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Abbreviations used in this paper: IBD, Inflammatory Bowel Diseases; CD, Crohn's Disease; UC, Ulcerative Colitis; LTDs, Long-Term Diseases; anti-TNF, anti-Tumor Necrosis Factor agents; SNDS, Système National des Données de Santé; ATC, Anatomical Therapeutic Chemical; ICD-10, International Classification of Diseases, 10th edition; CCAM, French Common Classification of Medical Procedures; PY, Person-Years

ABSTRACT

Background and aims: Patients with inflammatory bowel disease (IBD) are at increased risk of acute arterial events. Treatment with anti-tumor necrosis factor agents (anti-TNF) has been associated with a protective effect against the first occurrence of acute arterial events, but the impact of treatment with anti-TNF in patients with a previous history of acute arterial events has not been assessed until now. We assessed the effect of anti-TNF and thiopurines on the risk of recurrent acute arterial events in patients with IBD in a nationwide cohort.

Methods: Based on the French nationwide health insurance database, patients with IBD and a previous history of an acute arterial event were followed from January 1, 2009 until December 31, 2018. The risk of acute arterial event recurrence associated with anti-TNF and thiopurines exposures was assessed using marginal structural Cox proportional hazard models adjusted for baseline and time-varying covariates.

Results: A total of 27 185 patients were included. During 121 822 person-years (median follow-up 4.0 years), 6 865 recurrent acute arterial events occurred (incidence rate per 1000 person-years, 56.4; 95% CI, 55.0-57.7). Both exposure to anti-TNF and thiopurines were associated with a decreased risk of recurrent acute arterial events compared to the absence of exposure to either treatment (HR 0.75; 95% CI 0.63-0.90 and HR 0.76; 95% CI 0.66-0.88, respectively).

Conclusions: In a nationwide cohort study of patients with IBD and a previous history of acute arterial event, both exposure to anti-TNF and thiopurines were associated with a decreased risk of recurrent acute arterial events.

Keywords: Inflammatory bowel disease; cardiovascular risk; anti-TNF; thiopurines.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic, systemic, relapsing and remitting inflammatory disorders which include Crohn's disease (CD) and ulcerative colitis (UC).[1] Several studies have highlighted an increased risk of acute arterial events (cerebrovascular disease, ischaemic heart disease, and peripheral artery disease) in patients with IBD compared to the general population.[2,3] This increased risk may be driven by the contribution of chronic systemic inflammation to atherosclerosis,[4] as well as disease activity which has been identified as an independent risk factor for acute arterial events.[3,5] Additionally, systemic inflammation is now considered to be a therapeutic target in cardiovascular diseases,[6] and use of IBD treatments may be associated with reduced acute arterial events in patients with IBD due to their anti-inflammatory properties. A nationwide French cohort study evaluating the impact of anti-TNF and thiopurines for primary prevention found exposure to anti-TNF to be associated with a decreased risk of acute arterial events, while the risk reduction associated with thiopurines exposure was at the limits of statistical significance.[7] However, that study excluded patients with a previous history of acute arterial events and other cardiovascular diseases, yet these patients may be at the highest cardiovascular risk and may particularly benefit from a potential protective effect. Notably, acute myocardial infarction recurrence after a first event affects approximately one in eight men and one in seven women within five years,[8] and stroke recurrence affects one in ten patients within five years.[9] To our knowledge, no study has specifically evaluated the impact of IBD treatments for the secondary prevention of acute arterial events in patients with IBD. The aim of this study was to assess the impact of anti-TNF and thiopurines exposures on the risk of recurrent acute arterial events in patients with IBD and a previous history of an acute arterial event.

METHODS

Data sources

We used the French administrative health databases 2006-2018 (*Système national des données de santé* [SNDS], which includes the French hospital discharge database (PMSI), to conduct a French nationwide cohort study. The SNDS includes details of clinical management such as prescriptions (indexed by Anatomical Therapeutic Chemical [ATC] codes), medical and surgical procedures, and diagnoses (indexed by International Classification of Diseases, 10th edition [ICD-10]). Three classifications of hospital discharge diagnoses are registered: the 'main' diagnosis is the reason for hospital admission, the 'related' diagnosis is a disease underlying the main diagnosis, and 'associated' diagnoses are other comorbidities. Chronic disease diagnoses that have been approved by a physician for complete reimbursement of related healthcare costs are designated 'long-term diseases' (LTDs).

Study population

The study population included all patients aged 18 years or older identified with IBD based on listed LTDs and/or main or related discharge diagnosis related to CD or UC, and with a previous history of an acute arterial event (ischaemic heart disease, cerebrovascular disease, or peripheral artery disease) based on listed LTDs and/or main, related, or associated discharge diagnosis, and/or medical procedures before January 1, 2018 from the SNDS). IBD diagnosis was adapted from a previously published definition applied in the SNDS, shown to produce treatment exposure, hospitalization, and surgery rates similar to current standard of care.[10] If a patient had multiple hospitalizations with ICD-10 codes related to both CD and UC, the most recent diagnosis at cohort entry was retained for IBD subtype classification. The date of IBD diagnosis was defined as the earliest of either the starting date

of the LTD status or the first date of hospitalization discharge related to IBD. See Supplementary Table 1 for inclusion criteria, ICD-10 and procedure codes.

Follow-up

All the patients had both an IBD diagnosis and a first acute arterial event at cohort entry. They were followed from the date of latest of the two diagnoses, or from January 1, 2009 if both occurred before this date. If the first acute arterial event occurred after January 1, 2009 and after IBD diagnosis, a 3-month gap between first acute arterial event diagnosis and cohort entry was introduced to reduce misclassification between a first event-related intervention and a real recurrent event. The date of cohort entry was limited to January 1, 2018, so each patient was followed for at least one year. Patients were followed until recurrence of an acute arterial event (either identical or different from the previous history), loss to follow-up, death, or the end of the study (December 31, 2018), whichever occurred first. In case of loss to follow-up, the end of follow-up was the last known contact date, defined as the last claim in the database. Graphical visualization of the cohort study design is available in Supplementary Figure 1.

Drug exposure

Exposure to anti-TNF (including infliximab, adalimumab, and golimumab) or thiopurine (azathioprine and mercaptopurine) was assessed at cohort entry and during follow-up. Patients who received adalimumab, golimumab, or thiopurines were considered exposed for one month following delivery, those who received infliximab were considered exposed for two months following the infusion. Treatment withdrawal was defined by a period of at least three months, after the last day of exposure, without any new treatment delivery. See Supplementary Table 2 for IBD treatments related ATC codes.

Outcomes

The primary outcome was the recurrence of any acute arterial event subtype leading to hospitalization, including ischaemic heart disease, cerebrovascular disease, or peripheral artery disease. These diagnoses were identified as the main discharge diagnosis and/or medical procedures. We did not use LTDs since these codes could be related to the patient's first acute arterial event. We did not include acute mesenteric ischaemia, since local intestinal inflammation rather than systemic inflammation may be associated with acute mesenteric ischaemia in patients with IBD.[11] The secondary outcomes were each individual subtype separately assessed. See Supplementary Table 3 for outcomes related ICD-10 and procedure codes.

Covariates

Time-fixed covariates presented in Table 1 were assessed at cohort entry and included: sex; age; socio-economic status (coverage of universal complementary healthcare insurance available for people with low annual income); IBD subtype (CD or UC); IBD disease duration; exposure to methotrexate, oral aminosalicylates, thiopurines, and anti-TNF within the previous six months; exposure to oral corticosteroids within the previous three months; IBD-related endoscopy (lower or upper), gastrointestinal imaging, hospitalization ≥ 24h, and surgery related to IBD within the last year; exposure to anticoagulants or antiplatelets within the previous six and three months, respectively. We also assessed various comorbidities with potential cardiovascular impact (chronic pulmonary, kidney, and liver diseases; rheumatic diseases: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis; cancer; venous thromboembolism; serious infection; heart failure; atrial fibrillation; cardiomyopathy; cardiac or vascular prosthesis, implant or graft; and atherosclerosis), traditional cardiovascular risk factors (arterial hypertension, dyslipidemia, diabetes, obesity, smoking behavior, and chronic

alcohol abuse), and history of acute arterial events. Of note, patients with a previous history of acute arterial events before January 1, 2009 could have been diagnosed with more than one subtype of acute arterial events. Duration since the first acute arterial event was also evaluated at cohort entry.

Time-varying covariates were assessed at 3-month intervals throughout follow-up. These included: surrogate markers of severe IBD activity (including exposure to corticosteroids and occurrence of IBD-related hospitalization or surgery) and exposure to antiplatelet drugs. Covariates were identified using all available listed LTDs, main, related, or associated discharge diagnosis, medical procedures, and drug reimbursements. Only the main discharge diagnoses were used to identify a hospitalization related to IBD activity or serious infection. See Supplementary Table 1 for covariates related ICD-10, procedure, and ATC codes and Supplementary Table 2 for IBD treatments related ATC codes.

