ORIGINAL ARTICLE

# Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study

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## ABSTRACT

**Objective** Magnitude and independent drivers of the risk of acute arterial events in IBD are still unclear. We addressed this question in patients with IBD compared with 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; UC, n=112 454), 5554 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% CI 1.30 to 1.41 and SIR 1.10; 95 CI 1.06 to 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 (HR 1.74; 95 CI 1.44 to 2.09 and 1.87; 95% CI 1.58 to 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.

### Significance of this study

**What is already known on 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 previous contradicting 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 ischaemic heart disease, cerebrovascular disease and peripheral artery disease in patients with IBD, notably in younger patients and those with severely active disease. Strategies for optimising control of inflammation should be assessed to decrease the risk of acute arterial events in this patient population.

## INTRODUCTION

IBD including Crohn's disease (CD) and 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 ischaemic 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 ischaemic heart disease, cerebrovascular disease and peripheral artery disease in patients with IBD as compared with 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 inhospital 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, inhospital 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 (ie, 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 catheterisation or coronary artery bypass grafting were excluded (see online 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) ischaemic heart disease (including myocardial infraction); (2) cerebrovascular disease (including stroke); (3) peripheral artery disease, excluding acute mesenteric ischaemia. We did not include acute mesenteric ischaemia, since local intestinal rather than systemic inflammation may be associated with acute mesenteric ischaemia in patients with IBD[15 16] (see online supplementary table 1 for the ICD-10 codes and procedure codes).

### Covariates

Traditional cardiovascular risk factors including hypertension, hyperlipidaemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders were assessed during each hospitalisation between 1 January 2008 and end of follow-up (see online 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 (IQR), 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). 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 with the general population and irrespective of the number of cardiovascular risk factors in the general population).

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 3 months before and after an IBD-related hospitalisation or surgery. In case of readmission related to IBD in the 3 months following an IBD-related hospitalisation, period of disease activity was extended to coincide with the date of the readmission. The 3 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, hyperlipidaemia, 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 HRs with 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) 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 1 month and extending it to 6 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 V.9.4 statistical software.

## 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 (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 with 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 with 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.

### Risk of any acute arterial event

A total of 5554 acute arterial events occurred in patients with IBD during 595 202 person-years of follow-up, including 3177 (57.2%) ischaemic 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 to 9.6) for all acute arterial event; 5.3 (95% CI 5.1 to 5.5) for ischaemic

