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Increased risk of acute arterial events in young patients and severely active inflammatory bowel disease: a nationwide French cohort study

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Short title: Acute arterial events and inflammatory bowel disease

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Abstract

Objective: Magnitude and independent drivers of the risk of acute arterial events in inflammatory bowel disease (IBD) are still unclear. We addressed this question in patients with IBD compared to the general population at a nationwide level.

Design: Using the French National Hospital Discharge Database from 2008 to 2013, all patients aged 15 years or older and diagnosed with IBD were identified and followed up until 31 December 2013. The rates of incident acute arterial events were calculated and the impact of time with active disease (period around hospitalisation for IBD flare or IBD-related surgery) on the risk was assessed by Cox regression adjusted for traditional cardiovascular risk factors.

Results: Among 210,162 individuals with IBD (Crohn's disease [CD], n=97,708; ulcerative colitis [UC], n=112,454), 5,554 incident acute arterial events were identified. Both patients with CD and UC had a statistically significant overall increased risk of acute arterial events (standardised incidence ratio [SIR] 1.35; 95% confidence interval [95% CI] 1.30-1.41 and SIR, 1.10; 95% CI, 1.06-1.13, respectively). The highest risk was observed in patients under the age of 55 years, both in CD and UC. The 3-month periods before and after IBD-related hospitalisation were associated with an increased risk of acute arterial events in both CD and UC (hazard ratio, 1.74; 95% CI, 1.44-2.09 and 1.87; 95% CI, 1.58-2.22, respectively).

Conclusion: Patients with IBD are at increased risk of acute arterial events, with the highest risk in young patients. Disease activity may also have an independent impact on the risk.

Keywords: Inflammatory bowel disease, cardiovascular disease, ischemic heart disease, cerebrovascular disease, peripheral arterial disease.

Abbreviations used in this paper: IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; PMSI: Programme de Médicalisation des Systèmes d'Information; ICD-10: WHO International Classification of Diseases, 10th revision; SIR: standardised incidence ratio.

Summary box

What is already known about this subject?

- Chronic systemic inflammation is associated with an increased risk of acute arterial events.

- Risk of acute arterial events in IBD remains debated, while risk differences between age categories and the impact of disease activity remain largely unexplored and may explain contradicting previous findings.

What are the new findings?

- Patients with IBD are at increased risk of acute arterial events, with the highest risk in younger patients for all arterial disease groups.

- Disease activity may be an independent risk factor of acute arterial events.

How might it impact on clinical practice in the foreseeable future?

- Our nationwide population-based cohort study suggests an increased risk of ischemic heart disease, cerebrovascular disease and peripheral artery disease in patients with IBD, notably in younger patients and those with severely active disease. Strategies for optimizing control of inflammation should be assessed, in order to decrease the risk of acute arterial events in this patient population.

INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterised by chronic intestinal and systemic inflammation. Chronic systemic inflammation is involved in the pathogenesis of atherosclerosis and associated with increased risk of acute arterial events.[1,2] However, the risk of acute arterial events in patients with IBD remains unclear, in contrast with other chronic inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus.[3–5] In one meta-analysis,[6] IBD was significantly associated with increased risks of ischemic heart disease and cerebrovascular disease, but no significant association was found for peripheral artery disease. In another meta-analysis,[7] no increased risk of acute arterial events was found in patients with IBD.[6] Thus the data are inconsistent and further generalisation of results is limited by the considerable heterogeneity found between studies.[6]

Several factors may explain the conflicting data on the association between IBD and acute arterial events, notably age and disease activity. Several studies reported an association between younger age and an increased risk of acute arterial events,[8–10] while an increased risk of myocardial infarction was reported specifically in patients of older age.[11] Regarding disease activity, only one study reported the association between disease activity and the risk of myocardial infarction and stroke, but did not include peripheral artery disease.[12] Hence, the magnitude of the risk and the independent risk factors of acute arterial events in patients with IBD remain unclear and need further investigation.

Our aim was to assess the risk of acute arterial events, including ischemic heart disease, cerebrovascular disease, and peripheral artery disease in patients with IBD

as compared to the general population, and to assess the impact of age and IBD activity on the risk of acute arterial events, at a nationwide level.

MATERIALS AND METHODS

Data source

The French National Hospital Discharge Database (*Programme de Médicalisation des Systèmes d'Information* [PMSI]) covers all public and private hospitals in France. The standardised discharge summary includes: patient's demographics; primary and associated discharge diagnosis codes (WHO International Classification of Diseases, 10th revision, ICD-10);[13] medical and surgical procedures performed (French Medical Common Procedure Coding System); length of stay, entry and in-hospital mortality, which accounted for 57.4% of all adult deaths recorded in France between 2008 and 2013.[14] A unique anonymous identifier allows linking all hospital claims of the patient since January 2008 and tracking the occurrence and progression of chronic conditions over time.

Study population

All patients, aged 15 years or older, identified with IBD between 2008 and 2013 from the PMSI were included. Identification of IBD cases was based on one hospitalisation discharge diagnosis both as primary or associated diagnosis related to CD (K50) or UC (K51). The ICD-10 code for indeterminate colitis (K52.3) was not considered in this study. Detailed individual-level information regarding hospitalisations was available from 1 January 2008. Date of cohort inclusion was 1 January 2010 for patients diagnosed with IBD before 1 January 2010 and the date of first hospital claim related to IBD for patients identified after 1 January 2010. In case of multiple hospitalisations related to both UC and CD, the most recent diagnosis at cohort inclusion was retained. All subjects were followed until occurrence of any outcome, in-hospital death, or end of the study, 31 December 2013, whichever came first.

The general population at risk consisted in all adults (15 years or older) residing in France (National Vital Statistics in January of each year of the study period), hence including IBD and non-IBD individuals. Incident acute arterial events among non-IBD individuals were assessed from the PMSI between 1 January 2008 and 31 December 2013. Individuals diagnosed with IBD after 1 January 2010 contributed person-time as non-IBD individuals until the date of IBD diagnosis.

The same exclusion criteria were applied in the IBD population and the general population and were identified between 1 January 2008 and date of cohort inclusion (i.e. at least during 2 years of follow-up for every patient). Individuals with a history of an acute arterial event or related cardiovascular disease, primary or associated discharge diagnosis of atrial fibrillation, heart failure, or cardiomyopathy, procedures related to cardiac electronic device, cardiac valve prosthesis, angiography, coronary catheterization, or coronary artery bypass grafting were excluded (Supplementary Table 1).

Outcomes

Study outcome was the first occurring acute arterial event following cohort entry, defined by a primary discharge diagnosis or procedures specifically related to: (1) ischemic heart disease (including myocardial infraction); (2) cerebrovascular disease (including stroke); (3) peripheral artery disease, excluding acute mesenteric ischemia. We did not include acute mesenteric ischemia, since local intestinal rather than systemic inflammation may be associated with acute mesenteric ischemia in patients with IBD.[15,16] See Supplementary Table 1 for the according ICD-10 codes and procedure codes.

Covariates

Traditional cardiovascular risk factors including hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking, and alcohol use disorders were assessed during each hospitalisation between 1 January 2008 and end of follow-up (Supplementary Table 2). Since assessment during hospitalisation may underestimate the prevalence of cardiovascular risk factors, which additionally may be undiagnosed although already present until the occurrence of an acute arterial event, cardiovascular risk factors were considered present at cohort entry in the main analysis if recorded at any time during follow-up. Disease activity prior to cohort entry for patients diagnosed with IBD before 1 January 2010 or at cohort entry for patients identified after 1 January 2010 was assessed by three mutually exclusive categories: (1) hospitalisation not related to IBD with an associated diagnosis of IBD (without day hospitalisation for IBD related endoscopy or hospitalisation related to IBD activity or surgery); (2) day hospitalisation for IBD related endoscopy (without hospitalisation related to IBD activity or surgery; (3) hospitalisation related to IBD activity or surgery.