Statistical analysis

Descriptive analysis

Descriptive analysis of patients' characteristics at cohort entry were performed according to subsequent treatment exposure (unexposed to anti-TNF and thiopurines, or exposed to anti-TNF and/or thiopurines at least once), and according to subsequent occurrence of recurrent acute arterial event during follow-up. Incidence rates of recurrent acute arterial events according to treatment exposure were estimated during follow-up. As patients could have been exposed successively to different treatment sequences, they could have therefore contributed follow-up time to more than one exposure classification. Cumulative incidences of recurrent acute arterial events were estimated for the whole cohort and also separately for patients entering the cohort three months after the first acute arterial event.

Outcome model

Marginal structural Cox proportional hazard models adjusted for all the time-fixed and time-dependent covariates were used to estimate the risk of acute arterial event recurrence associated with exposures to anti-TNF and thiopurines, both compared to the absence of exposure to either medication.[12] The use of marginal structural models is appropriate in the presence of time-varying cofounders that are associated with both subsequent exposure and outcomes, and that are also affected by past exposure, such as disease activity in our study. Time-varying inverse probability treatment weighting and time-varying inverse probability censoring weighting were used.[13] Since anti-TNF and thiopurines may be used as combination therapy in clinical practice, an interaction term was introduced in the outcome model between anti-TNF and thiopurines exposures to provide unbiased estimates for each drug class.[14] The impact of combination therapy, defined as concomitant exposure to anti-TNF and thiopurines, on the risk of acute arterial event recurrence was additionally assessed. More details of the applied statistical method are provided in the Supplemental methods.

Subgroup and sensitivity analyses

In subgroups analyses, the cohort was stratified by IBD subtype, sex, and age at cohort entry (< 55 or ≥ 55 years of age), as cardiovascular risk may differ with these key characteristics. Several sensitivity analyses were performed to test the robustness of the results, including restricting to patients with incident IBD diagnosis, to new users only, to patients included three months after the first acute arterial event, excluding patients with heart failure, and censoring at initiation of other biologics or small molecules. We performed analyses evaluating the risk of acute arterial events either different from or identical to the subtype of the previous event. See Supplementary Methods for details of these and further sensitivity analyses.

The study was approved by the French Data Protection Agency. All data were obtained from anonymized patient records. The statistical analyses were performed with SAS (V.9.4) statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the cohort

Our nationwide cohort of patients with IBD comprised 305 911 individuals, 27 185 (8.9%) of whom had a previous history of an acute arterial event.

During follow-up, 22 496 (82.8%) patients were unexposed to anti-TNF and thiopurines, while 2 578 (9.5%) and 3 157 (11.6%) were exposed to anti-TNF and thiopurines at least once, accounting for 7 435 person-years (PY), and 8 763 PY of follow-up, respectively (Table 1 and 2). The median duration of follow-up was 4.0 years (IQR 2.0-6.8). Combination therapy was prescribed to 147 (0.5%) patients during follow-up, accounting for 1 108 PY. Overall, the mean age of patients was 66.2 years (SD 14.2), 61.7% were men, and 63.4% were diagnosed with ulcerative colitis. Mean duration of IBD at cohort entry was 5.8 years (SD 7.2). Unexposed patients were older compared to patients exposed to anti-TNF or thiopurines, with a mean age of 67.8 years (SD 13.7), 56.6 years (SD 14.1), and 58.9 years (SD 14.1), respectively. The majority of unexposed patients were diagnosed with UC (67.3%), while CD was predominant in patients exposed to anti-TNF (59.0%) or exposed to thiopurines (51.4%). The most common previous acute arterial event was ischaemic heart disease (66.2%), followed by cerebrovascular disease (26.9%), and peripheral artery disease (14.7%). Mean duration since first acute arterial event at cohort entry was 3.1 years (SD 4.9).

Among patients with a recurrent acute arterial event, a higher proportion were male (69.1%) compared to patients without recurrent event (59.2%). As expected, prevalence of

traditional cardiovascular risk factors was higher in patients with recurrent event, especially for arterial hypertension, dyslipidemia, and diabetes (Supplementary Table 4).

Incidence rates of recurrent acute arterial events

Overall, 6 865 new acute arterial events occurred during follow-up representing a crude incidence rate of 56.4 (95% CI 55.0-57.7) events per 1000 PY (Table 2). Most of these events were ischaemic heart disease (56.7%), followed by peripheral artery disease (22.7%) and cerebrovascular disease (20.6%). Among the overall cohort, the cumulative incidence of recurrent acute arterial events after five years of follow-up was 24.8% (95% CI 24.2-25.4). The cumulative incidence rates after five years of follow-up for ischaemic heart disease, cerebrovascular disease, and peripheral artery disease, were 15.0% (95% CI 14.5-15.5), 5.6% (95% CI 5.2-5.9), and 6.3% (95% CI 6.0-6.7), respectively (Supplementary Figure 2).

Risk of recurrent acute arterial events associated with IBD treatments

Both anti-TNF and thiopurines were associated with a decreased risk of recurrent acute arterial events (HR 0.75; 95% CI 0.63-0.90 and HR 0.76; 95% CI 0.66-0.88, respectively) (Figure 1). Anti-TNF and thiopurines tended also to be associated with a decreased risk of ischaemic heart disease, cerebrovascular disease, and peripheral artery disease separately (Figure 1). Exposure to combination therapy tended to be associated with a decreased risk of recurrent acute arterial events although it did not reach statistical significance (HR, 0.77; 95% CI 0.55-1.09).

In subgroup analyses, the magnitude of risk reduction was similar for men and women for both exposure to anti-TNF and thiopurines (Figure 2). The magnitude of risk reduction was more pronounced for patients aged 18-54 years compared to patients aged ≥ 55 years under anti-TNF exposure, while it was similar between the two age categories under thiopurines exposure. Regarding IBD subtype, the trend for risk reduction was more

pronounced for patients with CD under anti-TNF exposure, while it was more pronounced for patients with UC under thiopurines exposure (Figure 2).

The results remained similar in sensitivity analyses (Supplementary Table 5). Analysis restricted to patients starting follow-up three months after the first acute arterial event were consistent with the main analysis (Supplementary Figure 3). Differences in risk reduction associated with anti-TNF or thiopurines according to the subtype of first or recurrent acute arterial events were minimal (Supplementary Figure 4).

DISCUSSION

Based on a nationwide population-based cohort of patients with IBD and a previous history of acute arterial event, our findings suggest a reduced risk for all recurrent acute arterial events associated with both exposure to anti-TNF (HR 0.75), and thiopurines (HR 0.76). Results were not substantially altered in sensitivity analyses. Our study also highlighted the high risk of recurrent acute arterial events in this population, with 24.8% of patients experiencing a recurrent acute arterial event within 5 years.

To our knowledge, no study had previously assessed the risk of subsequent acute arterial events according to treatment exposures in patients with IBD, while few studies assessed the risk of primary acute arterial event according to IBD treatments. A cohort study based on US claims data including patients with CD reported a decreased risk of major adverse cardiovascular events and a reduced risk of death associated with anti-TNF exposure compared to prolonged corticosteroids exposure.[15] A previous nationwide French cohort study reported a decreased risk of a first acute arterial event in patients with IBD and exposed to anti-TNF, however, exposure to thiopurines was not associated with a significantly decreased risk.[7] Our finding of a protective effect of anti-TNF exposure on acute arterial risk is consistent with the previous French study, whereas the beneficial effect of thiopurines exposure suggested in the present study may be related to the higher baseline cardiovascular risk in the population included.

Subgroup analyses revealed that the trend for risk reduction under anti-TNF exposure was similar for both men and women. However, the previous French study evaluating impact of IBD treatments for primary prevention showed a beneficial effect of anti-TNF exposure predominantly in men compared with women, explained by the hypothesis of a more severe IBD prognosis in male patients resulting in a higher acute arterial risk.[7,16,17] Our latest results suggest that previous history of acute arterial events may have a more pronounced impact

on global cardiovascular risk than patient's sex. Considering IBD subtype and age, we found a more pronounced risk reduction in patients with CD compared with patients with UC, and in patients aged 18-54 years compared with those aged ≥ 55 years, under anti-TNF exposure. This was similar to previous findings,[7] and may be related to higher systemic inflammation in CD,[18,19] and more traditional risk factors in older patients that outweigh the role of IBD in acute arterial events occurrence.

This study has several strengths. First, our study was based on a nationwide cohort of French patients with IBD. From this cohort, we included 27 185 patients with IBD and a previous history of acute arterial events, which provided adequate statistical for power subgroup and sensitivity analyses. Second, the SNDS provided a rich source of medical information which enabled us to adjust for many baseline covariates, either related to IBD or with potential cardiovascular impact. As corticosteroids and disease activity are associated with an increased risk of acute arterial events,[3,15,20] and both may be associated with past and future IBD treatments, we adjusted on these parameters as time-varying covariates in marginal structural Cox proportional hazard models to assess the unbiased effect of treatments.[12] Third, the median follow-up of patients was four years, which allowed medium term assessment of recurrent acute arterial events.

