# The role of coexisting cardiovascular disease on disease severity in patients with inflammatory bowel disease

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**Objectives:** Chronic inflammation has been implicated in the pathogenesis of atherosclerosis and cardiovascular disease. Data linking the severity of inflammatory bowel disease to coexisting cardiovascular disease are scarce. The aim of the present study was to investigate whether inflammatory bowel disease patients with coexistent cardiovascular disease have more severe disease.

**Methods:** We included 103 inflammatory bowel disease patients with coexisting cardiovascular disease compared to 206 age- and sex-matched inflammatory bowel disease patients without cardiovascular disease derived from three referral inflammatory bowel disease Centers. Traditional cardiovascular disease factors and parameters of inflammatory bowel disease severity were compared between the two groups.

**Results:** Cardiovascular disease was diagnosed after the inflammatory bowel disease diagnosis in 56.6% of cases. No significant difference was found in the prevalence of surrogate markers of severity (inflammatory bowel disease-related surgeries, hospitalizations, biologics or immunosuppressants' use, and persistent CRP elevation) between inflammatory bowel disease patients with and without cardiovascular disease. There was no difference between cardiovascular disease patients diagnosed before and after inflammatory bowel disease onset. All traditional risk factors (hypertension, dyslipidemia, smoking, obesity, diabetes mellitus) were significantly more common in cardiovascular disease patients. Cardiovascular disease patients had a trend for lower rates of multiple hospitalizations (16.5% vs. 24.3%, $P = 0.05$) and inflammatory bowel disease-related surgeries ($P = 0.09$).

**Conclusion:** The inflammatory burden possibly plays a less important role in the development of cardiovascular disease in inflammatory bowel disease patients but future larger prospective studies are needed. Eur J Gastroenterol Hepatol 2020: 581–587





## Introduction

The role of chronic inflammation as a triggering factor for atherosclerotic cardiovascular disease (CVD) in systemic autoimmune diseases, such as rheumatoid arthritis and lupus erythematosus, is well established [1,2]. Inflammatory bowel diseases (IBD) consisting of Crohn's disease (CD) and ulcerative colitis (UC) are characterized by chronic relapsing-remitting or continuous course leading to chronic intestinal and systemic inflammation. Although subclinical markers of CVD, including inflammatory mediators like CRP [3], or endothelial dysfunction indices, such as carotid intima-media thickness [4] and aortic pulse wave velocity [5] are increased among IBD patients, a strong link between IBD and cardiovascular risk has not been proven so far. The emerging role of gut microbiota and dysbiosis in both IBD [6] and CVD [7] raises even more questions on the possible association between these entities.

Cohort studies and a recent meta-analysis have shown that factors such as age, sex, and clinical characteristics such as disease extent and disease activity may be implicated in the development of CVD [8–13], but robust data are lacking.

In contrast to disease activity which reflects patient symptoms at a certain moment in time disease severity reflects the overall burden of disease since the diagnosis of IBD, including the impact of disease on patient's symptoms and daily activities, fatigue, social, and professional life, and also use of steroids or biologic agents, intestinal resections, and hospitalizations [14]. Therefore, patients with more severe disease are possibly at an increased risk for cardiovascular complications.

Because there are no published data on the severity of IBD in patients with established concomitant CVD, we hypothesized that IBD patients with coexistence of CVD could have more severe disease compared to patients

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without CVD. Thus, the aim of the present study was to investigate any possible effect of the inflammatory burden related to IBD on the cardiovascular system, by comparing disease severity parameters among IBD patients with or without a history CVD.

## Material and methods

### Study population

This is a multicenter, retrospective case-control study based on prospectively acquired data in IBD patients who were regularly followed at three Greek IBD referral centers, that is, the University Hospital of Heraklion, Crete, the Venizelion General Hospital of Heraklion, and the General Hospital of Athens 'Evangelismos-Ophthalmiatreion Athinon-Polykliniki'. The IBD study population comprised of two patient groups: patients with established IBD diagnosis and concurrent CVD (patient group) and age- and sex-matched IBD patients without CVD (control group).

All study participants after signing an informed consent were re-interviewed between 1 January 2017 and 1 September 2018 by a single gastroenterologist in each center. The focus of the interview was on parameters of disease severity of IBD and classical risk factors of CVD. Patients with malignant disease in the past 5 years (except for basal-cell skin carcinoma) and other autoimmune diseases were excluded.

