson Index demonstrated an independent association with ASCVD when entered into a logistic regression model; in particular, the adjusted OR for an event occurrence was doubled compared to controls (OR = 2.21 [1.47–3.31]) in patients with IBD (Table 3). The number of ASCVD events was slightly higher for the UC group when analyzing patients with CD and UC separately. However, the statistical significance was reached only for cerebrovascular events (0.5 % in CD vs. 2.8 % in UC, $p = 0.012$) (Fig. 2).

3.5. Analysis of VTE after PS

Forty-eight (2.9 %) patients in the PS cohorts experienced at least one venous thromboembolic event during their in-hospital stay. The VTE prevalence was similar between IBD and controls (Supplementary Table 3). In univariate and multivariate analyses, age was the only factor significantly associated with these events (Table 4). Venous thromboembolic events were more frequent in the UC group when the patients with CD and UC were analyzed separately; most of the observed difference was due to a significantly higher number of PE in patients with UC compared to CD (2.3 % vs. 0.5 %, $p = 0.012$) (Fig. 2).

4. Discussion

The present study revealed that IBD “per se” represents a significant risk factor for ASCVD, independently of the traditional risk factors. We observed a higher incidence of ASCVD in patients with IBD compared to those with AGC; this control group was explicitly selected to differentiate the effect of chronic and frequently long-lasting inflammation from that of acute intestinal inflammation. Thus, our data confirmed the inflammatory burden, which characterizes the IBD course, as a further risk factor for ASCVD [27]. The crucial inflammatory mediators, CRP and interleukin-6, which were elevated during IBD flares [28,29], have been associated with an increased risk of coronary artery disease and mesenteric ischemia [30,31]. Furthermore, an increased CD40 L expression by platelets contributes to the pro-inflammatory response in IBD [32,33], whereas the inflammatory events caused by CD40L-CD40 interaction caused unstable plaque in atherosclerosis, resulting in thrombosis [34]. IBD, particularly in young adults, is associated with increased carotid intima-media thickness compared to controls, suggesting early atherosclerosis as a finding to be considered in this population [35,36]. Additionally, arterial stiffness measured using aortic pulse wave velocity, which is another surrogate marker for cardiovascular disease, increases in patients with active IBD, whereas those in remission or treated with anti-TNF-α agents experienced aortic destiffening during follow-up [37,38]. Finally, gut-derived endotoxemia due to bacterial lipopolysaccharides (LPS) translocation from the “leaky” gut to the bloodstream and the bacterial metabolite trimethylamine-N-oxide (TMAO) has been determined as crucial molecules involved in gut dysbiosis-related thrombosis [39]. Data from the United States National Health Interview Survey recently confirmed the results of our study [40]. Among participants with IBD, the age-adjusted prevalence of ASCVD was 12.0 % compared to 6.9 % in controls ($p < 0.001$). Multivariable regression analyses revealed that IBD was associated with