Relevant limitations to this study include the use of disease definitions that were not previously validated, hence interpretation of the results should be tentative. Nevertheless, the definition of IBD diagnosis was similar to a definition applied in other studies using the SNDS.[7,10,21,22] Moreover, the method to identify acute arterial events produced crude incidence rates of recurrent events consistent with other studies: in a trial including patients with previous myocardial infarction, incidence rates for new nonfatal myocardial infarction and for nonfatal stroke in the placebo group were 24.3 per 1000 PY and 7.4 per 1000 PY, respectively),[6] and in a Scottish population-based cohort study of patients with rheumatoid

arthritis and a previous history of cardiovascular diseases the incident rate of new nonfatal myocardial infarction was 14.1 per 1000 PY in patients exposed to statins and 38.5 per 1000 PY in unexposed patients.[23]

Further limitations include incomplete data in the SNDS on factors such as tobacco smoking, obesity, and chronic alcohol abuse, and their prevalence may have been underestimated. Some behavioral factors with cardiovascular impact such as sedentary lifestyle, physical inactivity, or medication adherence to secondary prevention treatments were also not available. It has been identified that smoking reduces the risk of UC occurrence while increasing the risk of CD occurrence, and disease activity in patients with CD.[1] Additionally, patients with CD treated with thiopurines or anti-TNF are more likely to be smokers compared with patients not exposed to these drugs.[1] Thus, it is likely that underestimation of tobacco smoking does not alter the association between IBD treatments and the protective effect observed. Acute arterial events identified during follow-up might be related to the first acute arterial event rather than to an authentic recurrence in patients among whom the subtype of acute arterial event at cohort entry and during follow-up were similar. However, sensitivity analyses assessing the impact of treatments according to the subtype of first and recurrent acute arterial events, and analyses with reduction of the time interval between the first acute arterial event and cohort entry, all provided consistent results. As our data covered hospital discharge diagnoses, it was not possible to identify acute arterial events leading to sudden death outside of the hospital, so further studies are required to address this question. Finally, we were not able to differentiate disease control from an independent effect of thiopurines and anti-TNF by themselves, since disease activity is poorly captured in administrative healthcare databases. Further studies including clinical and biological data are required.

In summary, we observed that recurrent acute arterial events were substantial in patients with IBD and a previous history of such events. Both exposure to anti-TNF and thiopurines were associated with a protective effect on the risk of recurrent acute arterial events. This study provides new data for the benefit–risk assessment of anti-TNF and thiopurines in patients with IBD and a previous history of acute arterial event.

FIGURE LEGENDS

Figure 1: Multivariable adjusted hazard ratios for recurrent acute arterial events according to medication exposure periods

Figure 2: Multivariable adjusted hazard ratios for recurrent acute arterial events according to medication exposure periods: subgroup analyses according to IBD subtype, sex, and age

TABLE LEGENDS

Table 1: Patients' characteristics at cohort entry according to subsequent treatment exposure during follow-up

Table 2: Incidence of recurrent acute arterial events according to medication exposure

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Table 1: Patients' characteristics at cohort entry according to subsequent treatment exposure during follow-up

Characteristics	Unexposed to anti-TNF and thiopurines (n = 22 496, 82.7%)	Exposed to anti-TNF [a] (n = 2 578, 9.5%)	Exposed to thiopurines [a] (n = 3 157, 11.6%)	Total (n = 27 185)
Age at cohort entry (years), mean (SD)	67.8 (13.7)	56.6 (14.1)	58.9 (14.1)	66.2 (14.2)
Male sex, n (%)	13 784 (61.3)	1 573 (61.0)	2 073 (65.7)	16 767 (61.7)
Complementary universal health insurance, n (%) [b]	1 606 (7.1)	311 (12.1)	323 (10.2)	2 103 (7.7)
IBD subtype, n (%)				
Crohn's disease	7 366 (32.7)	1 521 (59.0)	1 623 (51.4)	9 937 (36.6)
Ulcerative colitis	15 130 (67.3)	1 057 (41.0)	1 534 (48.6)	17 248 (63.4)
IBD disease duration at cohort entry (years), mean (SD)	5.7 (7.2)	6.3 (7.4)	6.6 (7.3)	5.8 (7.2)
IBD drugs, n (%) [c]				
Methotrexate	279 (1.2)	138 (5.4)	25 (0.8)	429 (1.6)
Aminosalicylates (oral)	6 694 (29.8)	929 (36.0)	1 235 (39.1)	8 448 (31.1)
Thiopurines	138 (0.6)	434 (16.8)	1 614 (51.1)	1 829 (6.7)
Anti-TNF	85 (0.4)	1 028 (39.9)	246 (7.8)	1 129 (4.2)
Corticosteroids (oral)	2 532 (11.3)	593 (23.0)	714 (22.6)	3 585 (13.2)
IBD assessment, n (%) [c]				
Gastrointestinal endoscopy				
Upper	3 712 (16.5)	570 (22.1)	615 (19.5)	4 665 (17.2)
Lower	7 288 (32.4)	1 229 (47.7)	1 357 (43.0)	9 354 (34.4)
Imaging studies	7 013 (31.2)	1 045 (40.5)	975 (30.9)	8 642 (31.8)
Complications related to IBD before cohort entry, n (%) [c]				
Surgery related to IBD	601 (2.7)	144 (5.6)	108 (3.4)	801 (2.9)
Hospitalization related to IBD > 24 hours	4 449 (19.8)	631 (24.5)	583 (18.5)	5 428 (20.0)
Comorbidities, n (%)				
Chronic pulmonary disease	11 577 (51.5)	1 275 (49.5)	1 429 (45.3)	13 799 (50.8)
Chronic kidney disease	2 180 (9.7)	135 (5.2)	162 (5.1)	2 443 (9.0)
Chronic liver disease	572 (2.5)	62 (2.4)	70 (2.2)	681 (2.5)
Rheumatic disease				
Rheumatoid arthritis	528 (2.3)	136 (5.3)	49 (1.6)	693 (2.5)
Ankylosing spondylitis	544 (2.4)	301 (11.7)	110 (3.5)	901 (3.3)
Psoriatic arthritis	233 (1.0)	124 (4.8)	49 (1.6)	383 (1.4)
Cancer	4 624 (20.6)	295 (11.4)	326 (10.3)	5 158 (19.0)
Venous thromboembolism	1 491 (6.6)	197 (7.6)	235 (7.4)	1 857 (6.8)
Serious infection	3 235 (14.4)	311 (12.1)	296 (9.4)	3 751 (13.8)
Heart failure	3 294 (14.6)	195 (7.6)	278 (8.8)	3 703 (13.6)
Atrial fibrillation	4 771 (21.2)	293 (11.4)	416 (13.2)	5 370 (19.8)
Cardiomyopathy	1 452 (6.5)	112 (4.3)	145 (4.6)	1 673 (6.2)
Cardiac or vascular prosthesis, implant or graft	1 579 (7.0)	90 (3.5)	102 (3.2)	1 744 (6.4)
Atherosclerosis	3 503 (15.6)	283 (11.0)	394 (12.5)	4 075 (15.0)
History of acute arterial event, n (%)				
Ischaemic heart disease	15 079 (67.0)	1 552 (60.2)	2 011 (63.7)	18 007 (66.2)
Cerebrovascular disease	6 031 (26.8)	748 (29.0)	843 (26.7)	7 311 (26.9)
Peripheral artery disease	3 253 (14.5)	397 (15.4)	477 (15.1)	3 988 (14.7)
Duration since first acute arterial event (years), mean (SD)	3.2 (5.0)	2.4 (4.0)	2.7 (4.5)	3.1 (4.9)
Traditional cardiovascular risk factors, n (%)				
Arterial hypertension	19 773 (87.9)	1 960 (76.0)	2 525 (80.0)	23 490 (86.4)
Dyslipidemia	17 041 (75.8)	1 671 (64.8)	2 223 (70.4)	20 258 (74.5)
Diabetes	5 973 (26.6)	516 (20.0)	697 (22.1)	7 000 (25.7)
Obesity	3 534 (15.7)	396 (15.4)	457 (14.5)	4 241 (15.6)
Smoking behavior	4 852 (21.6)	797 (30.9)	840 (26.6)	6 171 (22.7)
Chronic alcohol abuse	1 772 (7.9)	170 (6.6)	168 (5.3)	2 054 (7.6)
Exposure to antiplatelet drugs, n (%) [c]	14 680 (65.3)	1 503 (58.3)	1 948 (61.7)	17 521 (64.5)
Exposure to anticoagulants, n (%) [c]	4 829 (21.5)	503 (19.5)	622 (19.7)	5 775 (21.2)

[a] Patients exposed to more than one exposure group during follow-up were considered in each corresponding group.
[b] Free access to healthcare for people with an annual income <50% of poverty threshold.
[c] As registered within 6 months before cohort entry (except for corticosteroids and antiplatelet drugs [within 3 months]) and IBD assessment and complications [within 1 year]).
Abbreviation: TNF, Tumor Necrosis Factor