Statistical analysis

Continuous data are expressed as median (interquartile range), while discrete data are given as percentages, and comparisons were made with Pearson's $\chi 2$ test**.**

The incidence rate of acute arterial events was assessed for patients with IBD and for the French general population, between 2010 and 2013. The expected number of cases of acute arterial events in the general population was obtained by multiplying person-years at risk in each 5-year age group by the corresponding sex-, age- and region-specific incidence rate for each year between 2010 and 2013. The reported number of cases of acute arterial events was divided by the expected number to obtain standardised incidence ratios (SIRs). Confidence intervals (CIs) were calculated with

an exact method based on the Poisson distribution. Lastly, subgroups analyses were performed by age groups (15-34; 35-54; 55-74; 75 years or older), sex, and number of traditional cardiovascular risk factors in patients with IBD (compared to the general population and irrespective of the number of cardiovascular risk factors in the general population).

In order to assess the impact of disease activity on the risk of acute arterial events among patients with IBD, hospitalisations or surgery related to IBD were used as surrogate markers for disease activity. Active disease was defined as the three months before and after an IBD-related hospitalisation or surgery. In case of readmission related to IBD in the three months following an IBD-related hospitalisation, period of disease activity was extended to coincide with the date of the readmission. The three months after cohort inclusion were likewise defined as a period of IBD activity in patients hospitalised for IBD activity at cohort entry. A Cox regression analysis was performed separately for each IBD subtype and adjusted for age at cohort entry, sex, region of residence, year of cohort entry, disease activity prior to cohort entry, and traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking, and alcohol use disorders). IBD activity was fitted as time-varying covariate, and periods of disease activity were compared with periods of no disease activity. All other covariates were included as time-fixed covariates. Results were reported as hazard ratios (HRs) with 95% confidence intervals (95% CI). The proportionality of hazards was evaluated using plots of Schoenfeld residuals and no violation of the proportional hazard assumption was detected.

Since data on out-of-hospital deaths, which may mostly affect elderly people, are not available in the database, subgroups analyses were stratified on age groups (patients aged 18-54 and 55 years or older) in order to assess the impact of these lacking mortality data. Additionally, we performed several sensitivity analyses to test the

robustness of our results. We varied the length of time patients were regarded as having active disease, reducing it to one month and extending it to six months before and after an IBD-related hospitalisation or surgery. Since cardiovascular risk factors were considered present in the main analysis if recorded at any time during follow-up, we only considered cardiovascular risk factors present at cohort entry in a sensitivity analysis. Furthermore, data on hospitalisations was available until 31 December 2013 and acute arterial events occurring between October and December 2013 may thus not be associated with IBD-related hospitalisations occurring in 2014 in our study. A sensitivity analysis was therefore performed by censoring follow-up to 30 September 2013. Lastly, we performed a sensitivity analysis excluding the postoperative period, since non-cardiac surgery is associated with a postoperative morbidity related to cardiac complications.[17]

Patients with a concomitant date of first IBD claim in the database and occurrence of acute arterial event were excluded from this analysis.

The study was approved by the French Data Protection Agency (CNIL DE-2015-025). All data used in this study only contained anonymous patient records. The statistical analyses were performed with SAS (version 9.4) statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Overall, 210,162 patients identified with IBD in the 2008-2013 French National Hospital Discharge Database were included (Figure 1): 97,708 with CD (46.5%) and 112,454 with UC (53.5%). The median follow-up was 3.4 years (interquartile range [IQR]:1.8-4.0). Patients' characteristics are shown in Table 1.

The majority of patients with IBD were women (53.8%), with significantly higher proportions in patients with CD (57.7%) as compared to UC (50.5%) ($p<0.0001$). Patients with CD were younger than patients with UC at cohort entry (median age at cohort entry [IQR]: 40 years [28 - 53] and 49 years [36 - 62], respectively). The proportion of patients with active disease prior to cohort entry was higher in patients with CD (25.9%) compared to patients with UC (14.6%). The majority of patients (66.3%) were identified at cohort entry by IBD-related endoscopy. At least one cardiovascular factor was recorded in 24.8% of patients with IBD, with higher rates of tobacco smokers recorded among patients with CD (9.6%) than patients with UC (4.4%) ($p<0.0001$). A total of 5232 of patients (2.5%) died in hospital during follow-up.

Table 1. IBD Patient characteristics

	Crohn's disease n = 97,708	Ulcerative colitis n = 112,454	Total N = 210,162
Male sex	41,369 (42.3)	55,636 (49.5)	97,005 (46.2)
Age at cohort entry (years)	40 (28-53)	49 (36-62)	45 (32-59)
Follow-up (years)	3.7 (1.9-4.0)	3.2 (1.6-4.0)	3.4 (1.8-4.0)
Disease activity prior to cohort entry			
Hospitalisation not related to IBD activity	17,695 (18.1)	11,532 (10.2)	29,227 (13.9)
Day hospitalisation for IBD related endoscopy	54,746 (56.0)	84,532 (75.2)	139,278 (66.3)
Hospitalisation related to IBD activity or surgery	25,267 (25.9)	16,390 (14.6)	41,657 (19.8)
Cardiovascular risk factors recorded			
Hypertension	10,477 (10.7)	16,906 (15.0)	27,383 (13.0)
Hyperlipidemia	3512 (3.6)	6757 (6.0)	10,269 (4.9)
Diabetes mellitus	3706 (3.8)	6205 (5.5)	9911 (4.7)
Obesity	5210 (5.3)	6464 (5.7)	11,674 (5.6)
Tobacco smoking	9349 (9.6)	4900 (4.4)	14,249 (6.8)
Alcohol use disorders	2383 (2.4)	2469 (2.2)	4852 (2.3)

Results are expressed as median (interquartile range) or number (%)

Risk of any acute arterial event

A total of 5554 acute arterial events occurred in IBD patients during 595,202 person-years of follow-up, including 3177 (57.2%) ischemic heart diseases, 1715 (30.9%) cerebrovascular diseases, and 662 (11.9%) peripheral artery diseases. Crude incidence rates per 1000 person-years were: 9.3 (95% CI 9.1–9.6) for all acute arterial event; 5.3 (95% CI 5.1–5.5) for ischemic heart disease; 2.9 (95% CI 2.7–3) for cerebrovascular disease; and 1.1 (95% CI 1–1.2) for peripheral artery disease. Crude incidence rates according to IBD subtype are provided in Supplementary Figure 1.

During the study period, 1,555,959 French adults of the general population were hospitalised for an incident acute arterial event with a similar distribution of acute arterial events at first hospitalisation compared to patients with IBD (Supplementary Table 3). Crude incidence rates are provided by age groups for IBD patients and the general population in Supplementary Figure 2.

The risk of acute arterial events was significantly increased in patients with IBD compared to the general population (SIR, 1.19; 95% CI 1.16-1.22) (Table 2). Similar findings were found for ischemic heart disease (SIR, 1.17; 95% CI 1.13-1.21); cerebrovascular disease (SIR, 1.19; 95% CI 1.13-1.24); and peripheral artery disease (SIR, 1.27; 95% CI 1.17-1.37).

The risk of acute arterial events was higher in patients with CD as compared to patients with UC (SIR 1.35; 95% CI 1.30-1.41 versus 1.10; 95% CI 1.06-1.13, respectively). The risk estimates were statistically significant for all arterial disease groups, except for peripheral artery disease in patients with UC (SIR 1.07; 95% CI 0.96-1.18). In patients with CD, the highest risk was observed for peripheral artery disease (SIR 1.65; 95% CI 1.46-1.83), while the risks of ischemic heart disease and cerebrovascular disease were comparable. In UC patients, risk of ischemic heart disease and

cerebrovascular disease were also comparable (Table 2). SIRs for arterial disease subgroups according to IBD subtype are provided in Supplementary Table 4.