The protocol of the study was approved by the institutional review board of the three participating IBD centers.

## Data collection

Disease duration, disease-related characteristics, CD, and UC phenotypes according to Montreal classification, history of IBD-related surgery and prior and current IBD treatments were reviewed longitudinally since diagnosis. A more detailed history was recorded regarding lifestyle and cardiovascular risk factors, such as smoking (history and current status), BMI, hypertension according to the European Society of Cardiology (ESC)/European Society of Hypertension guidelines [15] or by being treated with antihypertensive drugs, diabetes mellitus defined by established criteria [16] or by being treated with hypoglycemic drugs, and hyperlipidemia according to ESC/European Atherosclerosis society criteria [17] or being treated with lipid-lowering drugs. A history of CVD was also recorded, including any lifetime history of myocardial infarction (MI), angina, asymptomatic chronic coronary syndrome, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease (PAD), and heart failure (HF) of non-ischemic etiology. Diagnosis of CVD was based on cardiologist's or neurologist's diagnosis or hospitalization for an acute CVD event using ICD-10 codes. Additional information concerning date of cardiovascular event before or after IBD diagnosis, family history of premature CVD, history of venous thromboembolic episode and other heart conditions (i.e. arrhythmias, valvular heart disease) were available.

Data on IBD treatment were collected, including ever used 5-aminosalicylates, systemic corticosteroids, immunosuppressives (mercaptopurine, azathioprine, methotrexate) or biologics (i.e. infliximab, adalimumab, certolizumab pegol, golimumab, vedolizumab, or ustekinumab). Among non-IBD medications, ever use of antiplatelets, direct oral anticoagulants or low-molecular-weight heparin, antihypertensives, and statins were recorded. IBD severity was evaluated by the use of surrogate markers, such as (1) having a history of IBD related surgery, (2) ever use of systemic corticosteroids, biologics, immunomodulators, and (3) increased number (>3) of hospitalizations for IBD flares. The presence of at least one or more of a-c criteria was considered as severe disease and the absence of all of them as mild disease.

IBD clinical activity at the time of interview was evaluated according to Harvey Bradshaw Index [18] for CD patients or the Simple Colitis Activity Index [19] for UC patients. Quality of life during the last 2 weeks was calculated using the Short Quality of Life in IBD Questionnaire [20] with a minimum score of 10 and a maximum of 70. In cases that CVD was diagnosed after IBD diagnosis endoscopic activity, if an endoscopy was done in 3 months before or after CVD diagnosis, was evaluated using a Mayo endoscopic subscore ≥2 for UC or the presence of large ulcers in endoscopy for CD.

Among laboratory parameters serum fasting glucose (Glu), total cholesterol (Chol), triglycerides, high-density lipoprotein, CRP, were measured during the interview visit. Successive CRP values were recorded and patients were classified as demonstrating persistent (for more than 1 year), transient (for only 1 year) or no CRP elevation during the last 3 years. Especially we searched for CRP values during the period that preceded the CV event in the group of IBD patients with a CV event following IBD diagnosis.

### Statistical analysis

Comparisons between groups were made by Student's *t*-test for continuous variables and Fisher's exact probability test or the $\chi^2$ test for the analysis of categorical variables. All variables found to be significant in the univariate analyses for IBD patients in correlation with variables related to IBD severity and sex, age at diagnosis, IBD diagnosis were entered into the multivariate analyses using a forward step-wise logistic regression model (0.05 for entry and 0.10 for removal probability). A *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed, using the SPSS software package (version 24; SPSS Inc., Chicago, Illinois, USA).

## Results

Overall, 103 IBD patients with concurrent established diagnosis of CVD were included in the study group and 206 matched (2:1) IBD patients in the control group. Patient demographics, lifestyle factors and disease characteristics are shown in Table 1. Among the 103 IBD patients with CVD, history of IHD (ischemic heart disease) including MI, angina or asymptomatic chronic coronary disease was reported in 63 (61.2%) patients, cerebrovascular disease (ischemic stroke, hemorrhagic stroke, or transient ischemic attack) in 29 (28.2%), PAD in three (2.9%), and HF in 17 (16.5%) IBD patients. Combination of more than one CVD was found in four IBD patients. The