Table 2: Incidence of recurrent acute arterial events according to medication exposure

	Total 121 822 PY		**Unexposed to anti-TNF and thiopurines* 106 732 PY**		**Exposed to anti-TNF [a] 7 435 PY**		**Exposed to thiopurines [a] 8 763 PY**	
	Events	IR [b] (95% CI)	Events	IR [b] (95% CI)	Events	IR [b] (95% CI)	Events	IR [b] (95% CI)
All acute arterial events	6 865	56.4 (55.0-57.7)	6 221	58.3 (56.9-59.8)	291	39.1 (34.9-43.9)	396	45.2 (41.0-49.9)
Ischaemic heart disease	3 894	32.0 (31.0-33.0)	3 507	32.9 (31.8-34.0)	178	23.9 (20.7-27.7)	234	26.7 (23.5-30.4)
Cerebrovascular disease	1 416	11.6 (11.0-12.2)	1 312	12.3 (11.6-13.0)	47	6.3 (4.8-8.4)	65	7.4 (5.8-9.5)
Peripheral artery disease	1 555	12.8 (12.1-13.4)	1 402	13.1 (12.5-13.8)	66	8.9 (7.0-11.3)	97	11.1 (9.1-13.5)

[a] As patients could have been exposed successively to different treatment sequences, they could have therefore contributed follow-up time to more than one exposure classification.
[b] Incidence rates per 1000 person-years
Abbreviations: PY, person-years; TNF, Tumor Necrosis Factor

Figure 1: Multivariable adjusted hazard ratios for recurrent acute arterial events according to medication exposure periods

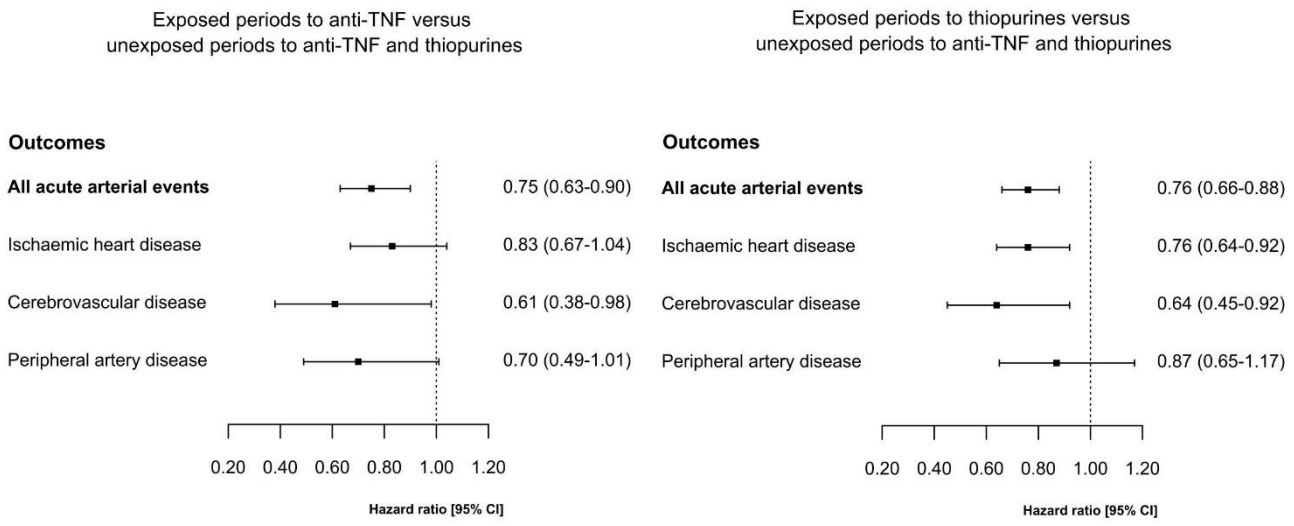
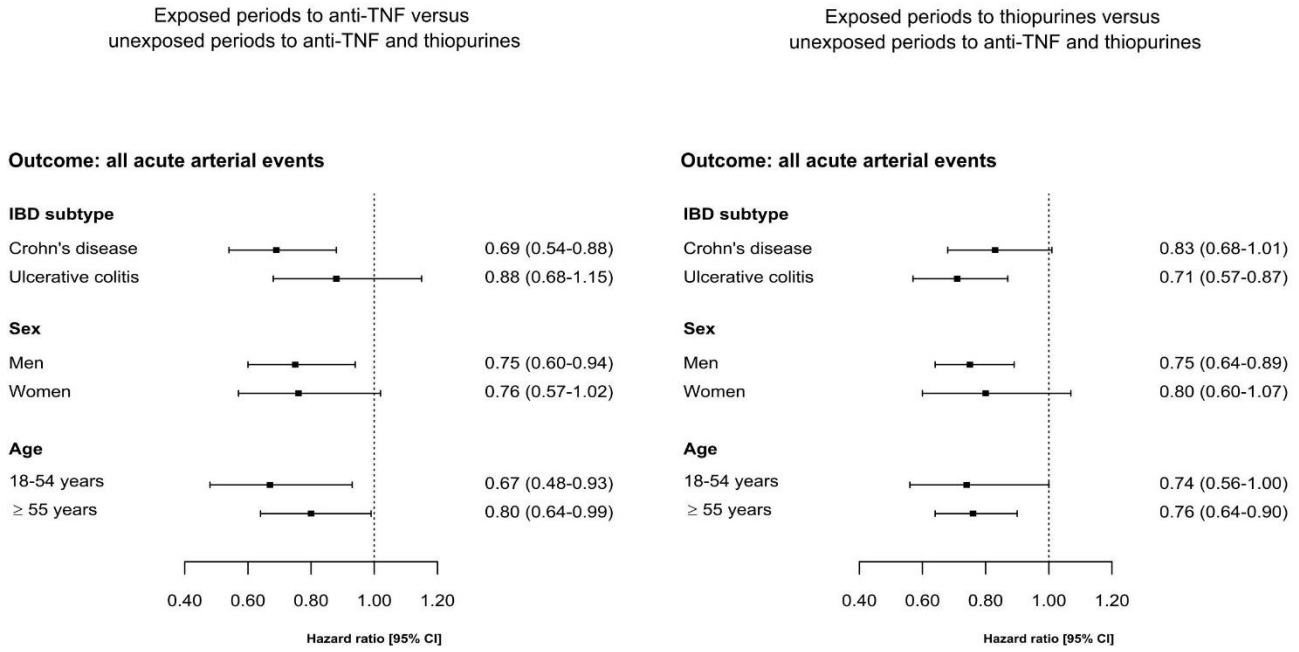


Figure 2: Multivariable adjusted hazard ratios for recurrent acute arterial events according to medication exposure periods: subgroup analyses according to IBD subtype, sex, and age