Table 2. Standardised incidence ratios of acute arterial events according to IBD subtype

	Person-years	Reported cases	Expected cases	SIR (95% CI)	P value
All IBD patients	595,202				
All acute arterial events		5554	4679	1.19 (1.16-1.22)	<.0001
Ischemic heart disease		3177	2706	1.17 (1.13-1.21)	<.0001
Cerebrovascular disease		1715	1446	1.19 (1.13-1.24)	<.0001
Peripheral artery disease		662	521	1.27 (1.17-1.37)	<.0001
Crohn's disease patients	287,134				
All acute arterial events		2244	1658	1.35 (1.30-1.41)	<.0001
Ischemic heart disease		1253	956	1.31 (1.24-1.38)	<.0001
Cerebrovascular disease		694	523	1.33 (1.23-1.43)	<.0001
Peripheral artery disease		297	180	1.65 (1.46-1.83)	<.0001
Ulcerative colitis patients	308,068				
All acute arterial events		3310	3021	1.10 (1.06-1.13)	<.0001
Ischemic heart disease		1924	1750	1.10 (1.05-1.15)	<.0001
Cerebrovascular disease		1021	923	1.11 (1.04-1.17)	<0.01
Peripheral artery disease		365	341	1.07 (0.96-1.18)	0.21

Subgroup analyses according to age, sex and cardiovascular risk factors

SIRs of acute arterial events are provided by age groups and IBD subtype in Figure 2 and Supplementary Table 5. In CD patients, the highest risk was observed in patients aged from 15 to 34 years (SIR, 1.42; 95% CI 1.09-1.75) and patients aged from 35 to 54 years (SIR, 1.58; 95% CI 1.45-1.70). The risk decreased for later age, while remaining statistically significant (SIR of patients aged from 55 to 74 years and aged of more than 75 years, 1.38; 95% CI 1.30-1.47 and 1.13; 95% CI 1.03-1.22, respectively). In UC patients, the highest risk was observed in patients aged from 15 to 34 years (SIR, 1.65; 95% CI 1.20-2.10). Conversely, the risk of acute arterial events was not increased in patients aged from 35 to 54 years (SIR, 1.02; 95% CI 0.93-1.11) nor in patients older than 75 years (SIR, 1.05; 95% CI 0.99-1.11), whereas patients aged from 55 to 74 years were at increased risk (SIR, 1.15; 95% CI 1.09-1.20).

Compared to the general population, women with IBD were at higher risk than men with IBD for all arterial disease groups in both CD and UC, with the highest risk in women with CD (Supplementary Figure 3). Among patients without any identified cardiovascular risk factors, an increased risk of acute arterial events was maintained in CD patients (SIR, 1.26; 95% CI 1.19-1.34), whereas no increased risk was observed in UC patients (SIR, 0.96; 95% CI 0.92-1.01). The risk increased progressively with an increasing number of cardiovascular risk factors (Supplementary Figure 4).

Impact of IBD activity on the risk of acute arterial events

Among 97,348 CD and 112,181 UC patients included in this analysis, 22,700 CD patients (23.3%) and 15,747 UC patients (14%) were hospitalised for IBD activity during follow-up. Median (IQR) duration of active disease period in CD and UC patients was 180 (90-205) and 92 (90-180) days, accounting for 4% and 2.1% of total follow-

up, respectively. Among patients hospitalised for IBD activity, period of active disease accounted for 24.8% of total follow-up, while 7857 CD patients (34.6%) and 3967 UC patients (24.7%) were hospitalised more than once. Surgical procedures for IBD were performed in 24.9% of hospitalisations.

In CD patients, disease activity was associated with an increased risk of acute arterial events (HR, 1.74; 95% CI 1.44-2.09). This increased risk remained statistically significant for all arterial disease groups and the magnitude of risk was highest for peripheral artery disease (Figure 3). In UC patients, disease activity was also associated with an increased risk of acute arterial events (HR, 1.87; 95% CI 1.58-2.22), however the risk of cerebrovascular disease was not statistically significant. (Figure 3)

Regarding other predictive factors, male sex and all traditional cardiovascular risk factors except obesity were, as expected, associated with an increased risk of acute arterial events (Table 3).

Sensitivity analyses confirmed the robustness of the main results (Supplementary Table 6). Results were consistent across age groups. When the definition of duration of active disease was reduced to one month before and after an IBD-related hospitalisation, the HR for acute arterial event at the time of active disease increased in both CD and UC patients, to 1.91 (95% CI 1.48-2.48) and 2.03 (95% CI 1.59-2.59), respectively. When the definition of the duration of active disease was increased to six months before and after an IBD-related hospitalisation, the HR for acute arterial event at the time of active disease was reduced in CD and UC patients, to 1.46 (95% CI 1.25-1.71) and 1.69 (95% CI 1.46-1.95), respectively. Similar results were observed in the sensitivity analyses considering only cardiovascular risk factors present at cohort entry, censoring follow-up to 30 September 2013 and excluding the postoperative period from the active disease definition.

Table 3. Predictive factors of acute arterial events according to IBD subtype: Cox multivariate analysis*

	HR (95% CI)	
	Crohn's disease	Ulcerative colitis
Male sex	1.71 (1.56-1.87)	2.08 (1.93-2.24)
Disease activity (3-month periods before and after IBD-related hospitalisation or surgery)	1.74 (1.44-2.09)	1.87 (1.58-2.22)
Cardiovascular risk factors		
Hypertension	1.18 (1.05-1.32)	1.24 (1.14-1.35)
Hyperlipidemia	1.34 (1.16-1.56)	1.16 (1.05-1.30)
Diabetes mellitus	1.32 (1.14-1.52)	1.48 (1.33-1.64)
Obesity	1.02 (0.86-1.20)	1.01 (0.89-1.15)
Tobacco smoking	1.82 (1.58-2.09)	1.49 (1.28-1.74)
Alcohol use disorders	1.52 (1.26-1.84)	1.51 (1.27-1.79)

Abbreviation: HR, hazard ratio.* Adjusted for age at cohort entry, sex, region of residence, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders.

DISCUSSION

Our study demonstrated that the overall risk of acute arterial events is increased in patients with IBD compared to the general population. The risk was higher in CD patients compared to UC patients. In CD patients, the increased risk was more prominent for younger patients with the highest risk in those aged from 35 to 54 years. For older patients, the SIRs appeared lower but the risk still remained increased compared to the general population. In UC patients, the risk was increased in patients younger than 35 years and in those aged from 55 to 74 years. Similarly to the observation in CD patients, the highest risk was observed in younger patients. Lastly, we demonstrated that the disease activity was independently associated with an increased risk of acute arterial events in both CD and UC.

With this study we have provided new evidence on the association between acute arterial events and inflammatory bowel diseases. The magnitude of the risk observed in our study for ischemic heart disease and cerebrovascular disease was similar to previous findings published in a recent meta-analysis.[6] Conversely, to the data published in the latter meta-analysis, we revealed an increased risk of peripheral artery disease in IBD patients. However, the meta-analysis only included 148 patients with peripheral artery disease, thus power limitations might explain the different findings. Moreover, systemic inflammation may be higher in peripheral artery disease than in coronary artery disease,[18] suggesting that the impact of inflammation may be higher in peripheral artery disease.