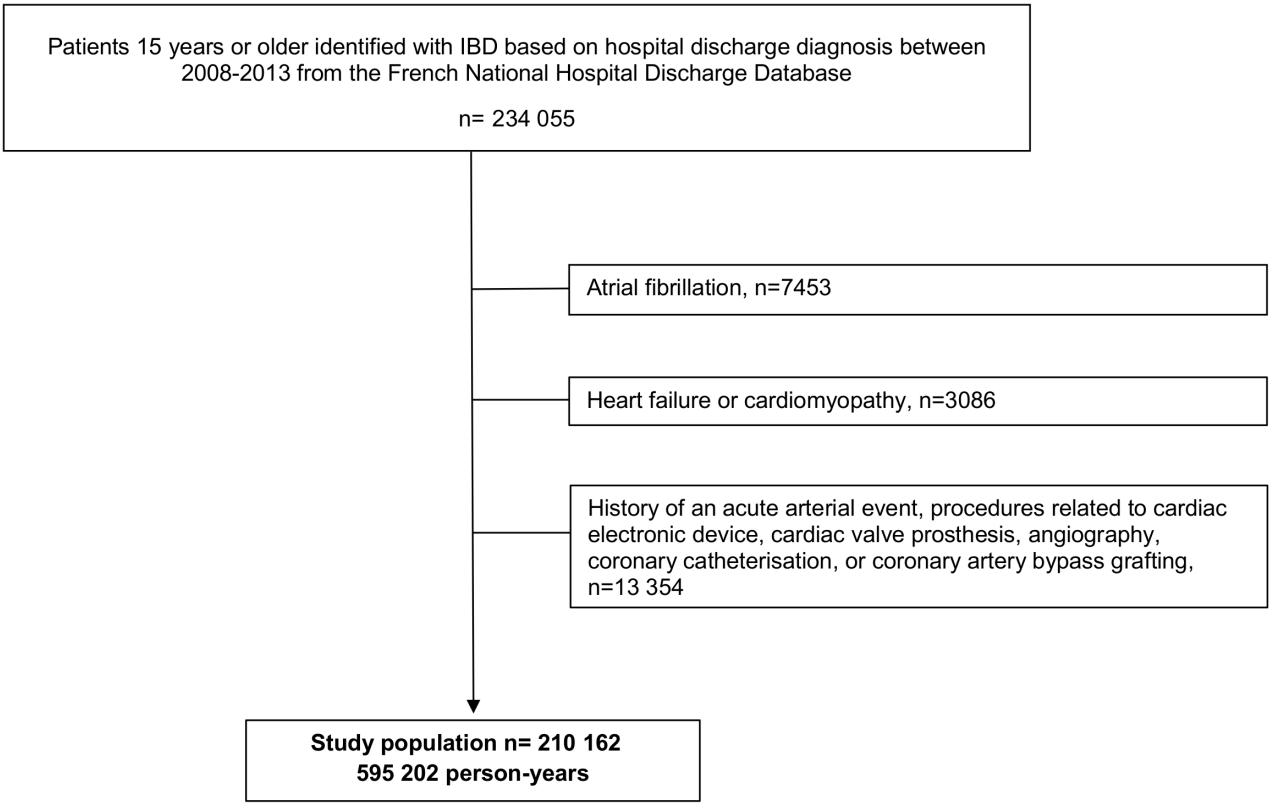


**Figure 1** Study population flowchart.

**Table 1** Characteristics of patients with IBD

| | CD (n=97 708) | UC (n=1 12 454) | 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) |
| Hyperlipidaemia | 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 (IQR) or number (%).

heart disease; 2.9 (95% CI 2.7 to 3) for cerebrovascular disease and 1.1 (95% CI 1 to 1.2) for peripheral artery disease. Crude incidence rates according to IBD subtype are provided in online 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 with patients with IBD (see online supplementary table 3). Crude incidence rates are provided by age groups for patients with IBD and the general population in online supplementary figure 2.

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

The risk of acute arterial events was higher in patients with CD as compared with patients with UC (SIR 1.35; 95% CI 1.30 to 1.41 vs 1.10; 95% CI 1.06 to 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 to 1.18). In patients with CD, the highest risk was observed for peripheral artery disease (SIR 1.65; 95% CI 1.46 to 1.83), while the risks of ischaemic heart disease and cerebrovascular disease were comparable. In patients with UC, risk of ischaemic heart disease and cerebrovascular disease were also comparable (table 2). SIRs for arterial disease subgroups according to IBD subtype are provided in online supplementary table 4.

### 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 online supplementary table 5. In patients with CD, the highest risk was observed in patients aged from 15 to 34 years (SIR, 1.42; 95% CI 1.09 to 1.75) and patients aged from 35 to 54 years (SIR, 1.58; 95% CI 1.45 to 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 to 1.47 and 1.13; 95% CI 1.03 to 1.22, respectively). In patients with UC, the highest risk was observed in patients aged from 15 to 34

