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Short title: Acute arterial events and treatment of IBD

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Abstract

Objective: Patients with inflammatory bowel disease (IBD) are at increased risk of acute arterial events. Anti–tumor necrosis factor agents (anti-TNFs) and thiopurines may, via their anti-inflammatory properties, lower the risk of acute arterial events. The aim of this study was to assess the impact of thiopurines and anti-TNFs on the risk of acute arterial events in IBD patients.

Design: Patients aged 18 years or older and affiliated to the French national health insurance with a diagnosis of IBD were followed from April 1, 2010 until December 31, 2014. The risks of acute arterial events (including ischemic heart disease, cerebrovascular disease, and peripheral artery disease) were compared between thiopurines and anti-TNFs exposed and unexposed patients with marginal structural Cox proportional hazard models adjusting for baseline and time-varying demographics, medications, traditional cardiovascular risk factors, comorbidities, and IBD disease activity.

Results: Among 177,827 patients with IBD (96,111 [54%] women; mean age at cohort entry 46.2 years [SD 16.3]; 90,205 [50.7%] with Crohn's disease), 4145 incident acute arterial events occurred (incidence rates: 5.4 per 1000 person-years). Compared to unexposed patients, exposure to anti-TNFs (hazard ratio [HR], 0.79; 95%CI 0.66-0.95), but not to thiopurines (HR, 0.93; 95%CI 0.82-1.05), was associated with a decreased risk of acute arterial events. The magnitude in risk reduction was highest in men with Crohn's disease exposed to anti-TNFs (HR, 0.54; 95%CI 0.40-0.72).

Conclusion: Exposure to anti-TNFs is associated with a decreased risk of acute arterial events in patients with IBD, particularly in men with Crohn's disease.

Keywords: Inflammatory bowel disease, cardiovascular disease, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, thiopurines, anti-TNFs.

Significance of this study

What is already known about this subject?

- Patients with inflammatory bowel disease (IBD) are at increased risk of acute arterial events and IBD disease activity has been reported as an independent risk factor after adjustment for traditional cardiovascular risk factors.
- While anti–tumor necrosis factor agents (anti-TNFs) and thiopurines may lower the risk of acute arterial events due to their anti-inflammatory properties, their impact on the risk of acute arterial events in patients with IBD is unknown.

What are the new findings?

- Using a large population-based nationwide cohort of IBD patients, we demonstrated that exposure to anti-TNFs, but not to thiopurines, is associated with a decreased risk of acute arterial events.
- The magnitude in risk reduction was highest in men with Crohn's disease exposed to anti-TNFs.

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

- Prevention of acute arterial events should be considered in the benefit-risk balance assessment of thiopurines and anti-TNFs in patients with IBD.

Abbreviations used in this paper: IBD: Inflammatory bowel disease; RA: rheumatoid arthritis; Anti-TNFs: Anti–tumor necrosis factor agents; CD: Crohn's disease; UC: Ulcerative colitis; PMSI: Programme de Médicalisation des Systèmes d'Information; ICD-10: WHO International Classification of Diseases, 10th revision.

INTRODUCTION

Patients with inflammatory bowel disease (IBD) are at increased risk of acute arterial events,[1,2] and disease activity has been reported as an independent risk factor after adjustment for traditional cardiovascular risk factors.[2] This increased risk may be driven by systemic inflammation, known to be involved in the pathogenesis of atherosclerosis and is associated to cardiovascular events.[3] Notably, the increased risk of cardiovascular disease is well established in other chronic inflammatory disorders, such as rheumatoid arthritis (RA), in which systemic inflammation and disease activity have been associated with cardiovascular events.[4,5] Anti–tumor necrosis factor agents (anti-TNFs) and thiopurines are effective in the treatment of patients with IBD and may lower the risk of acute arterial events due to their anti-inflammatory properties, as suggested by studies on patients with RA treated with anti-TNFs.[6] Additionally, anti-TNFs may have a specific effect on atherosclerosis independently of their anti-inflammatory effect, since TNF is directly involved in atherosclerogenesis.[7] However, the impact of anti-TNFs and thiopurines on the risk of acute arterial events in patients with IBD remains largely unexplored, potentially due to a lack of statistical power in most IBD populations, as seen in previous studies.[8] As long as the potential protective effect of IBD-related treatment is not well-established, an efficient prevention strategy cannot be elaborated, whereas recommendations for cardiovascular risk management in patients with RA, ankylosing spondylitis and psoriatic arthritis have been published since 2010.[5]

The aim of this study was to assess the impact of thiopurines and anti-TNFs on the risk of acute arterial events including ischemic heart disease, cerebrovascular disease, and peripheral artery disease in patients with IBD.