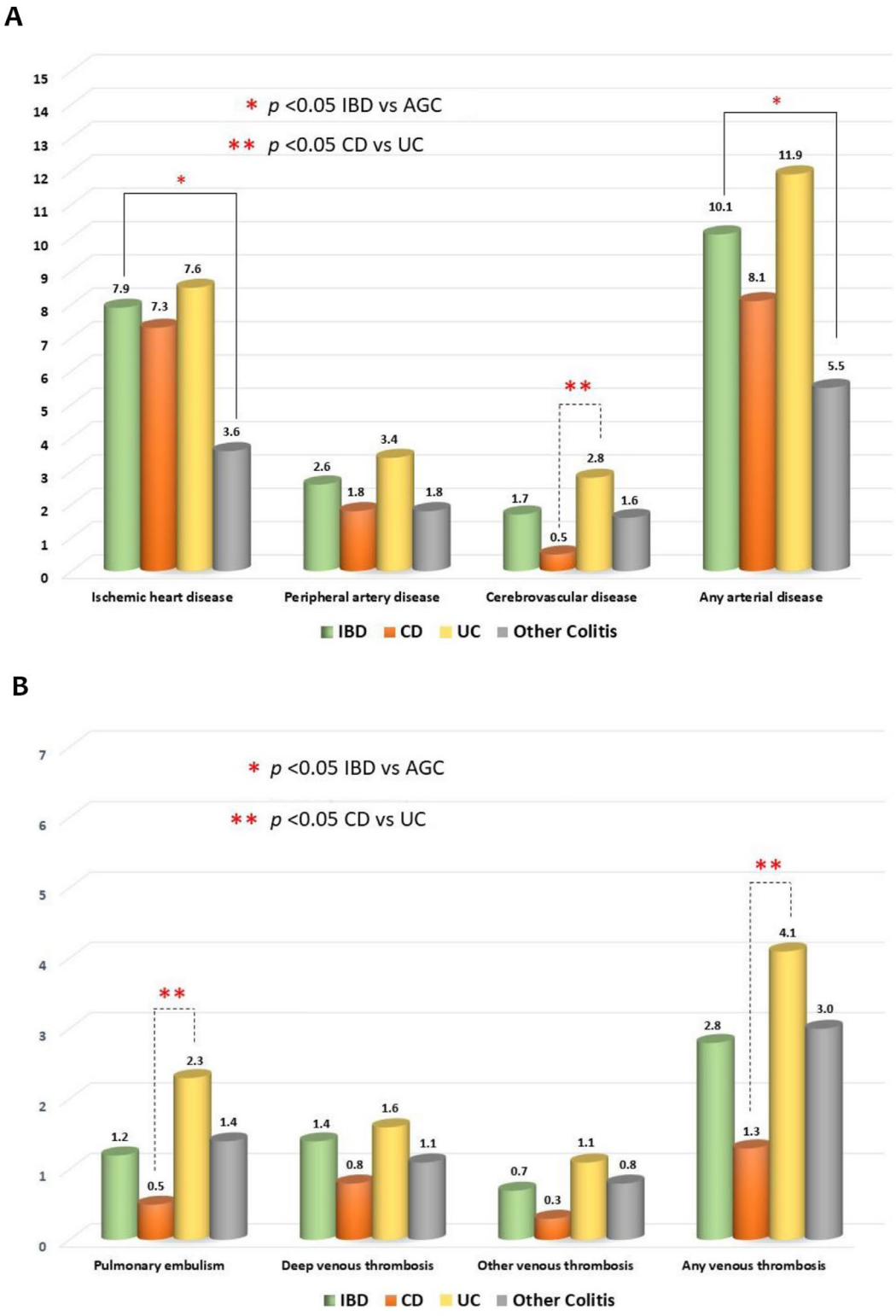

Fig. 2. A. Prevalence of overall atherosclerotic cardiovascular disease (ASCVD) events and separate ischemic heart disease, peripheral artery disease, and cerebrovascular disease in patients with inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) subpopulations, compared to patients with acute infective gastroenteritis and colitis AGC. B. Prevalence of overall venous thromboembolism (VTE) and separate pulmonary embolism, deep vein thrombosis, and other-site vein thrombosis in patients with IBD, including CD and UC subpopulations compared to those with AGC.

increased odds of developing ASCVD, even after adjusting for demographics and traditional risk factors (OR: 1.58, 95 % CI: 1.17–2.13), with the strongest association in the younger strata [40].

Conversely, we did not find an increased incidence of VTE in our IBD cohort compared to controls. Age was the only variable independently associated with VTE. A possible explanation of this finding is that VTE prophylaxis with low-molecular-weight heparin (LMWH) or fondaparinux was extensively used in hospitalized IBD patients, as it is considered the standard of care for such patients and, consequently, this therapeutical approach could have

Table 4
Univariate and multivariate (logistic regression model) analyses of factors associated with venous thromboembolism (VTE) (any), performed on the propensity score-matched study cohorts.