Several pathophysiological mechanisms, including structural and functional vascular changes, as well as biochemical and genetic changes may be involved in the risk of acute arterial events in patients with IBD.[19] Besides an increased carotid intima–media thickness and arterial stiffness,[20,21] microvascular endothelial dysfunction

was observed in patients with IBD.[22] These pathophysiological mechanisms may also support the hypothesis of a more pronounced increased risk of overall acute arterial events in CD as compared to UC patients. CD patients are more prone to a higher degree of systemic inflammation compared to UC patients, amongst others evidenced by higher level of C-reactive protein (CRP) production[23–25] and serum concentration of interleukin-6.[26] Interestingly, these markers of inflammation are increased in both IBD and atherosclerosis.[16] The difference in risk estimates between CD and UC patients could also be linked to the prothrombotic effect of hyperhomocysteinemia and low vitamin B6 plasma level, which may be related to malabsorption in CD patients.[27,28] Lastly, polymorphisms in NOD2/CARD15 have been associated with both coronary atherosclerosis and IBD with a stronger link with CD.[29] NOD2/CARD15 variants may predispose to CD.[30]

Higher risk of acute arterial events observed in younger IBD patients may reflect the different impact of inflammation across age groups. Indeed, patients diagnosed with CD at young age are more likely to have a severe disease course[31] and age ranges associated with an increased risk in patients with UC correspond to peak ages for UC onset.[32,33] Moreover, disease activity tends to decrease over time.[34] Traditional cardiovascular risk factors in older patients may also potentially outweigh the risk related to systemic inflammation owing to IBD.

Compared to the general population of similar sex and age, women were at higher risk of acute arterial events than men, whereas male sex was, as would be expected, an independent predictive factor of acute arterial event in IBD patients after adjustment of all cardiovascular risk factors. It suggests that the risk differences compared to the general population between men and women may be related to the higher prevalence of traditional cardiovascular risk factors in men compared with women.

This study has several strengths. Using nationwide register-based data on the entire French population provided a large sample size allowing for sufficient power to perform comprehensive and multiple subgroups analyses on the risk of acute arterial events, identify its independent drivers, and thus, strengthen our findings. Additionally, several studies have found the reliability, validity, and accuracy of medical coding in the PMSI database for various diseases to be good.[35–39] In particular, stroke as a primary discharge diagnosis code was associated with a positive predictive value of about 90%.[40] Regarding ischemic heart disease, the annual incidence rate observed in the general population was in the range of those recently reported in three French regional registries, thus supporting a high validity of the data.[41]

This study also has some limitations that need to be discussed. Cardiovascular risk factors were identified during hospitalisation. Rates of cardiovascular risk factors, including tobacco smoking, may be therefore underestimated,[42] while tobacco smoking may partly account in differences between CD and UC. However, the increased risk of acute arterial events was maintained in CD patients without traditional cardiovascular risk factors compared with the general population. Disease activity was also associated with an increased risk of acute arterial events in both CD and UC, after adjustment of all cardiovascular risk factors recorded. Furthermore, patients with CD had a nearly 2-fold increase in periods of disease activity compared to patients with UC. Despite the underestimation of tobacco smoking, it may highlight the fact that systemic inflammation is one of the trigger of acute arterial events in patients with IBD and the increased inflammatory burden in patients with CD may account for differences between CD and UC. Furthermore, adjustment for region of residence may to some extent have captured the effect of tobacco smoking, since the prevalence of tobacco smoking in France differs according to the region of residence.[43]

The definition of active disease was based on IBD-related hospitalisation. Thus, it excludes mild and moderate flares managed in an outpatient setting and treated with regimens such as aminosalicylates. Hence, the risks assessed in our study relate to flares severe enough to require hospitalisation. These flares may be associated with high systemic inflammation and further studies are needed to assess the risk related to mild and moderate flares managed in an outpatient setting. However, surgical procedures were performed in a minority of hospitalisations and we reported consistent findings after exclusion of the postoperative period from the active disease definition, which may exclude the most severe flares. Additionally, active disease was arbitrarily defined as the three months before and after an IBD-related hospitalisation or surgery, while the true duration of risk would vary between individuals. However, we reported consistent findings in sensitivity analyses varying active disease duration.

Data on treatment modalities were not included in the analysis. Therefore, we were not able to use corticosteroids exposure as a surrogate marker of active disease nor to adjust or stratify on the different treatment options. Anti-TNF agents reduce systemic inflammation and could decrease cardiovascular events and related mortality in IBD patients, which has been suggested in patients with rheumatoid arthritis.[5] Further studies are therefore required to assess the impact of treatment on the risk of acute arterial events in IBD patients.

Until now, there has been no validation study of the ICD-10 codes related to IBD in the PMSI. However, a similar cohort from the same inpatient database and including outpatient database has been extensively described and provides evidence on the validity of IBD diagnoses in these databases.[44]

In conclusion, this nationwide population-based cohort study including more than 200,000 patients diagnosed with IBD reported an increased risk of acute arterial events

in patients with IBD. We determined that the risk was the highest in patients with CD and in young patients compared to the corresponding persons of the general population. We also established a clear link between IBD activity and the risk of acute arterial events. Overall, this study supports the increasing concept that a tight control of inflammation is crucial in IBD patients to avoid IBD-related systemic complications. For arterial diseases and IBD, the impact of therapies, including anti-TNFs, still has to be addressed.

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Figure legends:

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Figure 1: Study Population Flowchart

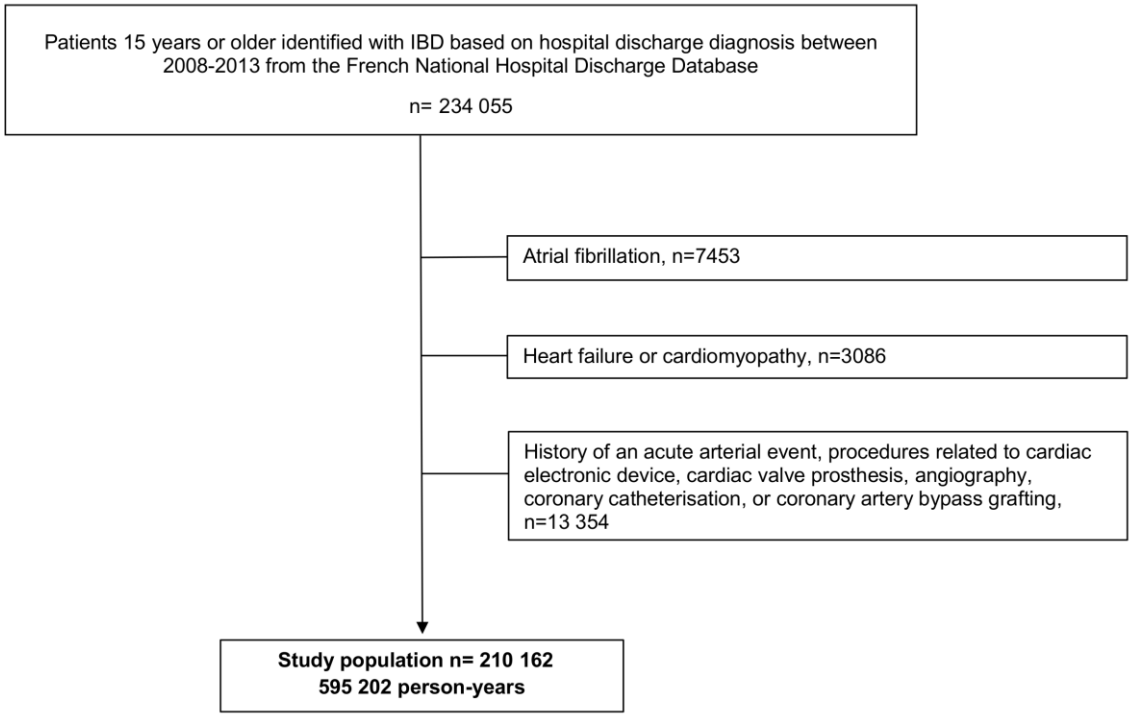
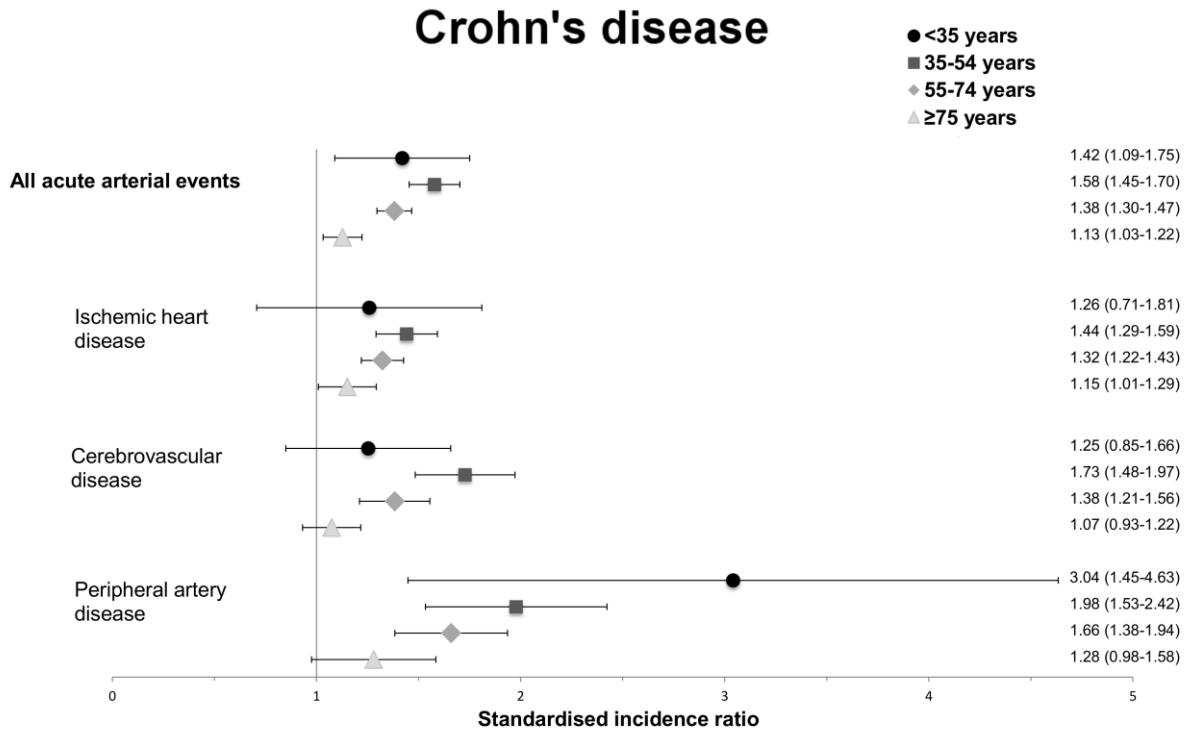