METHODS

Data source

The cohort study was based on the French National Health Insurance database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*, SNIIRAM),[9] which covers 95% of the French population with different insurance schemes based on employment situation. The general health insurance scheme covers employees in the industry, in the business and service sectors, as well as public service employees and students, accounting for approximately 88% of the French population. Due to data availability and quality, only individuals insured by the general scheme were considered. Excluded insurance schemes cover specific professions and do not depend on comorbidities or medical conditions.

The SNIIRAM provides individual data on all drug reimbursements and outpatient medical care prescribed by healthcare professionals as well as individuals' status with respect to full reimbursement of care for severe long-term diseases (LTD),[9] including Crohn's disease (CD) and ulcerative colitis (UC). Using a unique anonymous identifier, information from the SNIIRAM is linked to the French national hospital discharge database which provides individual medical information on all hospital admissions in France, including discharge diagnoses (International Classification of Diseases, 10th edition [ICD-10]) and medical procedures performed. These databases have been used previously for large pharmacoepidemiological studies.[10–13] Detailed individual-level information regarding hospitalizations and medical treatment were available from January 1, 2006 to December 31, 2014 and January 1, 2010 to December 31, 2014, respectively.

Study population

The source population included all patients aged 18 years or older identified with IBD before December 31, 2011. Identification of IBD cases was based on LTDs and/or hospitalization discharges including ICD-10 codes of CD or UC. Patients with a single hospital discharge diagnosis of IBD and no pharmacy claim for any IBD medication (aminosalicylates, enteral budesonide, thiopurines [azathioprine and mercaptopurine], and anti-TNFs), were considered to have a non-confirmed diagnosis of IBD. We did not include corticosteroids except enteral budesonide in this definition, since they are widely prescribed for a broad spectrum of diseases apart from IBD. In case of multiple hospitalizations with ICD-10 codes related to both CD and UC, the most recent diagnosis at cohort entry was retained. Date of diagnosis was the first date of IBD-related in- or outpatient care. Patients diagnosed with IBD before April 1, 2010 were referred to as prevalent cases of IBD while patients identified between April 1, 2010 and December 31, 2011 accounted for incident cases of IBD. Patients identified with IBD after December 31, 2011 were not included according to the approval of the French Data Protection Authority. This cohort has been extensively described elsewhere.[12]

Patients with a history of acute arterial event or cardiovascular disease, 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 (based on data from hospitalization discharges, LTDs, and specific procedures, see details in Supplementary Table 1).

Follow-up

Since baseline covariates identified with specific treatment exposure (e.g. antidiabetic agents) were assessed during the first three months of 2010, date of cohort entry was

April 1, 2010 for prevalent cases and the date of IBD diagnosis for incident cases. Patients were followed until December 31, 2014, loss of follow-up, death, or occurrence of acute arterial event, whichever occurred first. In case of loss to follow-up (defined as no more contact until December 31, 2014), end of follow-up was the last known contact date, defined by the last claim in the database.

Drug exposure

In France, infliximab, adalimumab, and golimumab are approved by the regulatory authorities for the treatment of IBD and are prescribed in hospitals or private clinics. Adalimumab, golimumab, and thiopurines are dispensed by pharmacies for one month.[14] Patients who received infliximab were considered exposed for two months following an infusion, those who received adalimumab, golimumab or thiopurines were considered exposed for one month following delivery.

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 infarction); (2) cerebrovascular disease (including stroke); (3) peripheral artery disease, excluding acute mesenteric ischemia. We did not include acute mesenteric ischemia, since local intestinal inflammation rather than systemic inflammation may be associated with acute mesenteric ischemia in patients with IBD.[15,16] In case of full reimbursement of care for an acute arterial event introduced before the first hospitalization or procedure related to an acute arterial event, the date of disease onset specified for full reimbursement was defined as the date of occurrence of the acute arterial event. See Supplementary Table 2 for related ICD-10 codes and procedure codes.