SUPPLEMENTAL MATERIAL

Supplementary Table 1: Codes used to define inclusion criteria and covariates

Inclusion criteria and covariates	ICD-10 codes	French Medical Common Procedure Coding System (CCAM)	Anatomical Therapeutic Chemical (ATC) Classification system code
Inclusion criteria			
IBD	K50, K51		
History of acute arterial event			
Ischaemic heart disease	I20, I21, I22, I23, I24, I25	Coronary catheterization with arterial dilation; CABG	
Cerebrovascular disease	G45, G46, I60, I61, I62, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9, I64	Cerebral angiography with arterial dilation or embolization	
Peripheral artery disease	I74	Angiography (excluding coronary catheterization and cerebral angiography and mesenteric angiography) with arterial dilation; Peripheral artery bypass	
Covariates			
Comorbidities			
Chronic pulmonary disease	J40, J41, J42, J43, J44, J45, J46, J47, J96.1		R03AC, R03AK, R03AL, R03B, R03D
Chronic kidney disease	I12, I13, N18, N19, Y84.1, Z49, Z99.2	JVJB001, JVJF004, JVJF008	
Chronic liver disease	I82.0, I85, I86.4, I98.2, I98.3, K70.0, K70.1, K70.3, K70.4, K71.1, K71.7, K72.1, K72.9, K74.1, K74.3, K74.4, K74.5, K74.6, K75.9, K76.4, K76.6, K76.7		
Rheumatic disease			
Rheumatoid arthritis	M05, M06, M08, M09		
Ankylosing spondylitis	M45, M46		
Psoriatic arthritis	M07		
Cancer	C0-C9, D63.0, E88.3, G53.3, G55.0, G63.1, G73.2, G94.1, J70.0, J70.1, K52.0, K62.7, L58.0, L58.1, L59.8, L59.9, M36.0, M36.1, M90.6, M90.7, M96.2, M96.5, N30.4, O35.6, Z08, Z51.1, Z54.2, Z85	Chemotherapy and radiotherapy	
Venous thromboembolism	I26, I80, I81, I82, O22.3, O22.9, O87.1, O88.2		
Serious infection	A00-A08, A15-A28, A31, A32, A34-A40, A41.0-A41.8, A42-A49, A51-A56, A60, A65-A69, A75-A89, A92-A96, A98, A99, B00.1-B00.9, B01, B02, B05, B06, B08, B09, B15, B17, B25-B83, B95-B97, B99, G00-G02, G04.0-G04.2, G05-G07, H00, H03.0, H03.1, H06.1, H13.1, H19.1, H19.2, H60.0-H60.3, H65.1, H66, H68.0, H70, I30.1, I33.0, J39.0, J39.1, I98.0, J01-J22, J36, J85, J86, K11.3, K12.2, K23.0, K23.80, K23.81, K67.3, K75.0, K80.0, K80.3, K80.4, K81.0, K83.0, K87.00, K93.0, K93.820, L00-L08, L30.3, M00, M01, M49.0, M60.0, M72.6, M86, M90.0, N10, N30.0, N33.0, N39.0, N41.0, N41.2, N41.3, N45, N70.0, N73.3, N74.0, N74.1, N77.1, R57.2, R65.0, R65.1, T82.6, T82.7, T84.5-T84.7, T85.7, U04		
Heart failure	I11.0, I13.0, I13.2, I50, K76.1		
Atrial fibrillation	I47.1, I48, I49		
Cardiomyopathy	I42, I43		
Cardiac or vascular prosthesis, implant or graft	T82.0, T82.3, T82.6, T82.7, Z45.0, Z95.0, Z95.2, Z95.3, Z95.4		
Atherosclerosis	I70		
History of acute arterial event			
Ischaemic heart disease	I20, I21, I22, I23, I24, I25	Coronary catheterization with arterial dilation; CABG	
Cerebrovascular disease	G45, G46, I60, I61, I62, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9, I64	Cerebral angiography with arterial dilation or embolization	
Peripheral artery disease	I74	Angiography (excluding coronary catheterization and cerebral angiography and mesenteric angiography) with arterial dilation; Peripheral artery bypass	
Traditional cardiovascular risk factors			
Arterial hypertension	I10, I11, I12, I13, I15		C02, C03, C07, C08, C09
Dyslipidemia	E78.0, E78.1, E78.2, E78.3, E78.4, E78.5		C10

Diabetes	E10, E11, E12, E13, E14, G59.0, G63.2, H28.0, H36.0, I79.2, M14.2, N08.3		A10
Obesity	E66		A08AB, A08AX
Smoking behavior	F17, J41, J42, T65.2, Z71.6, Z72.0		N07BA
Chronic alcohol abuse	E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, O35.4, T51, X45, X65, Y15, Z50.2, Z71.4		N07BB
Exposure to antiplatelet drugs			B01AC04, B01AC05, B01AC06, B01AC07, B01AC16, B01AC17, B01AC22, B01AC24, B01AC25, B01AC30
Exposure to anticoagulants			B01AA, B01AB, B01AF, B01AE03, B01AE07
IBD-related endoscopy			
Lower gastrointestinal endoscopy		HGQD002, HHAE001, HHEE001, HHFC001, HHFE001, HHFE002, HHFE004, HHFE005, HHFE006, HHGE002, HHJE001, HHLH001, HHNE001, HHNE002, HHNE003, HHNE004, HHQE002, HHQE003, HHQE004, HHQE005, HHSE001, HHSE002, HHSE003, HHSE004, HJQE001, HJQE002, HZQE900	
Upper gastrointestinal endoscopy		HEAE001, HEAE002, HEAE003, HEAH001, HEFE001, HEFE002, HEFE003, HEGE001, HEGE002, HEGE003, HEKE001, HELE002, HELE900, HELH001, HEME900, HENE001, HENE002, HENE004, HENE900, HEQE001, HEQE002, HEQE003, HEQE005, HESE001, HESE002, HFAE001, HFAH001, HFLE001, HFLH001, HFLH002, HGFE005, HGGE001, HGKE001, HGLE001, HGNE001	
IBD-related imaging		HEQH001, HEQH002, HGQH001, HGQH002, HHQH001, ZCQH001, ZCQH002, ZCQJ004, ZCQJ005, ZCQK002, ZCQK004, ZCQK005, ZCQN001, ZCQN002	
Markers of IBD activity			
IBD-related hospitalization	K50, K51, K56, K60, K61, K62.4, K62.5, K63.0, K63.1, K63.2, K65.0, K92.2, R10		
IBD-related surgery			
Colectomy		HHFA002, HHFA004, HHFA005, HHFA006, HHFA008, HHFA009, HHFA010, HHFA014, HHFA017, HHFA018, HHFA021, HHFA022, HHFA023, HHFA024, HHFA026, HHFA028, HHFA029, HHFA030, HHFA031	
Intestinal resection		HGCA005, HGCC015, HGFA003, HGFA004, HGFA005, HGFA007, HGFC014, HGFC016, HGFC021	
Perineal surgery and minor digestive surgery		HGCA001, HGCA008, HGCC003, HGCC026, HGLA001, HHCA002, HHCA003, HHCC007, HHCC011, HKPA004, HKPA005, HKPA006, HKPA007, HKPA008, HPPA002, HPPC003, ZCJA001, ZCJA002, ZCJA004	

Abbreviation: CABG, Coronary Artery Bypass Graft Surgery

Supplementary Table 2: IBD treatments

Drugs	Anatomical Therapeutic Chemical (ATC) Classification system code
Anti-TNF	
Adalimumab	L04AB04
Infliximab	L04AB02
Golimumab	L04AB06
Thiopurines	
Azathioprine	L04AX01
Mercaptopurine	L01BB02
Methotrexate	L04AX03, L01BA01
Aminosalicylates (oral)	A07EC01, A07EC02, A07EC03
Corticosteroids (oral)	H02AB06, H02AB07
Tofacitinib	L04AA29
Ustekinumab	L04AC05
Vedolizumab	L04AA33

Supplementary Table 3: Codes used to define outcomes

Outcomes	ICD-10 codes	French Medical Common Procedure Coding System (CCAM)
Ischaemic heart disease	I20, I21, I22, I23, I24, I25	Coronary catheterization with arterial dilation; CABG
Cerebrovascular disease	G45, G46, I60, I61, I62, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9, I64	Cerebral angiography with arterial dilation or embolization
Peripheral artery disease	I74	Angiography (excluding coronary catheterization and cerebral angiography and mesenteric angiography) with arterial dilation; Peripheral artery bypass

Abbreviation: CABG, Coronary Artery Bypass Graft Surgery

Supplementary Table 4: Patients' characteristics at cohort entry according to subsequent occurrence of acute arterial event

Characteristics	Absence of recurrent acute arterial event occurrence (n = 20 320)	Recurrent acute arterial event occurrence (n = 6 865)	Total (n = 27 185)
Age at cohort entry (years), mean (SD)	65.8 (14.8)	67.4 (12.1)	66.2 (14.2)
Male sex, n (%)	12 021 (59.2)	4 746 (69.1)	16 767 (61.7)
Complementary universal health insurance, n (%) [a]	1 590 (7.8)	513 (7.5)	2 103 (7.7)
IBD subtype, n (%)			
Crohn's disease	7 459 (36.7)	2 478 (36.1)	9 937 (36.6)
Ulcerative colitis	12 861 (63.3)	4 387 (63.9)	17 248 (63.4)
IBD disease duration at cohort entry (years), mean (SD)	5.9 (7.4)	5.5 (6.9)	5.8 (7.2)
IBD drugs, n (%) [b]			
Methotrexate	309 (1.5)	120 (1.7)	429 (1.6)
Aminosalicylates (oral)	6 232 (30.7)	2 216 (32.3)	8 448 (31.1)
Thiopurines	1 368 (6.7)	461 (6.7)	1 829 (6.7)
Anti-TNF	928 (4.6)	201 (2.9)	1 129 (4.2)
Corticosteroids (oral)	2 634 (13.0)	951 (13.9)	3 585 (13.2)
IBD assessment, n (%) [b]			
Gastrointestinal endoscopy			
Upper	3 451 (17.0)	1 214 (17.7)	4 665 (17.2)
Lower	6 985 (34.4)	2 369 (34.5)	9 354 (34.4)
Imaging studies	6 424 (31.6)	2 218 (32.3)	8 642 (31.8)
Complications related to IBD before cohort entry, n (%) [b]			
Surgery related to IBD	614 (3.0)	187 (2.7)	801 (2.9)
Hospitalization related to IBD > 24 hours	4 053 (19.9)	1 375 (20.0)	5 428 (20.0)
Comorbidities, n (%)			
Chronic pulmonary disease	10 344 (50.9)	3 455 (50.3)	13 799 (50.8)
Chronic kidney disease	1 695 (8.3)	748 (10.9)	2 443 (9.0)
Chronic liver disease	527 (2.6)	154 (2.2)	681 (2.5)
Rheumatic disease			
Rheumatoid arthritis	524 (2.6)	169 (2.5)	693 (2.5)
Ankylosing spondylitis	683 (3.4)	218 (3.2)	901 (3.3)
Psoriatic arthritis	289 (1.4)	94 (1.4)	383 (1.4)
Cancer	3 889 (19.1)	1 269 (18.5)	5 158 (19.0)
Venous thromboembolism	1 467 (7.2)	390 (5.7)	1 857 (6.8)
Serious infection	2 890 (14.2)	861 (12.5)	3 751 (13.8)
Heart failure	2 687 (13.2)	1 016 (14.8)	3 703 (13.6)
Atrial fibrillation	4 090 (20.1)	1 280 (18.6)	5 370 (19.8)
Cardiomyopathy	1 214 (6.0)	459 (6.7)	1 673 (6.2)
Cardiac or vascular prosthesis, implant or graft	1 281 (6.3)	463 (6.7)	1 744 (6.4)
Atherosclerosis	2 390 (11.8)	1 685 (24.5)	4 075 (15.0)
History of acute arterial event, n (%)			
Ischaemic heart disease	12 979 (63.9)	5 028 (73.2)	18 007 (66.2)
Cerebrovascular disease	6 076 (29.9)	1 235 (18.0)	7 311 (26.9)
Peripheral artery disease	2 567 (12.6)	1 421 (20.7)	3 988 (14.7)
Duration since first acute arterial event (years), mean (SD)	2.8 (4.7)	3.7 (5.4)	3.1 (4.9)
Traditional cardiovascular risk factors, n (%)			
Arterial hypertension	17 178 (84.5)	6 312 (91.9)	23 490 (86.4)
Dyslipidemia	14 542 (71.6)	5 716 (83.3)	20 258 (74.5)
Diabetes	4 901 (24.1)	2 099 (30.6)	7 000 (25.7)
Obesity	3 140 (15.5)	1 101 (16.0)	4 241 (15.6)
Smoking behavior	4 515 (22.2)	1 656 (24.1)	6 171 (22.7)
Chronic alcohol abuse	1 487 (7.3)	567 (8.3)	2 054 (7.6)
Exposure to antiplatelet drugs, n (%) [b]	12 413 (61.1)	5 108 (74.4)	17 521 (64.5)
Exposure to anticoagulants, n (%) [b]	4 408 (21.7)	1 367 (19.9)	5 775 (21.2)