Figure 2: Standardised incidence ratios of all acute arterial events according to IBD subtype and age groups



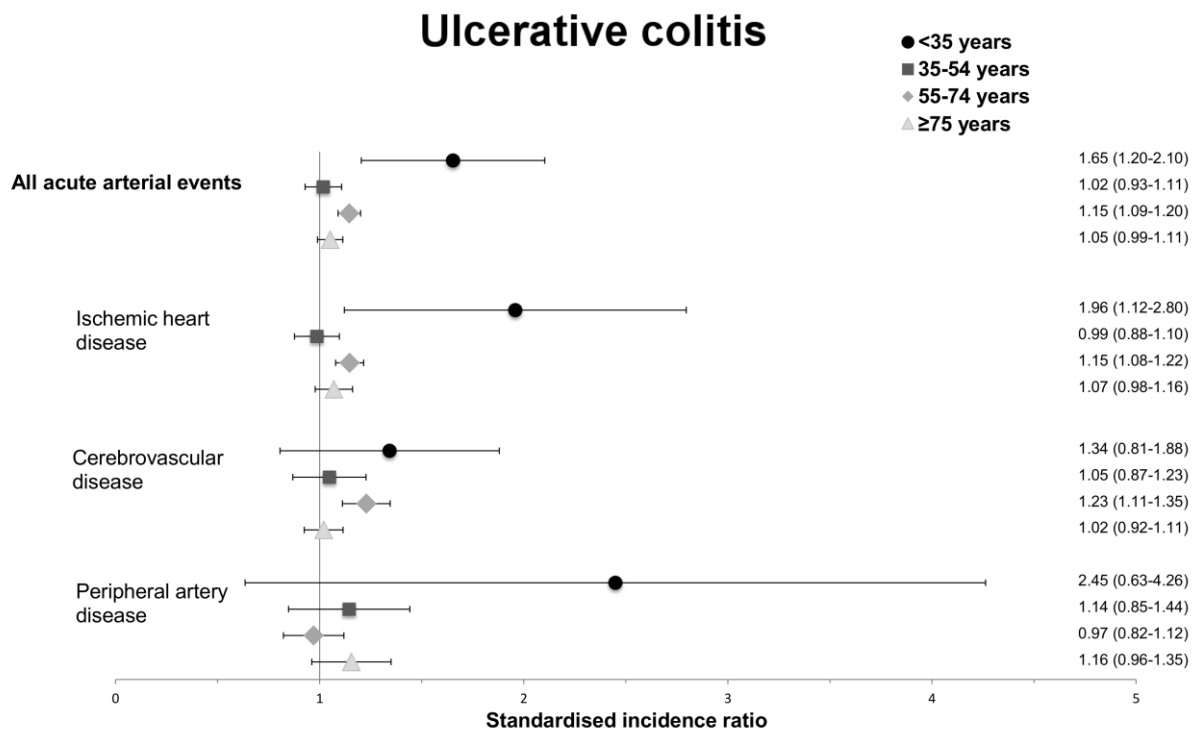
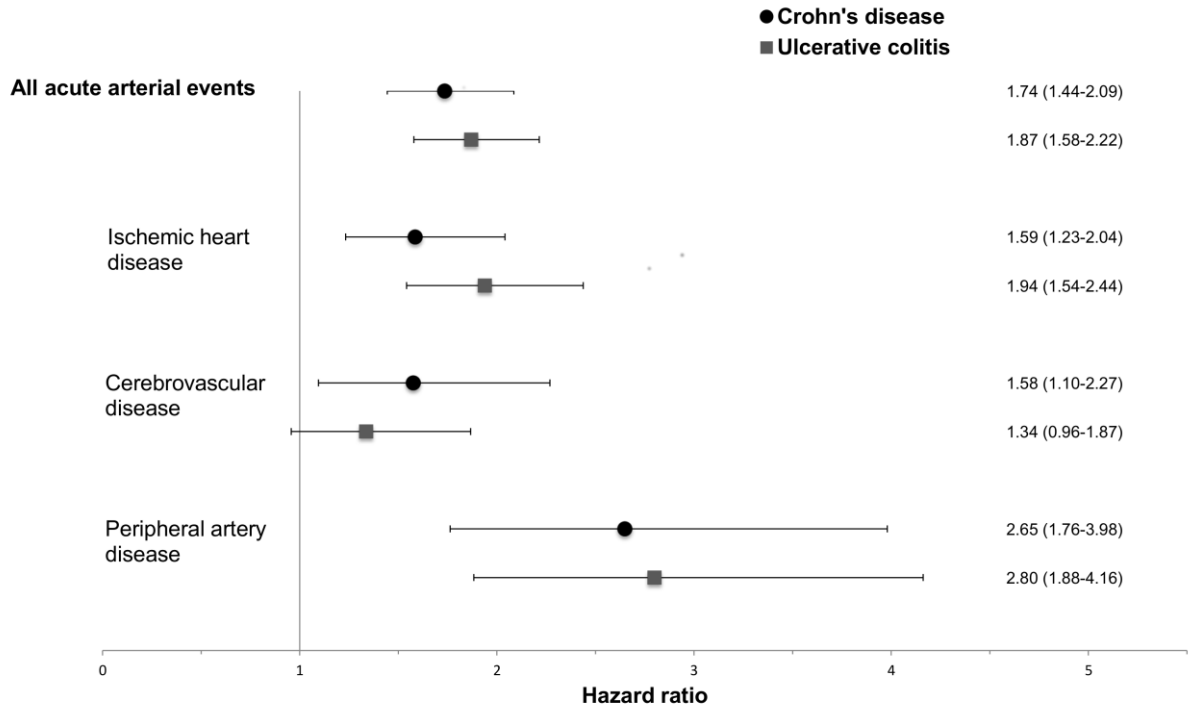


Figure 3: Impact of disease activity (3-month periods before and after IBD-related hospitalisation or surgery) on the risk of acute arterial events according to IBD subtype. Legend: adjusted for age at cohort entry, sex, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidemia, diabetes melittus, obesity, tobacco smoking and alcohol use disorders.