Variable	Absence of VTE $n = 1614$	Any VTE $n = 48$	Univariate analysis *p-value*	Multivariate analysis Odds Ratio [95 % confidence interval]	Multivariate analysis *p*-value
IBD	808 (50.1 %)	23 (47.9 %)	0.770	0.94 [0.53–1.66]	0.821
Age[§]	59 [46–72]	66 [53–74]	**0.006**	1.03 [1.01–1.04]	**0.004**
Sex (Male)	835 (51.7 %)	24 (50.0 %)	0.813		
Cardiovascular risk factors					
Hypertension	342 (21.2 %)	15 (31.3 %)	0.094		
CKD	152 (9.4 %)	3 (6.3 %)	0.617		
Diabetes	168 (10.4 %)	2 (4.2 %)	0.160		
Dyslipidemia	69 (4.3 %)	0	0.262		
Heavy smoker	168 (10.4 %)	6 (12.5 %)	0.640		
Severe obesity	13 (0.8 %)	0	1.000		
Other comorbidities					
Charlson Index[§]	2 [1–4]	3 [2–5]	1.000		
History of CAD[*]	139 (8.6 %)	2 (4.2 %)	0.428		
Congestive heart failure	75 (4.6 %)	1 (2.1 %)	0.722		
Cerebrovascular disease	53 (3.3 %)	0	0.401		
History of atrial fibrillation	86 (5.3 %)	1 (2.1 %)	0.513		
Dementia	31 (1.9 %)	2 (4.2 %)	0.246		
COPD	86 (5.3 %)	0	0.173		
Therapy					
Cardioaspirin	202 (12.5 %)	6 (12.5 %)	0.997		
Steroid	85 (5.3 %)	1 (2.1 %)	0.327		
Biological therapy	58 (3.6 %)	2 (4.2 %)	0.691		
Statin	55 (3.4 %)	0	0.404		
Estroprogestinic therapy	4 (0.2 %)	0	1.000		
Oral anticoagulation	87 (5.4 %)	3 (6.3 %)	0.742		

§ Values are expressed as Median [Interquartile range];.

* CAD: coronary artery disease; CKD: Chronic kidney disease; COPD: chronic obstructive pulmonary disease; IBD: inflammatory bowel disease. IBD diagnosis was forced into the model. The Logistic model had an overall accuracy of 96.5 %, (Model Chi: 36.59; log-likelihood^{-2}: 741.3; Hosmer & Lemeshow test Chi^2: 7.38; $p = 0.496$; constant was included in the model).

significantly decreased the incidence of VTE in IBD patients [18–20]. However, due to the retrospective nature of the study, we have only partial data on the prevalence of antithrombotic prophylaxis during hospitalization, lacking reliability for statistical analysis. Additionally, the highest relative risk of VTE in IBD has been reported in younger patients [8]; thus, our IBD population's relatively high mean age (56 years) could have hindered a significant difference. Therefore, the results of this study emphasize the crucial role of the tight control of intestinal inflammation since it ultimately prevents potentially devastating atherosclerotic cardiovascular events. Recently, several guidelines on cardiovascular disease primary prevention have included "chronic inflammatory conditions" or "chronic immune-mediated inflammatory disorders" as risk-enhancing or risk modifier factors; thereby, patients with IBD need to be considered as a population with peculiar overall risk for ASCVD, where early screening and risk mitigation strategies are required [41,42].