**Table 1.** Demographics and clinical characteristics of the inflammatory bowel disease study population

| | IBD + CVD (N = 103) | IBD without CVD (N = 206) | *P* value | OR (95% CI) |
|---|---|---|---|---|
| Mean age at diagnosis (±SD) | 53.04 ± 14.85 | 49.92 ± 14.26 | 0.075 | 3.12 (0.31–6.55) |
| Mean age at study entry (±SD) | 65.71 ± 10.67 | 64 ± 10.38 | 0.176 | 1.71 (0.77–4.20) |
| Duration of IBD (years) | 13.11 ± 10.76 | 13.96 ± 9.85 | 0.488 | 1.22 (1.56–3.26) |
| Sex | | | 1 | |
| Female, N (%) | 24 (23.3) | 48 (23.3) | | |
| Mean BMI (kg/m$^2$) | 31.62 ± 27.41 | 29.17 ± 25.44 | 0.47 | 3.38 (4.22–9.11) |
| BMI > 30 | 44 (34) | 35 (21.4) | <0.001 | |
| Smoking history (N = 306) | | | 0.08 | |
| Ever smokers | 86 (83.5) | 154 (74.8) | | |
| Never smokers | 15 (14.6) | 51 (24.7) | | |
| Smoking status (N = 306) | | | 0.13 | |
| Active smoker | 23 (22.3) | 39 (18.9) | | |
| Ex-smoker | 63 (61.2) | 125 (55.8) | | |
| Non-smoker | 15 (14.6) | 51 (24.7) | | |
| Diagnosis, N (%) | | | 0.72 | |
| UC | 59 (57.3) | 113 (54.9) | | |
| CD | 44 (42.7) | 93 (45.1) | | |
| CD location, N (%) | | | 0.68 | |
| L1 | 20 (45.5) | 40 (43) | | |
| L2 | 10 (22.7) | 15 (16.1) | | |
| L3 | 14 (31.8) | 38 (40.9) | | |
| CD behavior, N % | | | 0.79 | |
| B1 | 30 (68.2) | 63 (67.7) | | |
| B2 | 10 (22.8) | 17 (18.3) | | |
| B3 | 4 (9) | 13 (14) | | |
| Perianal CD | 6 (5.8) | 16 (7.8) | 0.81 | |
| UC extent, N (%) | | | 0.66 | |
| E1 | 8 (13.6) | 16 (14.2) | | |
| E2 | 33 (55.9) | 53 (46.9) | | |
| E3 | 18 (30.5) | 44 (38.9) | | |

B1, non-structuring – non-penetrating; B2, structuring; B3, penetrating; CD, Crohn's disease; CI, confidence interval; CVD, cardiovascular disease; E1, proctitis; E2, left-sided colitis; E3, extensive colitis; IBD, inflammatory bowel disease; L1, ileal location; L2, colonic location; L3, ileocolonic location; OR, odds ratio; UC, ulcerative colitis.

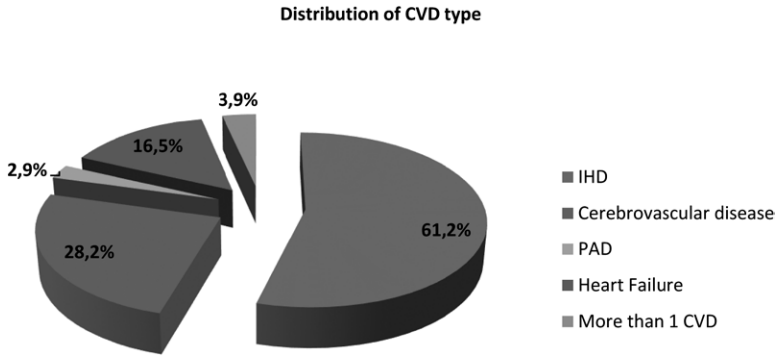


**Fig. 1.** Distribution of cardiovascular disease type among 103 IBD patients. CVD, cardiovascular disease; IBD, inflammatory bowel disease; IHD, ischemic heart disease; PAD, peripheral artery disease.

distribution of the CVD type in IBD patients is depicted in Fig. 1. The diagnosis of CVD followed the diagnosis of IBD in 56.6% of cases. The mean time to a cardiovascular event after IBD diagnosis was 11.2 ± 9.7 years. In this group of IBD patients, endoscopic data in 3 months period before or after CVD diagnosis were available only in 19/58 (32.76%) of IBD patients diagnosed with CVD after IBD diagnosis. Almost half of them 10/19 had endoscopic active disease. No difference in the prevalence of severe disease was found irrespective whether the diagnosis of IBD preceded CVD diagnosis or not (64.1% vs. 72.5%, $P = 0.692$).