Supplementary material

Supplementary Table 1. Exclusion criteria and outcomes

Comorbidities prior to cohort entry	ICD-10 codes	French Medical Common Procedure Coding System
Exclusion criteria		
Ischemic heart disease	I20-I25, T820, T822,T823, T826, T827 Z45.0, Z86.71, Z95 (except Z95.8,Z95.9)	Coronary catheterization with arterial dilation; CABG
Cerebrovascular disease	I60-I66, G45, G460-G462, I670 , I671, I68, I69, Z86.60, Z86.70	Cerebral angiography with arterial dilation or embolization
Peripheral artery disease	I74	Angiography (excluding coronary catheterization, cerebral and mesenteric angiography) with arterial dilation; Peripheral artery bypass
Heart Failure	I50	-
Atrial fibrillation	I48	-
Cardiomyopathies	I42-I43	-
Outcomes		
Ischemic heart disease	I20-I25	Coronary catheterization; CABG
Myocardial infarction	I21-I22	Coronary catheterization with arterial dilation; CABG
Cerebrovascular disease	I60-I64, G45	Cerebral angiography with arterial dilation or embolization
Stroke	I60-I64 (except I63.6)	Cerebral angiography with arterial dilation or embolization
Peripheral artery disease	I74	Angiography (excluding coronary catheterization, cerebral and mesenteric angiography) with arterial dilation; Peripheral artery bypass

Supplementary Table 2. Cardiovascular risk factors and variables related to IBD activity

Covariates	ICD-10 codes	French Medical Common Procedure Coding System
Cardiovascular risk factors		
Hypertension	I10-I13, I15	-
Hyperlipidemia	E78.0-E78.5	-
Diabetes mellitus	E10-E14, M14.2 , M14.6, N08.3, H28.0, H36.0, G59.0, G63.2, G73.0, G99.0, I79.2	-
Obesity	E66	-
Tobacco smoking	F17, Z71.6, Z72.0, T65.2	-
Alcohol use disorders	F10.1, F10.24, F10.25, F10.26, F10.3, F10.4, Z50.2, Z71.4, Z72.1, E24.4, E51.1, K70x, G31.2, G62.1, G72.1, I42.6, K29.2, K85.2, K86.0, F10.5, F10.6, F10.7, F10.8, F10.9, F10.20, F10.21, F10.22, F10.23	-
Digestive endoscopy	-	Colonoscopy, Upper GI endoscopy, Capsule Endoscopy
Hospitalisation related to IBD		
IBD	K50, K51	-
Occlusion	K56	-
Fistula, perforation	K63.1, K63.2	-
Abscess	K63.0	-
Perianal complications	K60, K61	-
Surgery related to IBD	-	Colectomy, Intestinal resection, Abscess drainage, Surgical procedure related to anal abscess or fistula

Supplementary Table 3.Characteristics of patients with acute arterial events among patients with IBD and the French general population

	Crohn's disease n = 2244	Ulcerative colitis n = 3310	IBD Total N = 5554	French general population n= 1,555,959
Male sex	1208 (53.8)	2137 (64.6)	3310 (59.6)	945,396 (60.8)
Age at event (years)	61 (50-73)	67 (57-77)	65 (55-75)	68 (57-78)
Acute arterial event subtype				
Ischemic heart disease	1253 (55.9)	1924 (58.1)	3177 (57.2)	884,457 (56.9)
Myocardial infraction	410 (18.3)	680 (20.5)	1090 (19.6)	326,115 (21.0)
Cerebrovascular disease	694 (30.9)	1021 (30.9)	1715 (30.9)	500,138 (32.1)
Stroke	626 (27.9)	915 (27.6)	1541 (27.7)	452,544 (29.1)
Peripheral artery disease	297 (13.2)	365 (11.0)	662 (11.9)	171,364 (11.0)
Cardiovascular risk factors recorded precluding acute arterial events				
Hypertension	688 (30.7)	1202 (36.3)	1890 (34.0)	361,622 (23.2)
Hyperlipidemia	244 (10.9)	452 (13.7)	696 (12.5)	129,389 (8.3)
Diabetes mellitus	258 (11.5)	509 (15.4)	767 (13.8)	160,061 (10.3)
Obesity	175 (7.8)	279 (8.4)	454 (8.2)	81,370 (5.2)
Tobacco smoking	279 (12.4)	200 (6.0)	479 (8.6)	67,111 (4.3)
Alcohol use disorders	133 (5.9)	159 (4.8)	292 (5.3)	51,707 (3.3)

Results are expressed as median (interquartile range) or number (%)

Supplementary Table 4. Standardised incidence ratios of arterial events according to IBD subtype

	Person-years	Reported cases	Expected cases	SIR (CI 95%)	P value
All IBD patients	595,202				
All acute arterial events		5554	4679	1.19 (1.16-1.22)	<.0001
Ischemic heart disease		3177	2706	1.17 (1.13-1.21)	<.0001
Myocardial infraction		1090	1004	1.09 (1.02-1.15)	<0.01
Cerebrovascular disease		1715	1446	1.19 (1.13-1.24)	<.0001
Stroke		1541	1302	1.18 (1.12-1.24)	<.0001
Peripheral artery disease		662	521	1.27 (1.17-1.37)	<.0001
Crohn's disease patients	287,134				
All acute arterial events		2244	1658	1.35 (1.30-1.41)	<.0001
Ischemic heart disease		1253	956	1.31 (1.24-1.38)	<.0001
Myocardial infraction		410	351	1.17 (1.05-1.28)	<0.01
Cerebrovascular disease		694	523	1.33 (1.23-1.43)	<.0001
Stroke		626	470	1.33 (1.23-1.44)	<.0001
Peripheral artery disease		297	180	1.65 (1.46-1.83)	<.0001
Ulcerative colitis patients	308,068				
All acute arterial events		3310	3021	1.10 (1.06-1.13)	<.0001
Ischemic heart disease		1924	1750	1.10 (1.05-1.15)	<.0001
Myocardial infraction		680	653	1.04 (0.96-1.12)	0.30
Cerebrovascular disease		1021	923	1.11 (1.04-1.17)	<0.01
Stroke		915	832	1.10 (1.03-1.17)	<0.01
Peripheral artery disease		365	341	1.07 (0.96-1.18)	0.21

Supplementary Table 5. Standardised incidence ratios of all arterial events according to IBD subtype and age category