Patients with IBD should be considered as a distinctive population for the ASCVD risk, which was reported by a recent European cross-sectional study that included 252 consecutive patients with IBD aged ≥45 years and 829 matched controls [43]. History of ASCVD and CVD risk factors were investigated: the Systematic Coronary Risk Evaluation (SCORE2) algorithm was used to estimate 10-year CVD risk in IBD. Patients with IBD experienced ASCVD events more frequently compared with controls (OR: 2.01, 95 % CI: 1.23–3.27], specifically heart failure and coronary heart disease [43]. However, the mean 10-year CVD risk was 4.0 % (standard deviation [SD] ±2.6) in IBD vs. 6.0 % (SD ±1.6) in controls. This finding indicates that, despite the increased CVD risk observed in patients with IBD, the SCORE2 algorithm may underestimate this CVD risk due to differing CVD risk profiles compared with the general population [43]. Thus, a corrective factor applied to the available risk score algorithms or different tools to evaluate the ASCVD risk, such as coronary artery calcium scoring measured at coronary-CT scan [44], should be experimented within patients with IBD to better predict the probability of future ASCVD. Another topic of interest is the association of the IBD therapeutic armamentarium with the risk of VTE and ASCVD [45,46]. The available evidence indicates that steroids increase this risk for both arterial and venous vascular disease [47–49]. Concurrently, anti-TNF-α agents exhibited a protective effect on VTE occurrence compared to steroids [48,49] or are comparable to placebo in randomized controlled studies [50]. JAK-inhibitors deserve a separate discussion since evidence shown an increased risk of major adverse cardiovascular events in patients affected by rheumatoid arthritis who are ≥50 years of age and have at least one additional cardiovascular risk factor treated with tofacitinib compared to those treated with a TNF-α inhibitor [51]. However, these data observed in a cohort of patients at increased ASCVD risk were not replicated in patients with IBD or in therapy with other JAK-inhibitors [52]. Our study revealed no significant effect of steroids or biological agents on the risk of VTE or ASCVD. Meanwhile, no data are available regarding JAK inhibitors, which were later introduced in clinical practice.

This study has some limitations that must be considered when interpreting the results. First, our analysis did not include some risk factors involved in ASCVD and VTE, including the family history of vascular events or characteristics associated with IBD activity, such as disease duration, age at diagnosis, or disease extension. Second, as with all studies using administrative data, this study exhibited a risk of misclassifying either exposure or outcomes. However, we used validated algorithms and codes to determine patients with IBD, classify IBD subtypes, and identify VTE and ASCVD. Finally, as previously highlighted, information regarding venous thromboprophylaxis during hospitalization is incomplete, as we only have data for patients taking anticoagulants at admission. We assume most patients with IBD received LMWH or fonda-

parinux during hospitalization, aiming at VTE prevention since this therapeutic procedure is the standard of care, as recommended by international guidelines. However, prospective studies are needed to evaluate the actual prevalence of venous thromboprophylaxis in inpatients with IBD and their clinical efficacy. Conversely, the present study has several strengths. First, we reported an exhaustive set of data on vascular arterial and venous thrombotic events occurring in a large cohort of patients with IBD compared to those with an acute infective intestinal disease, which enabled us to evaluate the significant role of chronic inflammation in the pathogenesis, particularly of ASCVD. Thus, these results suggest that early and aggressive control of IBD activity, with baseline risk assessment for ASCVD and lifestyle modifications, may improve cardiovascular health and help reduce the risk of significant vascular events.

Data availability

The data supporting this study's findings are available on request from the corresponding author [LL].

Author contributions

Conceptualization: Alfredo Papa, Lucrezia Laterza, Valerio Papa, Loris Riccardo Lopetuso, Marcello Covino

Methodology: Alfredo Papa, Marcello Covino

Writing - original draft, review & editing: Alfredo Papa, Lucrezia Laterza, Marcello Covino

Investigation, data curation: Alfredo Papa, Lucrezia Laterza, Valerio Papa, Loris Riccardo Lopetuso, Stefania Colantuono, Gaetano Coppola, Benedetta Simeoni, Franco Scaldaferri, Francesco Franceschi, Antonio Gasbarrini, Marcello Covino

Formal analysis: Marcello Covino

Conflict of Interest

All authors disclose no potential conflicts (financial, professional, or personal) that are relevant to the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.01.195.