Covariates

Two groups of covariates were considered. Time-fixed covariates were measured at cohort entry and included sex, age, disease duration (≥ 10 years, 0-10 years, incident patients), exposure to methotrexate, aminosalicylates, and antiplatelet drugs in the preceding 3 months, IBD-related endoscopy and imaging in the preceding year, history of IBD-related hospitalization or surgery, comorbidities (based on data from hospitalization discharges, LTDs, and specific procedures or treatments, see details in Supplementary Table 1) including: history of respiratory chronic disease, chronic kidney disease, cirrhosis and portal hypertension, rheumatic disease, cancer, serious infections, venous thromboembolism, HIV, and atherosclerosis, and traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking, and alcohol use disorders). Charlson comorbidity score was not considered since it includes conditions defined as exclusion criteria, such as myocardial infarction, congestive heart failure, and cerebrovascular disease. Time-varying covariates, including IBD activity as measured by exposure to corticosteroids and occurrence of IBD-related hospitalization or surgery, were updated every month and six months during follow-up, respectively. Surrogate markers of IBD disease activity were defined similarly as our previous study assessing the impact of thiopurines and anti-TNFs on the risk of serious and opportunistic infections.[13]

Statistical analysis

We used marginal structural Cox proportional hazard models[17] adjusted for the time-fixed and time-varying covariates listed above to compare the risks of acute arterial events in patients of each exposure group (thiopurines and anti-TNFs) to unexposed patients (either never exposed or past-exposed). Marginal structural models are appropriate to use in the presence of time-dependent covariates (such as exposure to

corticosteroids and IBD activity) that might be associated with both exposure and outcomes[2,18] (i.e. time-dependent confounders) and that could be affected by past exposure to thiopurines and anti-TNFs. This approach is based on time-varying inverse probability treatment weights. Weights are updated at various time points to achieve balance between treatment groups not only at baseline but also during follow-up. Thus, marginal structural models allow for the control of time-dependent confounders, notably in patients switching to another treatment regimen during follow-up, e.g. from thiopurines to anti-TNFs. Weights calculation was performed as suggested by Cole and Hernan.[19] Since anti-TNFs and thiopurines may be used as combination therapy in clinical practice, we introduced an interaction term in our outcome model between anti-TNFs and thiopurines exposure in order to obtain unbiased estimates for each drug classes.[20] We additionally assessed the impact of combination therapy on the risk of acute arterial events. Combination therapy was defined as concomitant exposure to anti-TNFs and thiopurines. Details of the applied statistical method is provided in the supplementary appendix.

The main analysis was restricted to patients with a confirmed diagnosis of IBD. Additional analyses included subgroup analyses stratified on IBD phenotype, sex, and age (18-54 years, 55 years, or older). Several other sensitivity analyses were performed to test the robustness of our results. First, we performed sensitivity analyses restricted to incident cases of IBD, excluding patients only exposed to enteral budesonide and with a single hospital discharge diagnosis of IBD, or including patients with a non-confirmed IBD diagnosis. Second, we excluded all treatment sequences starting before cohort entry, to assess the impact of prevalent users.

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 (version 9.4) statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the cohort

Among the 232,722 individuals aged 18 years or older identified with IBD before 2014, 177,827 were included in the main analysis (Figure 1). During follow-up, 120,983 (68.0%) had never been exposed to thiopurines or anti-TNFs, while 43,881 (24.7%) and 26,447 (14.9%) had ever been exposed to thiopurines and anti-TNFs, respectively, accounting for 103,735 and 66,057 person-years (PY) of follow-up. Combination therapy was prescribed in 2405 (4.2%) patients during follow-up, with a median duration of 5.0 months, (IQR: 2.3-11.1).

