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EDITORIAL

Spotlight on Cardiovascular Risk Assessment in Patients with Inflammatory Bowel Disease

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Evidence is mounting that patients with inflammatory bowel disease (IBD) have an elevated risk of vascular complications, comprised of venous thromboembolism (VTE) and arterial cardiovascular disease (CVD). According to meta-analyses, the risk of VTE in patients with IBD is 2.5 times higher and the risk of CVD 1.2 times higher than the risk in the general population [1, 2]. These vascular complications probably result from a cumulative effect of traditional risk factors for VTE and CVD, combined with the chronic systemic inflammation typical of IBD.

In this issue of *Digestive Diseases and Sciences*, Guillo et al. [3] present data on the prevalence of patient-reported risk factors for VTE and CVD in 1071 patients with ulcerative colitis (UC). Strengths of this GETAID FOCUS study are the large (international) study population and extensive data collection based on patient surveys. This study provides noteworthy information on the prevalence of patient-reported risk factors for vascular complications in IBD.

With regard to VTE, chronic inflammation causes a hypercoagulable state leading to a prothrombotic tendency. According to the *European Society of Cardiology (ESC) and European Respiratory Society (ERS)* guidelines, VTE risk factors can be classified as either strong, moderate, or weak according to their association with VTE [4]. In the cohort reported by Guillo et al. [3], 91% of UC patients reported no strong risk factor, with 96% reporting ≤ 1 moderate risk factor. Autoimmune diseases, however, are regarded as permanent independent VTE risk factors. Moreover, important clinical risk factors predisposing IBD patients to VTE are not taken into account. Over the past decade, studies identified disease flare, frequent or prolonged hospitalization, surgery, and extensive colonic disease as such [5]. The *European Crohn's and Colitis Organisation (ECCO)* guideline recommends treating all admitted IBD patients with thromboprophylaxis to reduce VTE risk, irrespective of the indication for hospitalization. The debate on VTE risk in IBD primarily concerns the use of thromboprophylaxis in certain conditions, for instance, post-hospitalization, after recent surgery, and during disease flares [6, 7].

Despite evidence and reasonable awareness, uptake of and adherence to guideline-derived recommendations on thromboprophylaxis appear to be low. Illustrative is a US survey study which shows that 80% of gastroenterologists acknowledge the increased VTE risk among IBD patients and 71% are aware of guideline recommendations. Nevertheless, only one in three prescribes thromboprophylaxis to hospitalized patients with severe UC [8]. Moreover, historical cohort studies show that actual thromboprophylaxis rates in hospitalized IBD patients vary from 50 to 79%, and only two-thirds of IBD patients receive an adequate dose [9–11]. Strikingly, the thromboprophylaxis rate is even lower for IBD patients as compared with the general inpatient population, most likely explained by hesitance due to the risk of hematochezia [12, 13]. Therefore, we laud the study group of Guillo et al. [3] for increasing the awareness on the augmented VTE risk in IBD.

In the case of CVD, dysregulation of the innate and adaptive immune system contributes to all stages of atherosclerosis, from plaque formation to atherothrombosis [14]. Chronic inflammation may well explain the observations of increased (early) signs of atherosclerosis measured by markers of endothelial dysfunction as well as subclinical atherosclerosis in patients with IBD [15]. An additional clue to the link between IBD and CVD is the association between reduced microbial diversity and metabolic dysfunction, including insulin resistance and dyslipidemia.

Guillo et al. [3] demonstrate that up to one-third of UC patients reported no risk factors for CVD with only 25%

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of patients reporting ≥ 1 risk factor. Nonetheless, the simple conclusion that the prevalence of traditional CVD risk factors is not increased in patients with UC may be invalid, since data collection via self-reporting of risk factors may underestimate their true presence. First, the validity of self-reported results relies on the recollection of study participants. Second, there may be a social desirability element affecting subjects' responses to questions regarding lifestyle, with consequent overestimation of the prevalence of ideal health behavior. Third, risk factors may be present, even when not (previously) diagnosed. To overcome these issues, confirmation of patient-reported outcomes with objective data from medical records could have reduced these forms of bias. A preferred study design concerns prospective structured CVD screening, including physical examination and laboratory testing. A structured screening may identify a significant number of risk factors unknown to patients and prevents misclassification by variation in diagnostic criteria for hypertension, hypercholesterolemia, and hyperglycemia.