References

[1] Dolinger M, Torres J, Vermeire S. Crohn's disease. Lancet 2024;403:1177–91.
[2] Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. Lancet 2023;402:571–84.
[3] Bernstein CN, Blanchard JF, Houston DS, et al. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost 2001;85:430–4.
[4] Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. Clin Gastroenterol Hepatol 2008;6:41–5.
[5] Cohen JB, Comer DM, Yabes JG, et al. Inflammatory bowel disease and thrombosis: a national inpatient sample study. TH Open 2020;4 e51-e8.
[6] Feng W, Chen G, Cai D, et al. Inflammatory bowel disease and risk of ischemic heart disease: an updated meta-analysis of cohort studies. J Am Heart Assoc 2017;6.
[7] Fumery M, Xiaocang C, Dauchet L, et al. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. J Crohns Colitis 2014;8:469–79.
[8] Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet 2010;375:657–63.
[9] Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut 2011;60:937–43.
[10] Nylund CM, Goudie A, Garza JM, et al. Venous thrombotic events in hospitalized children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2013;56:485–91.
[11] Panhwar MS, Mansoor E, Al-Kindi SG, et al. Risk of myocardial infarction in inflammatory bowel disease: a population-based national study. Inflamm Bowel Dis 2019;25:1080–7.
[12] Rungoe C, Basit S, Ranthe MF, et al. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. Gut 2013;62:689–94.
[13] Singh S, Kullo IJ, Pardi DS, et al. Epidemiology, risk factors and management of cardiovascular diseases in IBD. Nat Rev Gastroenterol Hepatol 2015;12:26–35.
[14] Sun HH, Tian F. Inflammatory bowel disease and cardiovascular disease incidence and mortality: a meta-analysis. Eur J Prev Cardiol 2018;25:1623–31.
[15] Papay P, Miehsler W, Tilg H, et al. Clinical presentation of venous thromboembolism in inflammatory bowel disease. J Crohns Colitis 2013;7:723–9.
[16] Naik Vietti N, Vietti Violi N, Schoepfer AM, et al. Prevalence and clinical importance of mesenteric venous thrombosis in the Swiss Inflammatory Bowel Disease cohort. AJR Am J Roentgenol 2014;203:62–9.
[17] Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. Am J Gastroenterol 2008;103:2272–80.
[18] Papa A, Papa V, Marzo M, et al. Prevention and treatment of venous thromboembolism in patients with IBD: a trail still climbing. Inflamm Bowel Dis 2015;21:1204–13.
[19] Olivera PA, Zuily S, Kotze PG, et al. International consensus on the prevention of venous and arterial thrombotic events in patients with inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2021;18:857–73.
[20] Harbord M, Annese V, Vavricka SR, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis 2016;10:239–54.
[21] Keller JJ, Wang J, Hwang YL, et al. Increased risk of stroke among patients with Crohn's disease: a population-based matched cohort study. Int J Colorectal Dis 2015;30:645–53.
[22] Lin TY, Chen YG, Lin CL, et al. Inflammatory bowel disease increases the risk of peripheral arterial disease: a nationwide cohort study. Medicine (Baltimore) 2015;94:e2381.
[23] Ghoneim S, Shah A, Dhorepatil A, et al. The risk of cerebrovascular accidents in inflammatory bowel disease in the United States: a population-based national study. Clin Exp Gastroenterol 2020;13:123–9.
[24] Kirchgesner J, Beaugerie L, Carrat F, et al. Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study. Gut 2018;67:1261–8.
[25] Miehsler W, Reinisch W, Valic E, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? Gut 2004;53:542–8.
[26] Danese S, Papa A, Saibeni S, et al. Inflammation and coagulation in inflammatory bowel disease: the clot thickens. Am J Gastroenterol 2007;102:174–86.
[27] Libby P, Loscalzo J, Ridker PM, et al. Inflammation, immunity, and infection in atherothrombosis: JACC Review topic of the week. J Am Coll Cardiol 2018;72:2071–81.
[28] Cainzos-Achirica M, Glassner K, Zawahir HS, et al. Inflammatory bowel disease and atherosclerotic cardiovascular disease: JACC Review topic of the week. J Am Coll Cardiol 2020;76:2895–905.
[29] Henriksen M, Jahnsen J, Lygren I, et al. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. Gut 2008;57:1518–23.
[30] Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. Int J Cardiol 2013;168:5126–34.
[31] Toptas M, Akkoc I, Savas Y, et al. Novel hematologic inflammatory parameters to predict acute mesenteric ischemia. Blood Coagul Fibrinolysis 2016;27:127–30.
[32] Danese S, Katz JA, Saibeni S, et al. Activated platelets are the source of elevated levels of soluble CD40 ligand in the circulation of inflammatory bowel disease patients. Gut 2003;52:1435–41.
[33] Danese S, de la Motte C, Sturm A, et al. Platelets trigger a CD40-dependent inflammatory response in the microvasculature of inflammatory bowel disease patients. Gastroenterology 2003;124:1249–64.
[34] Aukrust P, Muller F, Ueland T, et al. Enhanced levels of soluble and membrane-bound CD40 ligand in patients with unstable angina. Possible reflection of T lymphocyte and platelet involvement in the pathogenesis of acute coronary syndromes. Circulation 1999;100:614–20.
[35] Papa A, Santoliquido A, Danese S, et al. Increased carotid intima-media thickness in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2005;22:839–46.
[36] Papa A, Danese S, Urgesi R, et al. Early atherosclerosis in patients with inflammatory bowel disease. Eur Rev Med Pharmacol Sci 2006;10:7–11.
[37] Zanoli L, Ozturk K, Cappello M, et al. Inflammation and aortic pulse wave velocity: a multicenter longitudinal study in patients with inflammatory bowel disease. J Am Heart Assoc 2019;8:e010942.
[38] Zanoli L, Mikhailidis DP, Bruno RM, et al. Aortic stiffening is an extraintestinal manifestation of inflammatory bowel disease: review of the literature and expert panel statement. Angiology 2020;71:689–97.
[39] Papa A, Santini P, De Lucia SS, et al. Gut dysbiosis-related thrombosis in inflammatory bowel disease: potential disease mechanisms and emerging therapeutic strategies. Thromb Res 2023;232:77–88.
[40] Nasir K, Acquah I, Dey AK, et al. Inflammatory bowel disease and atherosclerotic cardiovascular disease in U.S. adults-A population-level analysis in the national health interview survey. Am J Prev Cardiol 2022;9:100316.