Overall, the were a slight predominance of female IBD patients (54.0%) with a mean age of 46.2 (SD, 16.3) years at cohort entry. An equal proportion of patients had a diagnosis of CD (50.7%) and UC (49.3%). Incident cases accounted for 16% of the cohort, while 55.6% had an IBD diagnosis for less than 10 years. IBD-related complications occurred, preceding cohort entry, in 16.5% of patients. These characteristics differed according to subsequent treatment exposure during follow-up (Table 1). Patients unexposed to thiopurines and anti-TNFs had a mean age of 49 years and the majority had longstanding uncomplicated UC. Those exposed to thiopurines or anti-TNFs were mostly younger than 40 years and recently diagnosed with CD and had high rates of IBD-related hospitalization or surgery at cohort entry.

Risk of acute arterial events according to treatment exposure

Overall, 4145 acute arterial events occurred, 2155 (52.0%) ischemic heart diseases, 1326 (32.0%) cerebrovascular diseases, and 664 (16.0%) peripheral artery diseases. Patients with an acute arterial event during follow-up were predominantly males (64.1%) and diagnosed with UC (55.1%), with a mean age of 62.3 years (SD, 14.0) at

the first occurrence of an acute arterial event. The prevalence of traditional cardiovascular risk factors was as expected higher among acute arterial event cases compared to patients without an acute arterial event during follow-up (Supplementary Table 3).

Incidence rates per 1000 PY were 5.4 for all acute arterial event, 2.8 for ischemic heart disease, 1.7 for cerebrovascular disease, and 0.9 for peripheral artery disease. Among patients younger than 55 years, incidence rates of all acute arterial events were 2.2 per 1000 PY. Incidence rates increased expectedly with age, with 13.4 acute arterial events per 1000 PY in patients aged 55 years, or older. Incidence rates according to treatment exposure are provided in Table 2.

Exposures to anti-TNFs (hazard ratio [HR], 0.79; 95% CI 0.66-0.95) but not to thiopurines (HR, 0.93; 95% CI 0.82-1.05) was associated with a decreased risk of acute arterial event compared to no thiopurines and anti-TNFs exposure. Among specific arterial disease groups, the hazard ratio was below 0.90 for all subgroups in patients exposed to anti-TNFs, but did not reached statistical significance (Table 3). Exposure to combination therapy was not associated with a decreased risk of acute arterial events compared to no thiopurines or anti-TNFs exposure (hazard ratio [HR], 0.95; 95% CI 0.55-1.65).

The magnitude in risk reduction was higher in men exposed to anti-TNFs compared to women exposed to anti-TNFs, and higher in patients with CD as compared with patients with UC in all treatment exposure groups (Figure 2). Among patients with CD, exposure to thiopurines was numerically associated with a decreased risk of an acute arterial event, but not reaching statistical significance (HR, 0.84; 95% CI 0.70-1.01). The highest magnitude in risk reduction was observed in men with CD exposed to anti-TNFs (HR, 0.54; 95% CI 0.40-0.72).

In sensitivity analyses results remained unchanged after exclusion of patients only exposed to enteral budesonide and with a single hospital discharge diagnosis of IBD, inclusion of patients with a non-confirmed IBD diagnosis or exclusion of treatment sequences starting before cohort entry. Corresponding HRs were similar in magnitude when the analysis was restricted to incident patients (Supplementary Table 4).

DISCUSSION

Our nationwide cohort study of 177,827 patients with IBD suggest that exposure to anti-TNFs is associated with a decreased risk of acute arterial events, while exposure to thiopurines was not associated with a decreased risk of acute arterial events. The most pronounced risk reduction was observed in men with CD exposed to anti-TNFs, exceeding 40%.

To our knowledge, this study is the first nationwide population-based cohort study assessing the risk of acute arterial events associated with thiopurines and anti-TNFs exposure in patients with IBD. Indeed, conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), as well as biologics, such as anti-TNFs, have been associated with a decreased risk of acute arterial events in patients with RA. A recent meta-analysis reported a 30% decreased risk of ischemic heart disease and cerebrovascular disease in patients with either RA, psoriasis or psoriasis arthritis exposed to the two treatment regimens compared to unexposed patients.[21] The underlying mechanisms of the risk reduction associated with immunosuppressive treatment in RA and IBD may be related to shared pathogenic processes, with chronic inflammation leading to development of atherosclerosis in both diseases. Accordingly, disease activity, characterized by systemic inflammation,[22] is associated with an increased risk of acute arterial events both in patients with RA[23,24] and IBD,[2] and atherosclerosis is now defined as a chronic inflammatory condition of the vessel wall.