In the univariate analysis, patients with IBD and concurrent CVD were more often obese (BMI > 30, $P < 0.001$) and ex- or current smokers ($P = 0.08$) than patients in the control group. Regarding parameters related to disease severity, no statistically significant differences between cases and controls were observed for exposure to immunosuppressants, anti-TNFs and systemic corticosteroids as well as in the rates of IBD related surgery. Interestingly, patients with CVD had a trend of lower rates of multiple (>3) hospitalizations for an IBD flare than non-CVD patients (16.5% vs. 24.3%, $P = 0.05$). As expected, diabetes, dyslipidemia, arterial hypertension, use of antiplatelets or antithrombotics were significantly more often reported in patients with CVD (Table 2). Mean value of glucose was greater in patients with CVD [$P = 0.007$, odds ratio (OR) 12.62, 95% confidence interval (CI): 3.54–21.7], in contrast to total cholesterol that was found greater in IBD patients without any history of CVD ($P = 0.035$, OR 5.1, 95% CI: 0.79–20.9) than in CVD patients (Table 3), probably explained by the most frequent use of statins in the latter group. CRP in terms of disease activity was available in 23/58 (39.66%) of IBD patients with a CV

**Table 2.** Comorbidities, healthcare utilization and co-administered medications among the study population

| | IBD + CVD (N = 103) | IBD without CVD (N = 206) | *P* value | OR (95% CI) |
|---|---|---|---|---|
| Hypertension | | | <0.001 | 3.89 (2.34–6.46) |
| Yes, N (%) | 72 (69.9) | 77 (37.4) | | |
| No, N (%) | 32 (30.1) | 129 (62.6) | | |
| Diabetes mellitus | | | <0.001 | 0.35 (0.20–0.62) |
| Yes, N (%) | 33 (32) | 29 (14.1) | | |
| No, N (%) | 70 (68) | 177 (85.9) | | |
| Statins/dyslipidemia | | | <0.001 | |
| Yes, N (%) | 62 (60.2) | 43 (20.9) | | 0.17 (0.10–0.93) |
| No, N (%) | 41 (39.8) | 163 (79.1) | | |
| Antiplatelets | | | <0.001 | 17.64 (6.78–45.9) |
| Yes, N (%) | 76 (73.8) | 4 (1.9) | | |
| No, N (%) | 27 (26.2) | 202 (98.1) | | |
| Antithrombotic agents | | | <0.001 | 5.6 (2.46–12.76) |
| Yes, N (%) | 21 (20.4) | 9 (4.4) | | |
| No, N (%) | 82 (79.6) | 197 (95.6) | | |
| IBD related surgery | 11 (10.7) | 24 (11.7) | 0.481 | |
| Hospitalizations for flare, N (%) | 59 (57.3) | 122 (59.2) | 0.447 | |
| Hospitalizations for flare (mean ± SD) | 1.63 ± 0.3 | 1.83 ± 0.2 | 0.56 | 0.35(0.478–0.88) |
| More than 3 hospitalizations for flare, N (%) | 17 (16.5) | 50 (24.3) | 0.045 | |
| Severe disease, N (%) | 70 (68) | 143 (69.4) | 0.896 | |
| Biologic agents, N (%) | 27 (26.2) | 70 (34) | 0.110 | |
| Lifetime steroids, N (%) | 60 (58.3) | 134 (65) | 0.175 | |
| Immunomodulators, N (%) | 36 (35) | 80 (38.8) | 0.296 | |
| 5-ASA, N (%) | 90 (87.4) | 181 (87.9) | 1 | |

5-ASA, 5-aminosalicylate; CI, confidence interval; CVD, cardiovascular disease; IBD, inflammatory bowel disease; OR, odds ratio.