	Person-years	Reported cases	Expected cases	SIR (CI 95%)	P value
Crohn's disease patients					
< 35 years	104,721				
All acute arterial events		71	50	1.42 (1.09-1.75)	0.01
Ischemic heart disease		20	16	1.26 (0.71-1.81)	0.36
Myocardial infraction		6	5	1.31 (0.26-2.35)	0.56
Cerebrovascular disease		37	30	1.25 (0.85-1.66)	0.22
Stroke		30	25	1.22 (0.78-1.66)	0.32
Peripheral artery disease		14	5	3.04 (1.45-4.63)	0.01
35-54 years	114,833				
All acute arterial events		621	394	1.58 (1.45-1.70)	<.0001
Ischemic heart disease		353	245	1.44 (1.29-1.59)	<.0001
Myocardial infraction		127	96	1.32 (1.09-1.55)	<0.01
Cerebrovascular disease		192	111	1.72 (1.48-1.97)	<.0001
Stroke		174	98	1.77 (1.51-2.03)	<.0001
Peripheral artery disease		76	39	1.97 (1.53-2.42)	<.0001
55-74 years	53,816				
All acute arterial events		1013	735	1.38 (1.29-1.46)	<.0001
Ischemic heart disease		627	475	1.32 (1.22-1.42)	<.0001
Myocardial infraction		182	166	1.10 (0.94-1.26)	0.22
Cerebrovascular disease		247	179	1.38 (1.21-1.55)	<.0001
Stroke		219	155	1.41 (1.22-1.60)	<.0001
Peripheral artery disease		139	84	1.66 (1.38-1.93)	<.0001
≥ 75 years	13,765				
All acute arterial events		539	479	1.13 (1.03-1.22)	0.01
Ischemic heart disease		253	220	1.15 (1.01-1.29)	0.04
Myocardial infraction		95	85	1.12 (0.89-1.34)	0.31
Cerebrovascular disease		218	203	1.07 (0.93-1.22)	0.32
Stroke		203	191	1.06 (0.91-1.21)	0.41
Peripheral artery disease		68	53	1.28 (0.97-1.58)	0.07
Ulcerative colitis patients					
< 35 years	61,942				
All acute arterial events		52	31	1.65 (1.20-2.10)	<0.01
Ischemic heart disease		21	11	1.96 (1.12-2.79)	0.03
Myocardial infraction		7	3	2.22 (0.57-3.86)	0.15
Cerebrovascular disease		24	18	1.34 (0.80-1.88)	0.21
Stroke		16	15	1.08 (0.55-1.60)	0.78
Peripheral artery disease		7	3	2.44 (0.63-4.26)	0.12

35-54 years	119,822				
All acute arterial events		497	489	1.02 (0.93-1.11)	0.72
Ischemic heart disease		309	314	0.98 (0.88-1.09)	0.79
Myocardial infraction		101	127	0.79 (0.64-0.95)	<0.01
Cerebrovascular disease		131	125	1.05 (0.87-1.23)	0.62
Stroke		118	111	1.06 (0.87-1.25)	0.52
Peripheral artery disease		57	50	1.14 (0.85-1.44)	0.35
55-74 years	96,526				
All acute arterial events		1660	1452	1.14 (1.09-1.20)	<.0001
Ischemic heart disease		1071	936	1.14 (1.08-1.21)	<.0001
Myocardial infraction		371	333	1.11 (1.00-1.23)	0.05
Cerebrovascular disease		424	346	1.23 (1.11-1.34)	<.0001
Stroke		369	299	1.23 (1.11-1.36)	<.0001
Peripheral artery disease		165	170	0.97 (0.82-1.12)	0.68
≥ 75 years	29,778				
All acute arterial events		1101	1049	1.05 (0.99-1.11)	0.12
Ischemic heart disease		523	490	1.07 (0.98-1.16)	0.15
Myocardial infraction		201	189	1.06 (0.92-1.21)	0.40
Cerebrovascular disease		442	434	1.02 (0.92-1.11)	0.71
Stroke		412	407	1.01 (0.92-1.11)	0.79
Peripheral artery disease		136	118	1.15 (0.96-1.35)	0.12

Supplementary Table 6. Sensitivity analyses on the hazard ratios for acute arterial events according to IBD subtype.

	Disease activity (3-month periods before and after IBD-related Hospitalisation discharge or surgery)	
	HR (95% CI)	
	Crohn's disease	**Ulcerative colitis**
All acute arterial events		
Main analysis	1.74 (1.44-2.09)	1.87 (1.58-2.22)
Age at cohort entry		
18-54 years	2.22 (1.67-2.96)	1.87 (1.23-2.84)
≥ 55 years	1.52 (1.20-1.93)	1.88 (1.56-2.26)
Assessment of cardiovascular risk factors at cohort entry	1.83 (1.52-2.20)	1.95 (1.65-2.31)
Exclusion of postoperative period as period of disease activity	1.65 (1.36-2.00)	1.78 (1.49-2.13)
Follow-up censored at 30 September 2013	1.78 (1.47-2.15)	1.92 (1.62-2.29)

Abbreviation: HR, hazard ratio.* Adjusted for age at cohort entry, sex, region of residence, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders.

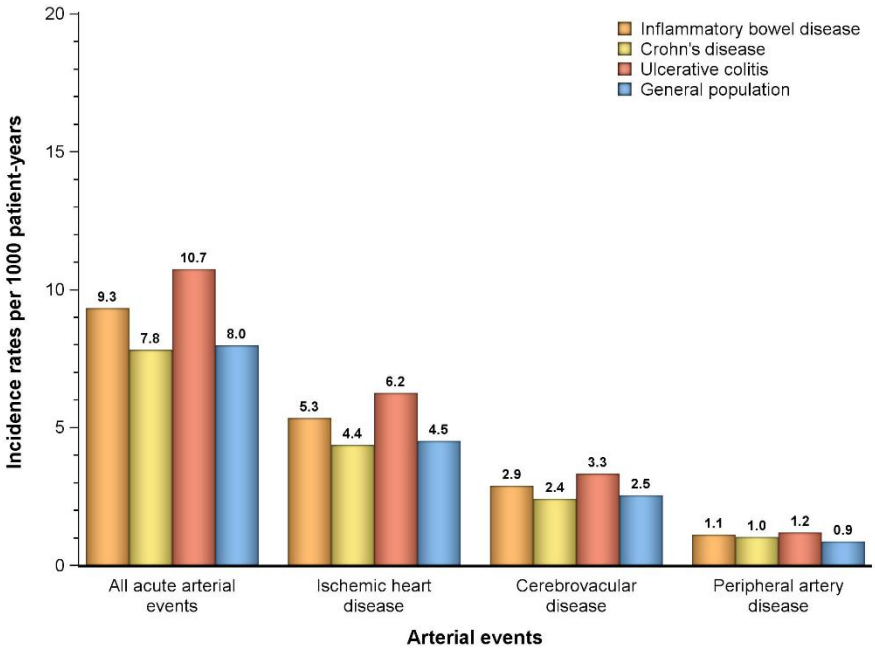
Figure Legends :

Supplementary figure 1: Crude incidence rates of acute arterial events in patients with IBD and the general population

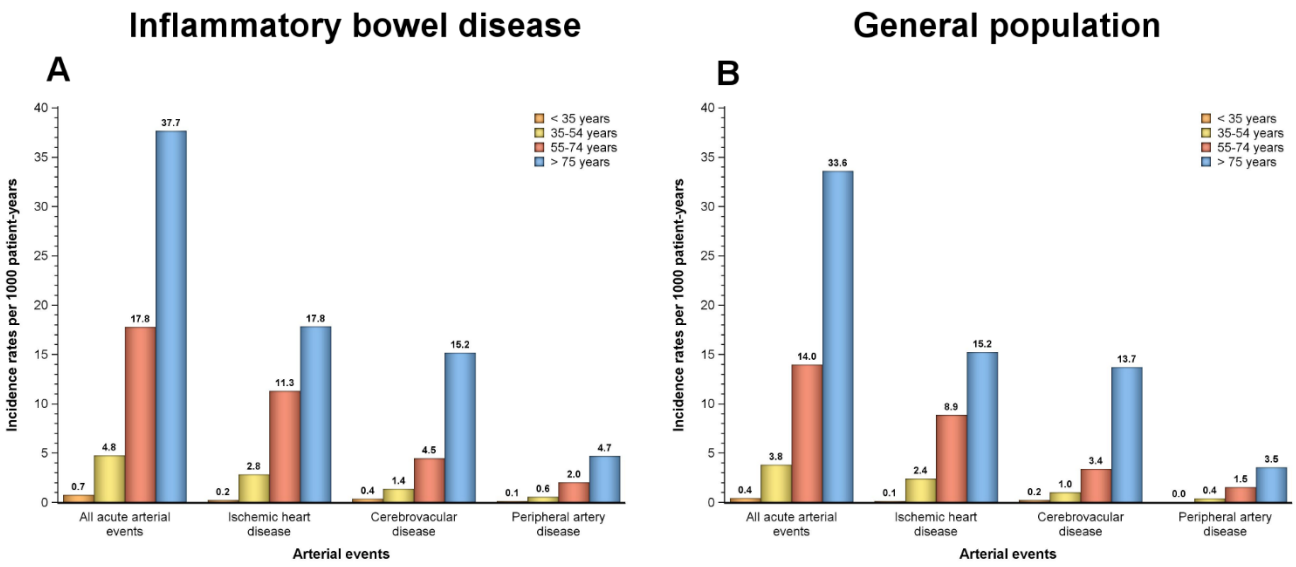
Supplementary figure 2: Crude incidence rates of acute arterial events according to age in patients with IBD (A) and the general population (B)