**Table 2** SIRs of acute arterial events according to IBD subtype

| | Person-years | Reported cases | Expected cases | SIR (95% CI) | p Value |
|---|---|---|---|---|---|
| All patients with IBD | 595 202 | | | | |
| All acute arterial events | | 5554 | 4679 | 1.19 (1.16 to 1.22) | <0.0001 |
| Ischaemic heart disease | | 3177 | 2706 | 1.17 (1.13 to 1.21) | <0.0001 |
| Cerebrovascular disease | | 1715 | 1446 | 1.19 (1.13 to 1.24) | <0.0001 |
| Peripheral artery disease | | 662 | 521 | 1.27 (1.17 to 1.37) | <0.0001 |
| Patients with CD | 287 134 | | | | |
| All acute arterial events | | 2244 | 1658 | 1.35 (1.30 to 1.41) | <0.0001 |
| Ischaemic heart disease | | 1253 | 956 | 1.31 (1.24 to 1.38) | <0.0001 |
| Cerebrovascular disease | | 694 | 523 | 1.33 (1.23 to 1.43) | <0.0001 |
| Peripheral artery disease | | 297 | 180 | 1.65 (1.46 to 1.83) | <0.0001 |
| Patients with UC | 308 068 | | | | |
| All acute arterial events | | 3310 | 3021 | 1.10 (1.06 to 1.13) | <0.0001 |
| Ischaemic heart disease | | 1924 | 1750 | 1.10 (1.05 to 1.15) | <0.0001 |
| Cerebrovascular disease | | 1021 | 923 | 1.11 (1.04 to 1.17) | <0.01 |
| Peripheral artery disease | | 365 | 341 | 1.07 (0.96 to 1.18) | 0.21 |

SIR, standardised incidence ratio.