**Table 3.** Laboratory data, clinical activity and quality of life indices for both groups of inflammatory bowel disease patients

| | IBD + CVD (N = 103) | IBD without CVD (N = 206) | *P* value | OR (95% CI) |
|---|---|---|---|---|
| Mean PLT (±SD) (K/μl) | 244 ± 64 | 253 ± 68 | 0.27 | 8.31 (7.21–25.49) |
| Mean GLU (±SD) (mg/dl) | 119 ± 50.77 | 106.4 ± 27.34 | 0.007 | 12.62 (3.54–21.7) |
| Mean CHOL (±SD) (mg/dl) | 171.3 ± 35.4 | 182.1 ± 41.9 | 0.04 | 5.1 (0.79–20.9) |
| Mean HDL (±SD) (mg/dl) | 48.3 ± 14 | 55.9 ± 42 | 0.13 | 4.67 (2.17–16.22) |
| Mean TRG (±SD) (mg/dl) | 142.4 ± 78.9 | 130.8 ± 92.1 | 0.30 | 11.35 (10.67–34.03) |
| Long term CRP (N = 244) | | | 0.23 | |
| Persistent elevation | 23 (22.3%) | 47 (22.8%) | | |
| Transient elevation | 21 (20.4%) | 26 (12.6%) | | |
| No CRP elevation | 36 (35%) | 91 (44.2%) | | |
| Mean HBI (±SD) | 3 ± 2 | 3 ± 3 | 0.91 | 0.05 (0.87–0.97) |
| Mean SCAI (±SD) | 2 ± 1 | 3 ± 1 | 0.36 | 0.89 (0.93–2.59) |
| Mean SIBDQ (±SD) | 56 ± 10 | 55 ± 12 | 0.89 | 1.63 (3.0–3.43) |

CHOL, cholesterol; CI, confidence interval; CVD, cardiovascular disease; Glu, glucose; HBI, Harvey Bradshaw Index; HDL, high-density lipoprotein; IBD, inflammatory bowel disease; OR, odds ratio; PLT, platelets; SCAI, Simple Colitis Activity Index; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TRG, triglycerides.

**Table 4.** Multivariate regression analysis for development of cardiovascular disease in inflammatory bowel disease patients

| | *P* value | aOR (95% CI) |
|---|---|---|
| BMI >30 | 0.001 | 0.284 (0.134–0.603) |
| Ever smokers | 0.005 | 3.922 (1.498–10.272) |
| Statins/dyslipidemia | <0.001 | 6.109 (3.159–11.814) |
| Hypertension | 0.015 | 0.46 (0.246–0.86) |
| IBD related surgery | 0.09 | 2.365 (0.874–6.402) |
| Male sex | 0.09 | 2.093 (0.902–4.854) |

aOR, adjusted odds ratio; CI, confidence interval; IBD, inflammatory bowel disease.

event following IBD diagnosis. Elevated CRP values were found only in 7/23 (30.4%) of them. Regarding clinical indices of disease activity, quality of life or biomarkers, no significant differences were found between the two groups (Table 3).

Multivariate regression analysis (Table 4) revealed significantly higher rates of classical CV risk factors in the patient group as expected. The number of IBD-related surgeries was lower in the CVD group, but NS different compared to the control group ($P = 0.09$). Subgroup analysis was performed in order to identify any possible disease-specific association with CVD. In the UC group, multivariable regression analysis showed significantly higher rates of obesity [BMI > 30, $P = 0.001$, adjusted odds ratio (aOR) 0.179, 95% CI: 0.063–0.51] and dyslipidemia ($P < 0.001$, aOR 7.588, 95% CI: 3.052–18.866), but not for smoking, hypertension or diabetes mellitus in UC patients with CVD compared to UC controls. Respectively, in the CD group diabetes mellitus ($P = 0.044$, OR 0.321, 95% CI: 0.106–0.972) and dyslipidemia ($P = 0.03$, OR 0.199, 95% CI: 0.07–0.569) were significantly associated with increased risk for CVD. There was no statistically significant difference between UC or CD patient and control groups in any parameter associated with disease severity, such as anti-TNF, immunomodulator or steroid use, IBD-related surgery, hospitalizations for flare or 3-year CRP. In line with the above findings, neither subgroup analysis of patients with CVD history after IBD diagnosis compared to control group confirmed any association between CVD risk and IBD severity related factors.