Supplementary figure 3: Standardised incidence ratios of all acute arterial events according to IBD subtype and sex

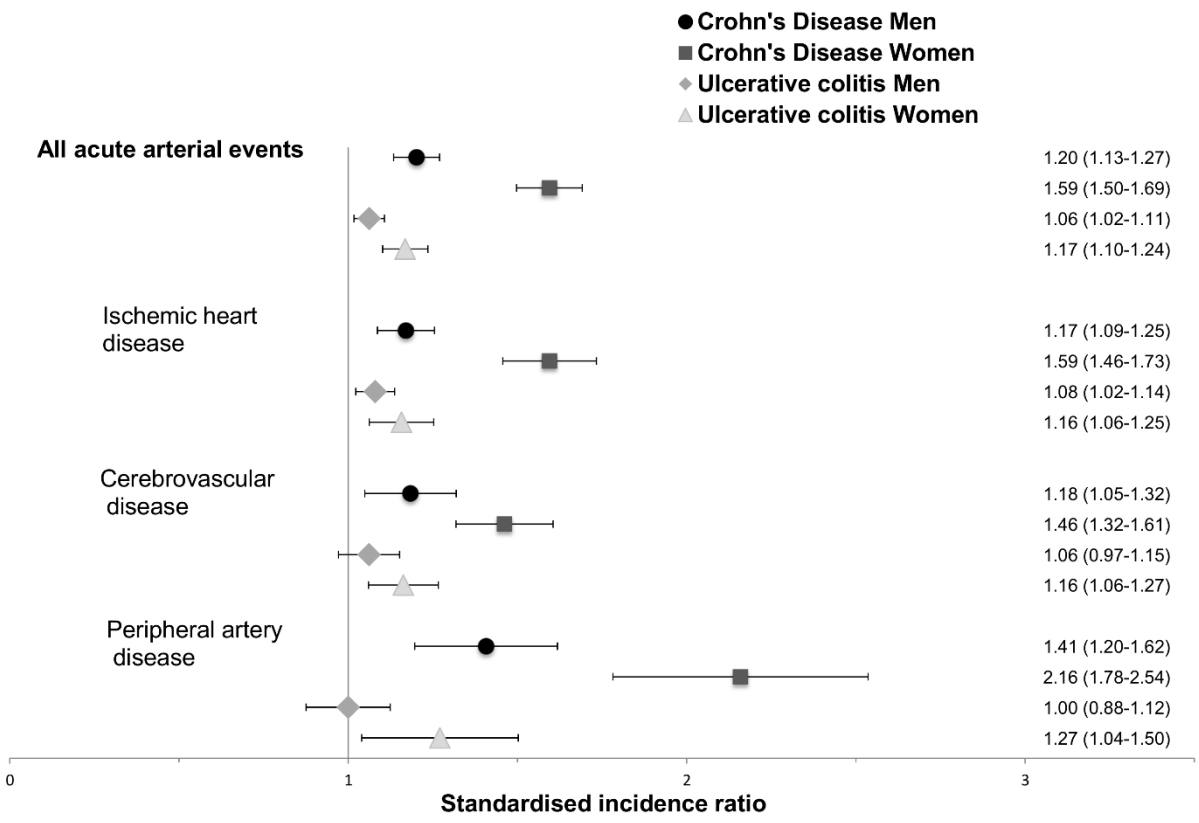
Supplementary figure 4: Standardised incidence ratios of all acute arterial events according to IBD subtype and number of traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes melittus, obesity, tobacco smoking and alcohol use disorders)



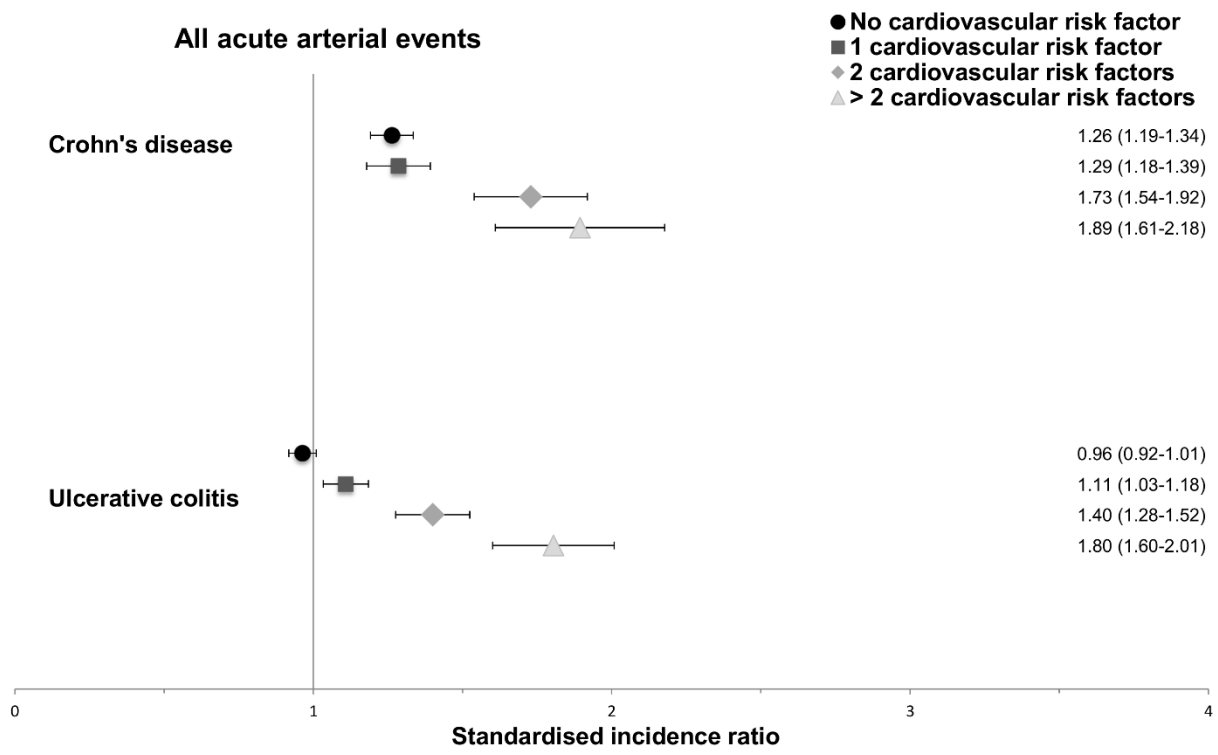
Supplementary figure 1: Crude incidence rates of acute arterial events in patients with IBD and the general population



Supplementary figure 2: Crude incidence rates of acute arterial events according to age in patients with IBD (A) and the general population (B)



Supplementary figure 3: Standardised incidence ratios of all acute arterial events according to IBD subtype and sex



Supplementary figure 4: Standardised incidence ratios of all acute arterial events according to IBD subtype and number of traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes melittus, obesity, tobacco smoking and alcohol use disorders)