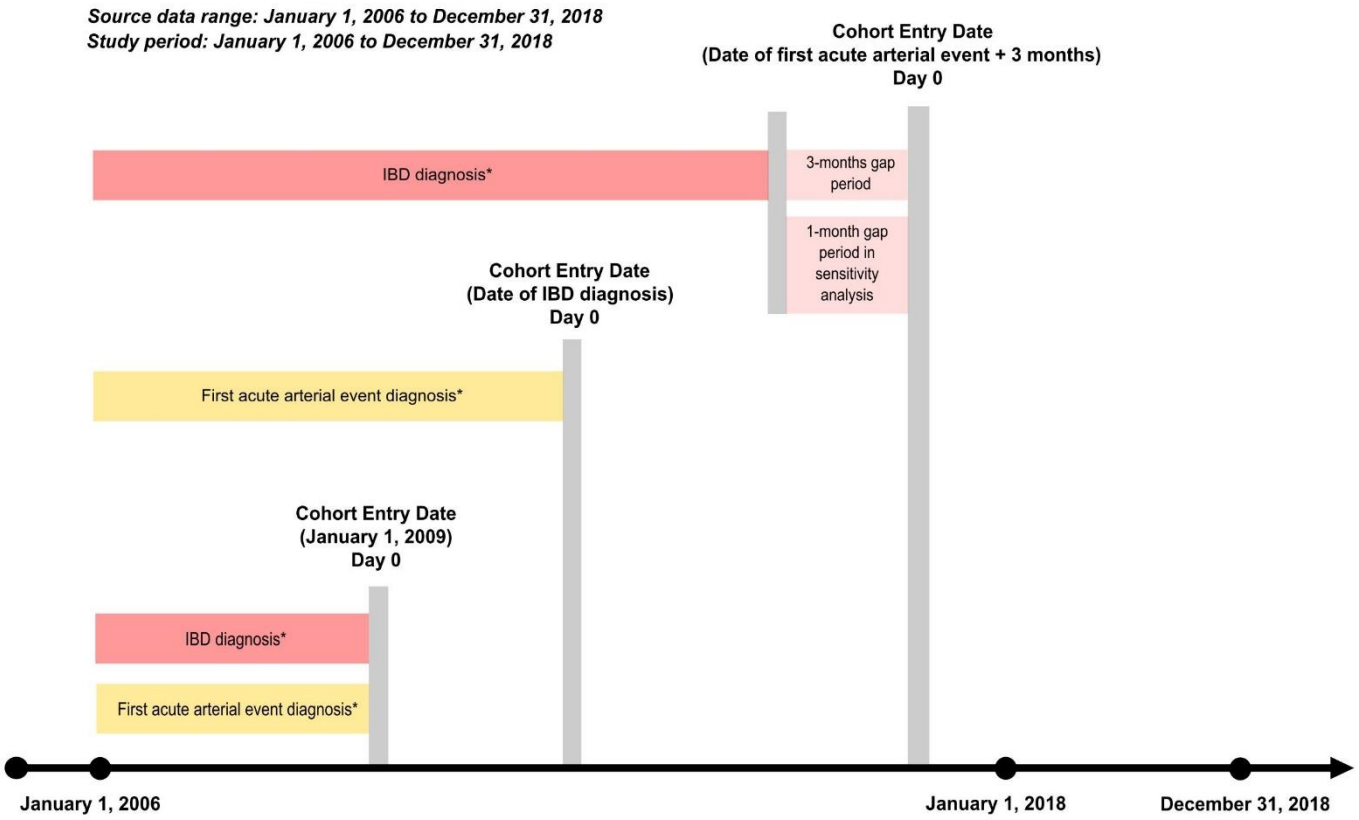
[a] Free access to healthcare for people with an annual income of <50% of poverty threshold.
[b] As registered within 6 months before cohort entry (except for corticosteroids and antiplatelet drugs [within 3 months] and IBD assessment and complications [within 1 year]).
Abbreviation: TNF, Tumor Necrosis Factor

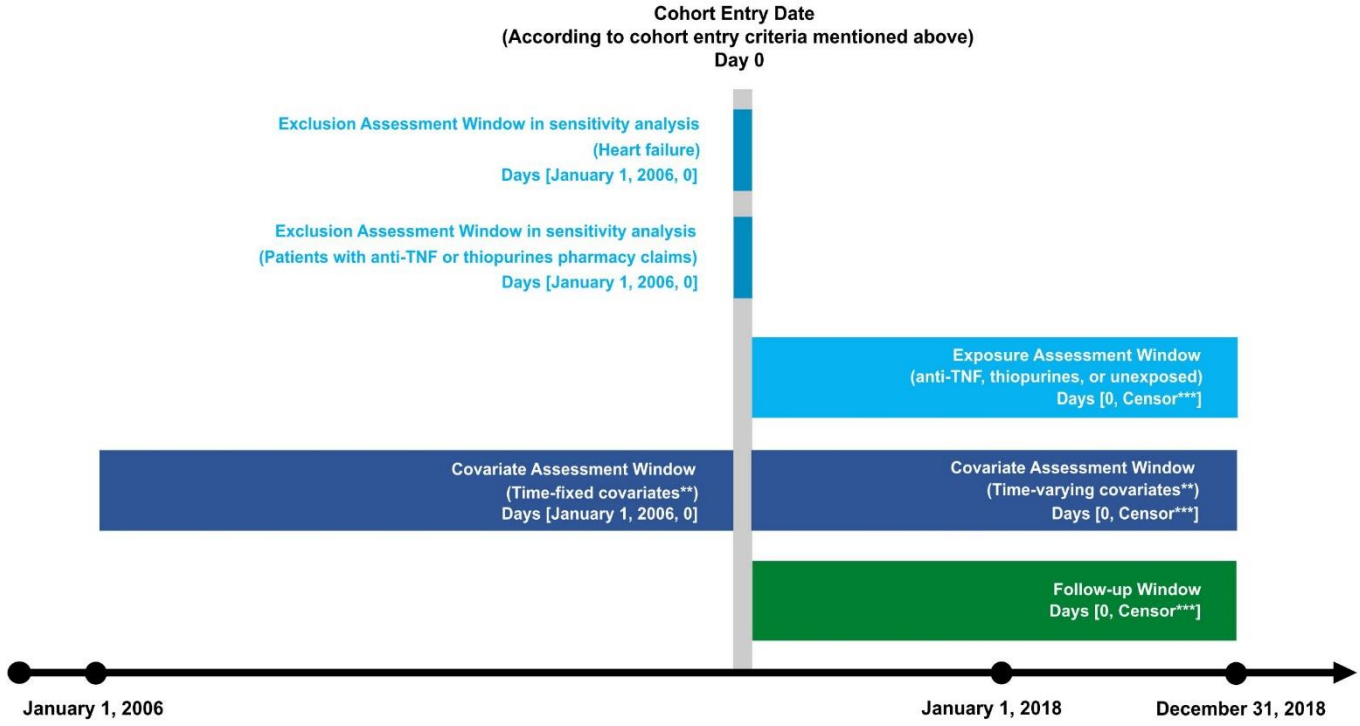
Supplementary Table 5: Multivariable adjusted hazard ratios for recurrent acute arterial events according to medication exposure periods in sensitivity analyses [a]