A history of thromboembolic episode was reported in four patients in the CVD patient group including two

cases with deep vein thrombosis (DVT) and two cases with pulmonary embolism and in six control cases including four cases with DVT, one with pulmonary embolism and one with thrombosis of right subclavian vein (MTHFR homozygote). Concerning other comorbidities of the cardiovascular system atrial fibrillation was reported in five patients with CVD compared to nine patients without CVD, other arrhythmias or history of pacemaker placement in four cases with CVD compared to three patients without CVD, thoracic aorta aneurysm was diagnosed in seven patients with CVD compared to two patients without CVD and valvular heart disease in five patients with CVD compared to two patients without CVD.

## Discussion

This study represents the first effort to investigate the effect of systemic inflammation linked to IBD, on cardiovascular system, taking into account not only traditional CV risk factors but also parameters associated with disease severity over time, since IBD diagnosis. However, no difference in terms of disease severity between IBD patients with and without coexistent CVD was found.

IBD clinical activity encoded with parameters such as symptoms, impact on professional and social life, hospitalizations, and surgeries related to disease activity has been recently associated with an increased risk for acute arterial events [21]. Furthermore, previous studies [8,22], having the limitation of using ICD-10 coding and drug prescription data, have correlated cardiovascular events with periods of IBD flare and persistent disease activity for a limited period of time.

Nationwide cohort studies in Denmark have shown an increased risk of IHD, especially within the first year after IBD diagnosis [29] and during periods of IBD activity including flares and persistent activity [8]. In a more recent meta-analysis [9] of 10 cohort studies female sex and younger age <50 years were associated with increased IHD risk in IBD patients. Regarding disease extent, Aniwan *et al.* [10] reported a three-fold higher risk of acute MI in CD patients with ileal/ileocecal localization and UC patients with extensive colitis.

Accordingly to IHD, cerebrovascular disease risk, PAD risk and overall acute arterial events rate have been found significantly increased during periods of IBD activity in female and younger patients [11,12]. Recent studies have shown an increased risk of hospitalization for HF during periods of active disease (incidence rate ratio 1.37; 95% CI: 1.26–1.49) [13] and a greater cumulative incidence of HF ($P = 0.02$) among IBD patients [10].

Our study originality relies on the comparison of sex- and age-matched patients with IBD with and without CVD in an attempt to isolate and examine the role of chronic disease inflammation in the atherosclerotic process, in contrast to other studies comparing IBD patients to general population from nationwide databases [8,10,22–24]. We assumed that chronic inflammation may be a possible extra CVD factor in both IBD groups and tried to identify if patients with a history of IHD, cerebrovascular event, PAD or HF had a more complicated disease course.

Contrary to our hypothesis the inflammatory burden as measured by our selected surrogate markers related to overall IBD course does not seem to impact on the cardiovascular system. Our study confirmed that traditional risk factors for CVD play the main and fundamental role for atherosclerosis in IBD patients. The fact that diagnosis of CVD followed IBD diagnosis in 56.6% of cases weakens even more the assumption of a possible association between chronic inflammation in IBD and CV risk. Danish [8,13,22] and French [12] nationwide studies have linked disease activity in terms of flare or persistent active disease, with the risk of adverse cardiovascular events. Unfortunately, in our study, we had limited information available to distinguish whether CV events took place in periods of active or quiescent IBD. Endoscopic data in 3 months period before or after CVD diagnosis was available in one-third of the patients and almost half of them had endoscopic active disease. Due to the small sample size, no further association could be evaluated. Regarding inflammatory biomarkers, a minority of IBD patients with a CV event following IBD diagnosis had elevated CRP but the small numbers do not permit us to draw firm conclusions.

In contrast to what we might have expected, patients with CVD had a trend for even lower hospitalizations for flare and IBD-related surgeries compared to controls. A possible explanation for this finding could be the influence of other factors such as the immunomodulatory effect of medications used in CVD on the intestinal epithelium.

In fact, clinical studies have shown that statins that are frequently used in CVD may improve disease activity scores, reduce rates of steroid use, and protect against new onset IBD [25–29]. Moreover, studies in experimental colitis have also found that statins may improve the macroscopic and microscopic inflammation, alter the intestinal epithelium, induce changes in the microflora and mitigate intestinal fibrosis [30].

Furthermore, antihypertensive use was significantly higher among IBD patients with history of CVD as expected. Given the antifibrotic and antinflammatory properties especially for certain classes of antihypertensives such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in experimental models of colitis [31], antihypertensives could possibly affect IBD course, but clinical studies have not investigated their role in IBD patients so far.