Recent findings suggest that the inflammatory response in atherosclerosis involves elements of both innate and adaptive immunity.[3] Additionally, several studies concluded that C-reactive protein (CRP) levels predict ischemic heart disease, cerebrovascular disease, and cardiovascular death after adjustment for traditional cardiovascular risk factors.[25]

We observed differences in risk reduction by treatment with, respectively, thiopurines and anti-TNFs, which may be explained by a higher proportion of patients obtaining clinical and mucosal healing with anti-TNFs.[26] Mucosal healing is known to be associated with lower CRP levels and sustained clinical remission.[27] However, we cannot exclude an effect of thiopurines per se, as risk reductions were at the limits of statistical significance, hence suggesting that the observed protective effect could be related to the reduction of systemic inflammation irrespective of the treatment regimen. The median duration of combination therapy was below 6 months in our cohort. Assessing the impact of a relatively short treatment exposure on an outcome such as acute arterial events may be questionable, since atherosclerosis leading to this outcome is a slow progressive condition. Thus, we assessed thiopurine and anti-TNF class effects by taking into account the use in combination.[20]

Differences in risk across IBD phenotype, sex and age categories may be related to the different distributions of systemic inflammation and traditional cardiovascular risk factors across these groups. We have previously shown that IBD patients, independent of disease activity, are more likely than the general population to have increased inflammation levels, while traditional cardiovascular risk factors are not altered.[28] Patients with CD are at increased risk of acute arterial events compared to UC patients, and patients with CD are more prone to a higher degree of systemic inflammation compared to UC patients, amongst others evidenced by higher level CRP production[22,29] and serum concentration of interleukin-6.[30]

Hyperhomocysteinemia and low vitamin B6 plasma level, [31,32] related to malabsorption in CD patients, and polymorphisms in NOD2/CARD15[33,34] may also be involved in the pathogenesis of atherosclerosis in patients with CD. Regarding age, exposure to anti-TNFs was associated with a decreased risk of acute arterial events in patients aged between 18-54 years but not in patients aged 55 years or older. Differences in risk across age categories may be related to the different distributions of traditional cardiovascular risk factors. Indeed, traditional cardiovascular risk factors in older patients may also potentially outweigh the risk related to systemic inflammation owing to IBD. The impact of anti-TNFs was predominantly observed in men. There are very few data on the impact of sex on disease activity in IBD. Several recent studies reported differences of disease activity across sex, with a more severe disease course in male patients.[35,36] These findings suggest that sex may affect the risk of acute arterial events owing to IBD and hence the potential protective effect of anti-TNFs. Further studies are required to assess the impact of sex on IBD disease course. The highest risk reduction associated with anti-TNFs was observed in the population with the highest absolute risk of acute arterial event, namely men and CD patients, while differences in risk reduction across sex were predominantly observed in patients exposed to anti-TNFs. These findings may highlight the specific impact of anti-TNFs by reversing preexisting atherosclerosis, as suggested in several studies.[37]

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. Additionally, several studies have found the reliability, validity, and accuracy of medical coding in the French administrative database for various diseases to be good.[38–42] The identification of acute arterial events in the present study was similar as in a

previous study, based on the same inpatient database, reporting an increased risk of acute arterial events in patients with IBD compared to the general population.[2]

We previously reported that disease activity was one of the strongest significant predictors of acute arterial events,[2] while corticosteroids exposure has also been associated with an increased risk of acute arterial events.[18,43] Disease activity and use of steroids may have an impact on treatment modification and occurrence of acute arterial events, whereas these time-varying covariates may also impact the future treatment assignment. Under the assumption of no unmeasured confounders, we used therefore marginal structural Cox proportional hazard models to account for time dependent confounding in treatment assignment.

This study also has some limitations that need to be discussed. Environmental factors are not accurately reported in the French administrative databases. Rates of tobacco smoking may therefore be underestimated.[44] Yet, tobacco smoking is a cardiovascular risk factor and smoking reduces the risk of UC occurrence, while increasing the risk of CD occurrence.[45–47] Furthermore, tobacco smoking increased disease activity in patients with CD,[48] and patients treated with thiopurines and anti-TNFs are more prone to be smokers compared to patients not exposed to these drugs.[44] A potential bias related to an underestimation of tobacco smoking may tend to underestimate the risk reduction of acute arterial event associated with anti-TNFs, suggesting that such a bias, if any, did not alter the association between immunosuppressive treatment and the protective effect observed.