[41] Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the primary prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical Practice Guidelines. Circulation 2019;140:e596–646.
[42] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111–88.
[43] Sleutjes JAM, van der Woude CJ, Verploegh PJP, et al. Cardiovascular risk profiles in patients with inflammatory bowel disease differ from matched controls from the general population. Eur J Prev Cardiol 2023;30:1615–22.
[44] Naami R, Tashtish N, Neeland IJ, et al. Coronary artery calcium scoring for cardiovascular risk assessment in patients with inflammatory bowel disease. Am Heart J 2023;266:120–7.
[45] Papa A, Tursi A, Danese S, et al. Venous thromboembolism in patients with inflammatory bowel disease: the role of pharmacological therapy and surgery. J Clin Med 2020;9.
[46] Sinh P, Cross R. Cardiovascular risk assessment and impact of medications on Cardiovascular disease in inflammatory bowel disease. Inflamm Bowel Dis 2021;27:1107–15.
[47] Zakroysky P, Thai WE, Deano RC, et al. Steroid exposure, acute coronary syndrome, and inflammatory bowel disease: insights into the inflammatory milieu. Am J Med 2015;128:303–11.
[48] Sarlos P, Szemes K, Hegyi P, et al. Steroid but not biological therapy elevates the risk of venous thromboembolic events in inflammatory bowel disease: a meta-analysis. J Crohns Colitis 2018;12:489–98.
[49] Higgins PD, Skup M, Mulani PM, et al. Increased risk of venous thromboembolic events with corticosteroid vs biologic therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol 2015;13:316–21.
[50] Ytterberg SR, Bhatt DL, Connell CA. Cardiovascular and cancer risk with Tofacitinib in rheumatoid arthritis. Reply New England J Med 2022;386:1768.
[51] Shehab M, Alrashed F, Alkazemi A, et al. Impact of biologic therapies and small molecules on the risk of major adverse cardiovascular events in patients with inflammatory bowel diseases: systematic review and meta-analysis of randomized controlled trials. Expert Rev Gastroenterol Hepatol 2023;17:469–77.
[52] Olivera PA, Lasa JS, Peretto G, et al. Review article: risk of cardiovascular events in patients with inflammatory bowel disease receiving small molecule drugs. Aliment Pharmacol Ther 2023;57:1231–48.