Patients with CVD are also often under aspirin or other antiplatelet agents with conflicting data on their possible effect on IBD onset [32,33] or disease activity in terms of disease relapse [34]. Low dose aspirin has been implicated in increasing over six times the risk for developing CD but a causative link has not been established so far. On the other hand, limited studies examining the possible protective role of clopidogrel or ridogrel on IBD course have not shown any effect in the induction of clinical remission over placebo [35,36]. In our study antiplatelet use was significantly greater in IBD patients with history of CVD, but its exact role in the IBD course is not clear.

Biomarkers of inflammation and especially CRP have been linked to the development of atherosclerosis. Limited studies have assessed the correlation between IBD related biomarkers and the risk of atherosclerosis. In the present study, the persistent elevation of CRP was not found different between patients with or without CVD. Markers of arterial stiffness have recently been reported associated

with longer disease duration, suggesting a role of disease duration in atherosclerosis [37].

Well-designed prospective studies could ultimately estimate the role of biomarkers of IBD in atherosclerotic process and the impact of cardio- and vasoprotective medications in gut inflammation.

Limitations of our study are the retrospective study design and the relatively small sample size corresponding to the low prevalence of CVD in IBD patients. We think however that using controls without CVD in a ratio 2:1 increases the strength of our study. Another limitation, as with all studies that use questionnaires, is that it comprehends the risk of putative reports that lead to bias. We lowered this risk by interviewing all participants by the same physician and validated the collected data by patient record and electronic prescription database review. Moreover, data on BMIs, lipid profile, fasting blood glucose, and other biochemical analyzes at the time of diagnosis of CVD were not available. As a fact, a point measurement of those parameters after CVD diagnosis could be influenced by several factors including IBD or non-IBD medications, comorbidities, and IBD course.

Considering that diagnosis of both CD and CVD determines smoking behavior leading to considerable reduction in tobacco smoking rates, we have noticed a remarkably high rate of ex-smokers >50% in both IBD groups of our study. Thus, lack of quantification for smoking in pack-years and the exact timing of cessation could probably underestimate its role as a risk factor for more severe disease.

In conclusion, our study showed no difference in disease severity as measured with surrogate markers (persistent elevation of CRP, IBD-related surgeries, hospitalizations, and use of biologics or immunosuppressants) between IBD patients with coexistent CVD and IBD patients without CVD. It could be suggested that the inflammatory burden possibly plays a less important role in the development of CVD in IBD patients. On the other hand, traditional risk factors for CVD seem to play the pivotal role for atherosclerosis in IBD patients. Data from larger prospective studies are essential to confirm our findings.

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A.M. has made substantial contributions to the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. E.T. and M.F. have participated in the study concept and design, acquisition of data, and interpretation of data. N.V. supervised acquisition of data and critically revised the manuscript. K.K. supervised acquisition of data and critically revised the manuscript. G.J.M. has participated in analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis and study supervision. I.E.K. has participated in the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis and study supervision.

### *Conflicts of interest*

N.V. has served as advisory board member for Abbvie, Hospira, Janssen, MSD, Sandoz, and Takeda; Speaker for Abbvie, Aenorasis, Ferring, Galenica, Janssen, MSD, and Takeda. K.K. has received speaker's fees from Abbvie, Aenorasis, Galenica, Janssen, MSD, Takeda, consultancy fees from Ferring and served as advisory board member for Abbvie, Genesis, MSD, Pfizer, Takeda. G.J.M. has served as advisory board member for Abbvie, Astellas, Celgene, Danone, Ferring, Genesis, Hospira, Janssen, Millennium Pharmaceuticals, MSD, Otsuka, Pharmacosmos, Pfizer, Sandoz, Takeda, and UCB; Speaker for AbbVie, Aenorasis, Angelini, Astellas, Danone, Falk Pharma, Ferring, Galenica, Genesis, Hospira, Janssen, MSD, Omega Pharma, Pfizer, and Takeda; Consultancies for MSD and Takeda; research support Abbvie, Galenica, Genesis, Menarini Group, MSD, and Pharmathen. I.E.K. has served as advisory board member for Abbvie, Astellas, Genesis, Janssen, MSD, Pharmacosmos, Pfizer, Shire, and Takeda; Speaker for AbbVie, Astellas, Genesis, Janssen, MSD, and Takeda; research support Abbvie and Ferring. For the remaining authors, there are no conflicts of interest.

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