The ESC guideline recommends screening for traditional CVD risk factors in all patients with inflammatory conditions, with documentation of relevant aspects of the patient history such as prior CVD events and medication use, combined with the measurement of blood pressure, glucose, and lipids (total cholesterol and HDL-c) [16]. The decision to intervene depends on total CVD risk assessed by the Systematic COronary Risk Evaluation (SCORE). In contrast, the *European Crohn's and Colitis Organisation (ECCO) guideline on Extra-Intestinal Manifestations in IBD* promotes reactive (i.e., treatment of diagnosed risk factors) but not proactive (i.e., screening for risk factors) CVD management in IBD [6]. Hence, the integration of CVD prevention strategies in IBD care is expected to be suboptimal. This contrasts with guidelines for individuals with rheumatological conditions (i.e., the *European Alliance of Associations for Rheumatology (EULAR)* guidelines), in which greater availability of empirical evidence led to the uptake of the better-defined recommendations [17]. These recommendations have had an evident impact on clinical practice, as has been observed in a UK study in which patients with rheumatoid arthritis had higher rates of CVD risk factors relative to patients with IBD, partially enhanced by higher rates of complete CVD screening. [18]

Observations on the prevalence of traditional CVD risk factors (hypertension, hyperlipidemia, diabetes, smoking, and obesity) in patients with IBD as compared with the general population are variable according to data from small cohort and population-based studies (Table 1). Despite the increased CVD burden, the majority of studies report no increased prevalence of traditional risk factors in patients with IBD [19–22]. Accordingly, two matched cohort studies screening complete CVD profiles report similar 10-year risk of CVD between groups [20, 21]. In contrast, in a US population-based study, IBD was associated with an overall unfavorable CVD risk profile [23]. The discrepancy between this US study and aforementioned studies may be explained by the use of self-administered patient surveys rather than data obtained from patient medical records that may bias the results as discussed above. The increased prevalence of CVD risk factors might be due to higher healthcare utilization and consequent CVD screening opportunities in the IBD population. Nevertheless, contributions from disease activity cannot be excluded since data regarding IBD characteristics were not collected.

Universal CVD risk calculators such as SCORE may underestimate the risk in patients with IBD. An important gap in current knowledge is the additional risk-enhancing effect of IBD diagnosis and accompanying disease characteristics. The literature provides important clues regarding IBD-specific risk factors that might be useful for accurate CVD risk estimation [5]. CVD risk appears to be associated with disease flares (specifically the 3 months before and after hospitalization), disease location (higher risk for colonic involvement as compared to ileal/ileocecal disease in those with Crohn's disease), and the extent of inflammation (higher risk in individuals with pancolonic UC than those with distal colitis/proctitis). Finally, the direction and magnitude to which immunomodulators induce cardiometabolic changes seem to differ between drug classes [24].

To conclude, the study of Guillo et al. [3] puts the spotlight on the relatively unexplored clinical area of cardiovascular disease in patients with IBD. As mentioned above, the results of this study on the prevalence of cardiovascular risk factors require careful interpretation. Future research may focus on implementation strategies of VTE guidelines. Furthermore, longitudinal studies are essential to clarify the contribution of both traditional and IBD-specific risk factors to CVD risk (assessment) in IBD patients.

Table 1 Literature overview on cardiovascular risk profiles in IBD

Ref #	Author (year of publication)	Country of origin	Study design	Outcome assessment	Patient selection criteria	Sample size, *N*		Male, %	Age, years	Prevalence/level of cardiovascular risk factors as compared to the general population		
						IBD	Controls			↓	=	↑
19	Yarur (2011)	USA	Longitudinal matched cohort study	Medical records	No history of CVD or VTE, no other IMID diagnosis	356	712	48	45	Hypertension Diabetes Hyperlipidemia TC LDL-c Triglycerides Obesity	Smoking HDL-c	
20	Aggarwal (2014)	USA	Historical matched cohort study	Self-administered survey, anthropometrics, laboratory	Positive history of CHD	131	524	74	65	Smoking BMI	Hypertension diabetes Hyperlipidemia CRP 10-year CVD risk	
21	Biondi Biondi (2020)	Brazil	Cross-sectional case–control study	Anthropometrics, laboratory, medical records	No history of CVD, no rheumatic or hepatic disease	52	37	48	49		Smoking Diabetes blood pressure BMI TC HDL-c LDL-c Triglycerides 10-year CVD risk	Glucose
22	Aarestrup (2019)	Denmark	Population-based study	Self-administered survey, anthropometrics, laboratory	–	1203	107,586	42	57	TC LDL-c WHR blood pressure	Smoking BMI Glucose HDL-c triglycerides	History of CVD CRP
23	Agrawal (2021)	USA	Population-based study	Self-administered survey	No history of CVD	786	59,299	37	53		Smoking Obesity	Hypertension diabetes hyperlipidemia

USA United States of America, *CVD* cardiovascular disease, *VTE* venous thromboembolism, *CHD* coronary heart disease, *IMID* immune-mediated inflammatory disease, *BMI* body mass index, *TC* total cholesterol, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *WHR* waist-to-hip ratio, *WBC* white blood cell count, *CRP* C-reactive protein, *CIMT* carotid intima media thickness

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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