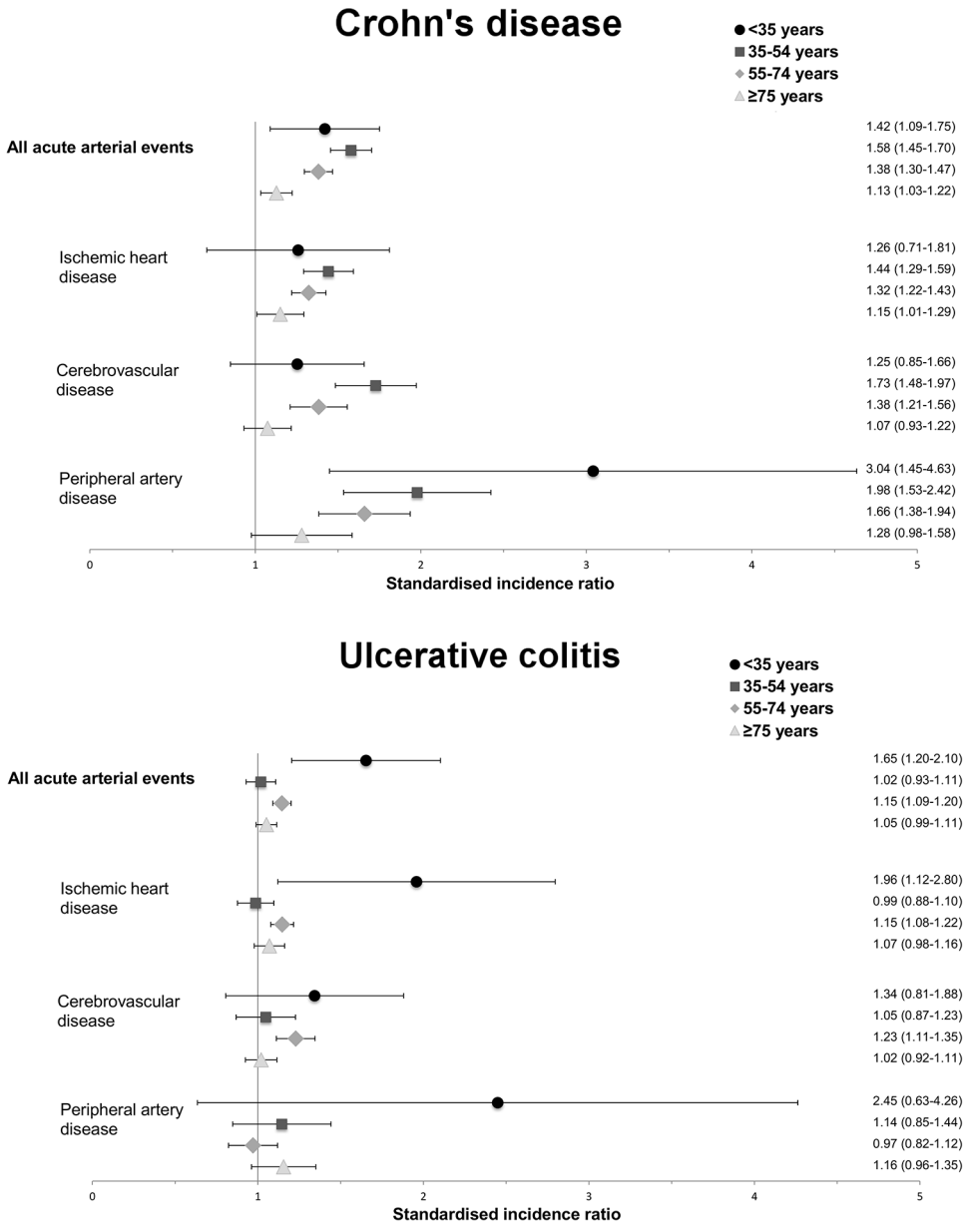


**Figure 2** Standardised incidence ratios of all acute arterial events according to IBD subtype and age groups.

years (SIR, 1.65; 95% CI 1.20 to 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 to 1.11) nor in patients older than 75 years (SIR, 1.05; 95% CI 0.99 to 1.11), whereas patients aged from 55 to 74 years were at increased risk (SIR, 1.15; 95% CI 1.09 to 1.20).

Compared with 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 (see online supplementary figure 3). Among patients without any identified cardiovascular risk factors, an increased risk of acute arterial events was maintained in patients with CD (SIR, 1.26; 95% CI 1.19 to 1.34), whereas no increased risk was observed in patients with UC (SIR, 0.96; 95% CI 0.92 to 1.01). The risk increased progressively with an increasing number of cardiovascular risk factors (see online supplementary figure 4).

### Impact of IBD activity on the risk of acute arterial events

Among 97 348 patients with CD and 112 181 patients with UC included in this analysis, 22 700 patients with CD (23.3%) and 15 747 patients with UC (14%) were hospitalised for IBD activity during follow-up. Median (IQR) duration of active disease period in patients with CD and UC 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 patients with CD (34.6%) and 3967 patients with UC (24.7%) were hospitalised more than once. Surgical procedures for IBD were performed in 24.9% of active disease periods.

In patients with CD, disease activity was associated with an increased risk of acute arterial events (HR, 1.74; 95% CI 1.44 to 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 patients with UC, disease

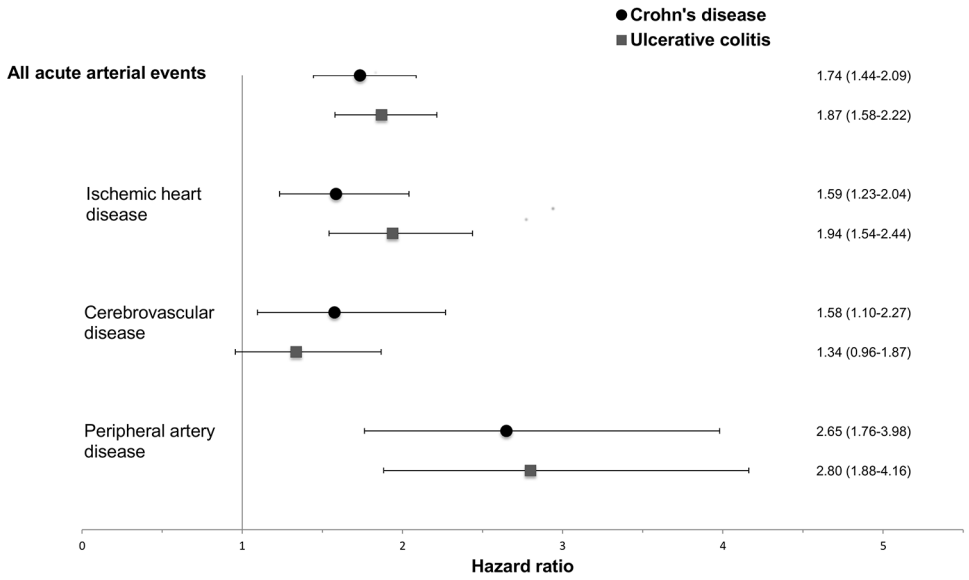


**Figure 3** Impact of disease activity (3-month periods before and after IBD-related hospitalisation or surgery) on the risk of acute arterial events according to IBD subtype. Legend: adjusted for age at cohort entry, sex, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidaemia,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