	Exposed periods to anti-TNF versus unexposed periods to anti-TNF and thiopurines	Exposed periods to thiopurines versus unexposed periods to anti-TNF and thiopurines
	HR (95% CI)	**HR (95% CI)**
All acute arterial events		
Analysis restricted to patients identified with IBD after January 1, 2009 [b]	0.85 (0.66-1.09)	0.79 (0.63-1.00)
Analysis restricted to patients untreated before inclusion	0.76 (0.64-0.91)	0.76 (0.66-0.88)
Analysis restricted to patients included three months after the first acute arterial event [c]	0.85 (0.66-1.09)	0.79 (0.63-1.00)
Analysis with exclusion of patients with heart failure	0.73 (0.60-0.89)	0.76 (0.65-0.89)
Analysis with patients censored at initiation of tofacitinib, vedolizumab, or ustekinumab	0.76 (0.63-0.91)	0.76 (0.65-0.87)
Analysis with a 1-month gap between first acute arterial event diagnosis and cohort entry	0.70 (0.59-0.82)	0.78 (0.68-0.89)
Analysis with an additional time of three months for drug exposure estimates	0.82 (0.69-0.98)	0.80 (0.69-0.93)

[a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.
[b] Patients with incident diagnosis of IBD
[c] Patients included into the cohort after January 1, 2009 and with diagnosis of IBD anterior to first acute arterial event
Abbreviations: HR, Hazard Ratio; TNF, Tumor Necrosis Factor.

Supplementary Figure 1: Graphical visualization of cohort study design based on methods developed by *Schneeweiss et al.*[1]





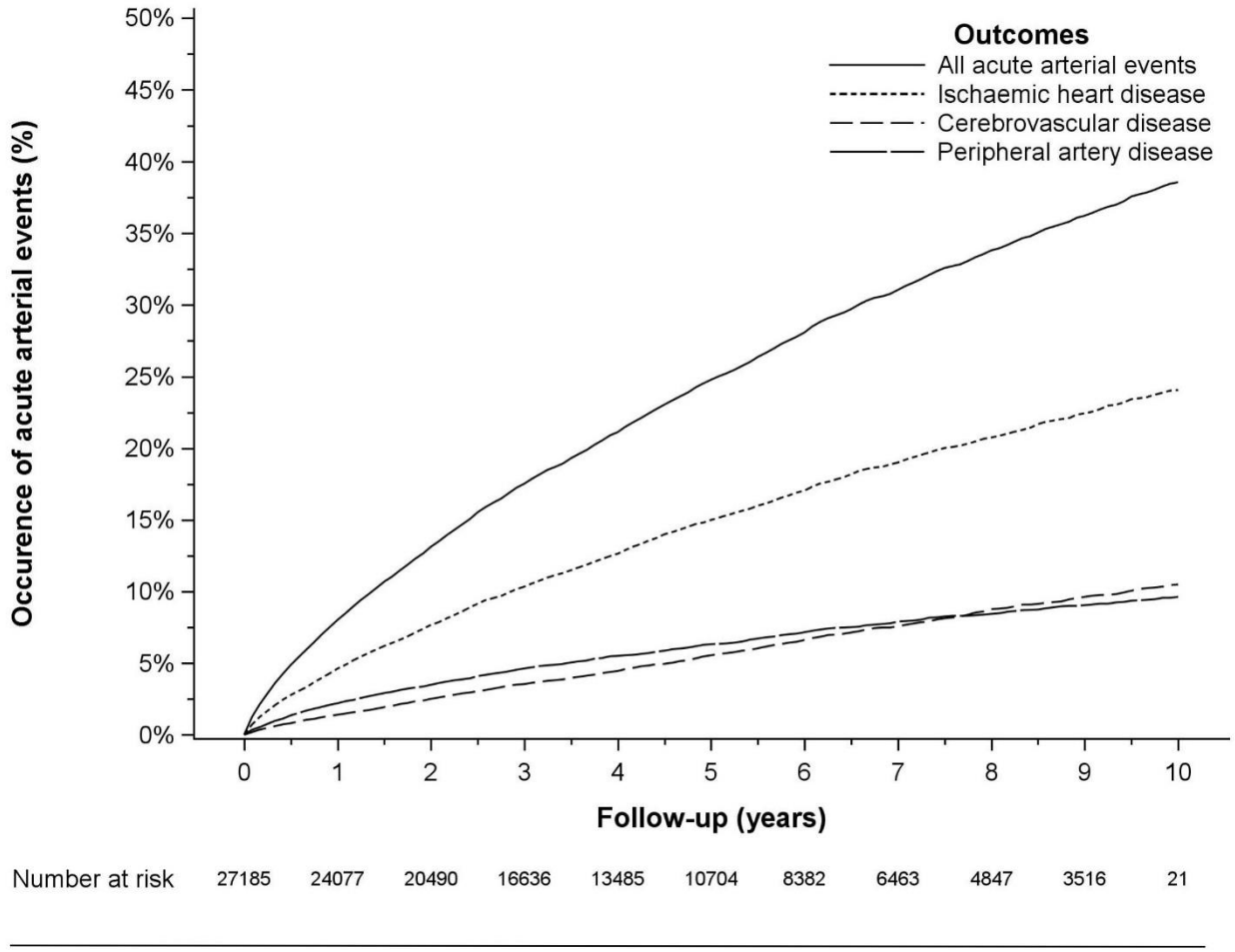
*If diagnosis was based on access to full reimbursement of care for long-term disease (LTD), it could be identified before January 1, 2006.

**Full list of covariates and details about assessment windows are available in the Methods section. Used codes are provided in Supplementary Table 1 and 2.

***Censored at earliest outcome of recurrent acute arterial event, loss to follow-up, death, or end of study (December 31, 2018). In a sensitivity analysis, patients were also censored at initiation of tofacitinib, vedolizumab, or ustekinumab.

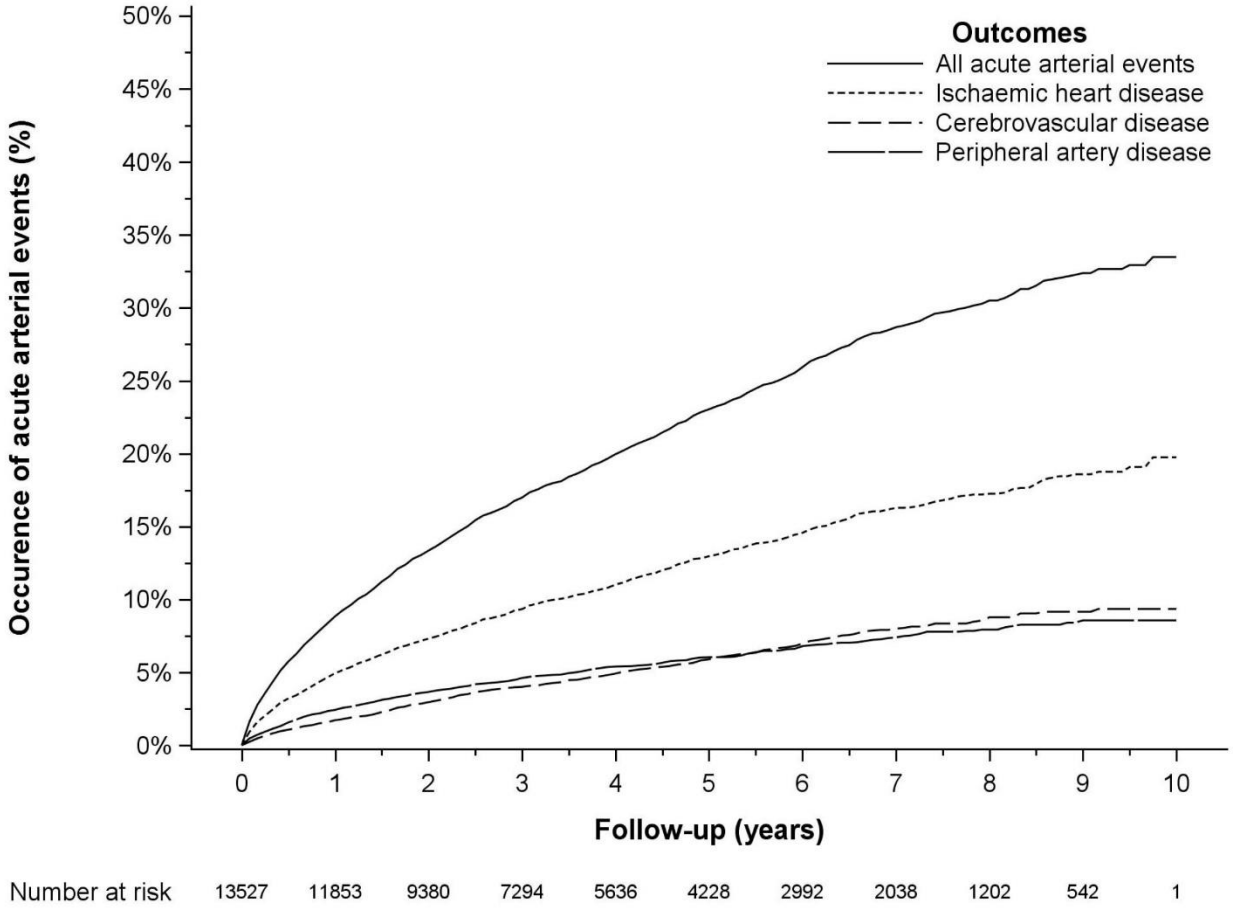
Abbreviations: IBD, Inflammatory Bowel Disease; TNF, Tumor Necrosis Factor