activity was also associated with an increased risk of acute arterial events (HR, 1.87; 95% CI 1.58 to 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 (see online supplementary table 6). Results were consistent across age groups. When the definition of duration of active disease was reduced to 1 month before and after an IBD-related hospitalisation, the HR for acute arterial event at the time of active disease increased in both patients with CD and UC to 1.91 (95% CI 1.48 to 2.48) and 2.03 (95% CI 1.59 to 2.59), respectively. When the definition of the duration of active disease was increased to 6 months before and after an IBD-related hospitalisation, the HR for acute arterial event at the time of active disease was reduced in patients with CD and UC to 1.46 (95% CI 1.25 to 1.71) and 1.69 (95% CI 1.46 to 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) | |
|---|---|---|
| | CD | UC |
| Male sex | 1.71 (1.56 to 1.87) | 2.08 (1.93 to 2.24) |
| Disease activity (3-month periods before and after IBD-related hospitalisation or surgery) | 1.74 (1.44 to 2.09) | 1.87 (1.58 to 2.22) |
| Cardiovascular risk factors | | |
| Hypertension | 1.18 (1.05 to 1.32) | 1.24 (1.14 to 1.35) |
| Hyperlipidaemia | 1.34 (1.16 to 1.56) | 1.16 (1.05 to 1.30) |
| Diabetes mellitus | 1.32 (1.14 to 1.52) | 1.48 (1.33 to 1.64) |
| Obesity | 1.02 (0.86 to 1.20) | 1.01 (0.89 to 1.15) |
| Tobacco smoking | 1.82 (1.58 to 2.09) | 1.49 (1.28 to 1.74) |
| Alcohol use disorders | 1.52 (1.26 to 1.84) | 1.51 (1.27 to 1.79) |

Adjusted for age at cohort entry, sex, region of residence, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidaemia, 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 with the general population. The risk was higher in patients with CD compared with patients with UC. In patients with CD, 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 with the general population. In patients with UC, the risk was increased in patients younger than 35 years and in those aged from 55 to 74 years. Similarly to the observation in patients with CD, 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 ischaemic 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 patients with IBD. 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 with UC. Patients with CD are more prone to a higher degree of systemic inflammation compared with patients with UC, among others evidenced by higher level of C-reactive protein 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 patients with CD and patients with UC could also be linked to the prothrombotic effect of hyperhomocysteinaemia and low vitamin B6 plasma level, which may be related to malabsorption in patients with CD.[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 patients with IBD 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 with 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 patients with IBD after adjustment of all cardiovascular risk factors. It suggests that the risk differences compared with 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 ischaemic 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 patients with CD 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 twofold increase in periods of disease activity compared with 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 3 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. Antitumour necrosis factor (TNF) agents reduce systemic inflammation and could decrease cardiovascular events and related mortality in patients with IBD, 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 patients with IBD.

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 with 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 patients with IBD to avoid IBD-related systemic complications. For arterial diseases and IBD, the impact of therapies, including anti-TNFs, still has to be addressed.

**Correction notice** This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

**Collaborators** Collaborators of the BERENICE study group are the following: Laurent Beaugerie, Anne-Marie Bouvier, Anne Buisson, Franck Carbonnel, Fabrice Carrat, Jacques Cosnes, Corinne Gower-Rousseau, Julien Kirchgesner, Alain Olympie, Laurent Peyrin-Biroulet, Jean-François Rahier, Frank Ruemmele, Michaël Schwarzinger, Tabassome Simon, Yazdan Yazdanpanah.

**Contributors** JK: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis. LB: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. FC: analysis and interpretation of data, critical revision of the manuscript for important intellectual content. NNA: analysis and interpretation of data, critical revision of the manuscript for important

intellectual content. TJ: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. MS: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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**Patient consent** All data used in this study only contained anonymous patient records.

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