Supplementary Figure 2: Cumulative incidences of all recurrent acute arterial events, ischaemic heart disease, cerebrovascular disease, and peripheral artery disease in the overall cohort*



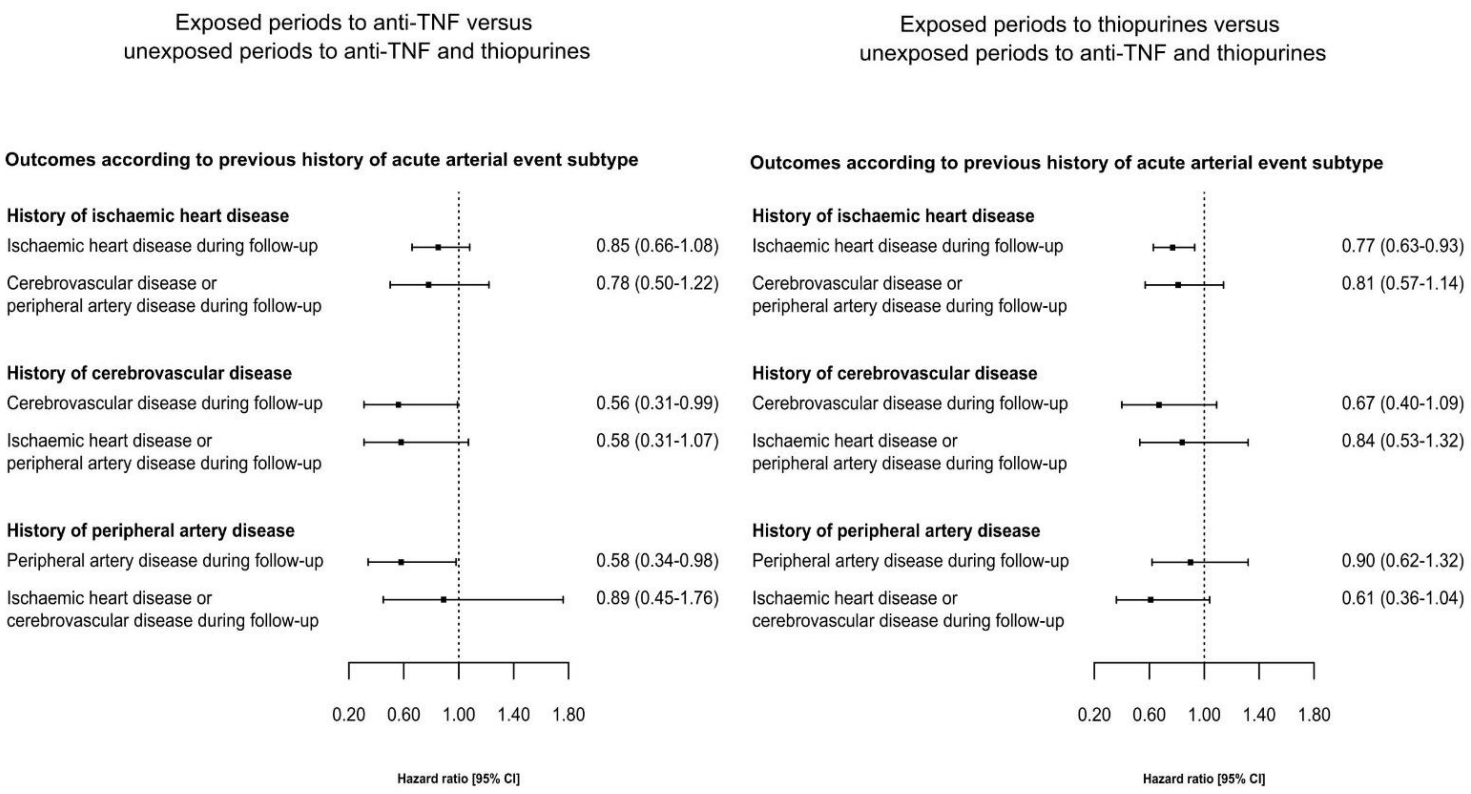
*Patients included into the cohort on January 1, 2009 (i.e. with both prevalent diagnoses of first acute arterial event and IBD on Januray 1, 2009), and also patients included into the cohort after January 1, 2009 (i.e. with incident diagnoses of first acute arterial event and/or IBD after January 1, 2009).

Supplementary Figure 3: Cumulative incidences of all recurrent acute arterial events, ischaemic heart disease, cerebrovascular disease, and peripheral artery disease, for patients included into the cohort three months after the first acute arterial event*



*Patients included into the cohort after January 1, 2009 and with diagnosis of IBD anterior to first acute arterial event

Supplementary Figure 4: Multivariable adjusted hazard ratios for recurrent acute arterial events according to subtype of first and subtype of recurrent event, and according to medication exposure periods



Supplemental Methods

Sensitivity analyses

First, we performed sensitivity analyses restricted to patients identified with IBD after January 1, 2009 in order to have only patients with incident IBD diagnosis, restricted to patients untreated before inclusion in order to assess the impact in new users, and restricted to patients included three months after the first acute arterial event in order to have a homogeneous population for time duration since the first acute arterial event. Second, we excluded patients with heart failure (as anti-TNF are contraindicated in patients with moderate or severe heart failure). Third, we censored patients at initiation of other biologics or small molecules approved after anti-TNF marketing approval, including tofacitinib, vedolizumab, or ustekinumab. Fourth, since the three-month interval between the first acute arterial event diagnosis and the cohort entry was arbitrary defined, we performed analyses evaluating the risk of acute arterial events either different from or identical to the subtype of the previous event, and we also reduced the interval from three months to one month Lastly, we performed analyses with an additional time of three months for drug exposure estimates.

Statistical analysis

In this study, under the assumption of no unmeasured confounders, marginal structural models estimated causal effects of anti-TNF, thiopurines and combination therapy exposure periods compared to periods with absence of exposure to anti-TNF and thiopurines.[3]

The follow-up time was arbitrary divided in 3-months intervals. At each time interval, patients were considered exposed to one treatment modality, that is exposed to anti-TNF, thiopurines, combination therapy, or unexposed. Time fixed covariates were evaluated at cohort entry and remained identical for all time intervals. Time dependent covariates were updated at each time interval. At the end of each time interval, occurrence of outcome or censorship (death or December 31, 2018) was evaluated. Follow-up continued until occurrence of outcome or censorship.

Time-varying inverse probability treatment weights (for both anti-TNF and thiopurines) and time-varying inverse probability censoring weights (to adjust for potential selection bias) were estimated.[4]

Binomial logistic regression models were used to estimate the conditional probability terms for the numerators and denominators for stabilized weights.[5] Stabilized weights from the exposure selection model were calculated as follows: the numerator was the probability of receiving the treatment actually received during follow-up conditional on baseline covariates and past treatment history. The denominator was the predicted probability of receiving the treatment actually received after treatment modification conditional on baseline covariates, past treatment history and time-varying covariates. Stabilized weights from the censoring model were calculated as follows: the numerator was the probability of being censored conditional on baseline covariates and past treatment history. The denominator was the predicted probability of being censored conditional on baseline covariates, past treatment history and time-varying covariates. The stabilized weights were the product of the weights from the exposure selection and the censoring models, updated at each time interval. They allowed to achieve balance between treatment groups not only at baseline but also during follow-up.

After calculation, the stabilized weights were truncated at 5th and 95th percentiles to minimize the impact of extreme weights and improve precision.[4,6] After truncation, mean (SD) of the weights were 1.12 (0.39). There was no tendency for the mean to deviate from 1 after a long period of follow-up, which supported the positivity assumption.

The outcome model was adjusted for baseline covariates. An interaction term between anti-TNF and thiopurines exposures was introduced in the outcome model.[5] Robust variance estimators were used to estimate conservative 95% confidence intervals. Consistency and correct specified model were admitted. Exchangeability was admitted under the assumption of no unmeasured confounders.

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