So far, there has been no validation study of the ICD-10 codes related to IBD in the French administrative health databases. However, a descriptive study on the same cohort[12] reported treatment exposure, hospitalization, and surgery rates similar to current standard of care, as well as incidence rates in the range of those reported in

the literature.[49] Data were only available until December 2014 for this study, according to the approval of the French Data Protection Authority. The most recent biological therapies, such as vedolizumab and ustekinumab, were not considered in the study as their marketing authorizations for IBD were obtained in November 2014 and 2016, respectively.

Finally, the present findings combined with the previous observations on risk of acute arterial events in patients with IBD (as compared to the general population) [2] underscores the fact that the magnitude of risk associated with IBD and the impact of treatment should be stratified according to key parameters, such as age, sex, and IBD subtype, in order to be useful for clinical decision-making.

In conclusion, this nationwide population-based cohort study including more than 170 000 patients diagnosed with IBD reported a decreased risk of acute arterial events associated with exposure to anti-TNFs, while risk reductions associated with thiopurines were at the limits of statistical significance. Notably, this risk reduction was highest in men with CD treated with anti-TNFs. Prevention of acute arterial events should be considered in the benefit-risk balance assessment of thiopurines and anti-TNFs in patients with IBD.

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Figure Legends:

Figure 1: Study Population Flowchart

Figure 2: Multivariable adjusted hazard ratios for any acute arterial event according to medication exposure between exposed and unexposed patients: subgroup analysis according to sex, age and IBD subtype

Table 1. Patients characteristics at cohort entry according to subsequent treatment exposure during follow-up[a]

Characteristics	Unexposed to thiopurines or anti-TNFs (n=120 983)	Exposed to thiopurines (n=43 881)	Exposed to anti-TNFs (n=26 447)	Total (n=177 827)
Age at cohort inclusion, *y*, mean (SD)	49.0 (16.4)	40.3 (14.6)	38.1 (13.6)	46.2 (16.3)
Male sex, n (%)	55 612 (46.0)	20 114 (46.4)	11 796 (44.8)	81 716 (46.0)
Complementary universal health insurance, n (%) [b]	9783 (8.1)	5071 (11.6)	3521 (13.3)	16 428 (9.2)
Inflammatory bowel disease subtype, n (%)				
Crohn's disease	51 876 (42.9)	28 368 (64.6)	19 616 (74.2)	90 205 (50.7)
Ulcerative colitis	69 107 (57.1)	15 513 (35.4)	6831 (25.8)	87 622 (49.3)
Age at IBD diagnosis, *y*, mean (SD)	41.6 (16.3)	34.0 (14.1)	31.9 (13.4)	39.1 (16.1)
Disease duration at cohort entry, n (%)				
≥ 10 years	36 851 (30.5)	10209 (23.3)	5889 (22.3)	50 447 (28.4)
0-10 years	65 465 (54.1)	25 463 (58.0)	15 732 (59.5)	98 840 (55.6)
Incident patients	18 667 (15.4)	8209 (18.7)	4826 (18.2)	28 540 (16.0)
Inflammatory bowel disease assessment, n (%) [c]				
Gastrointestinal endoscopy	30 755 (25.4)	14 992 (34.2)	9714 (36.7)	50 065 (28.2)
Imaging studies	9469 (7.8)	6144 (14.0)	4887 (18.5)	17 862 (10.0)
Inflammatory bowel disease drugs, n (%) [c]				
Corticosteroids	2875 (2.4)	1381 (3.1)	917 (3.5)	4684 (2.6)
Methotrexate	1232 (1.0)	236 (0.5)	1192 (4.5)	2495 (1.4)
Aminosalicylates	39 637 (32.8)	11 874 (27.1)	5999 (22.7)	54 200 (30.5)
Complications related to IBD before cohort entry, n (%)				
Surgery related to IBD	4913 (4.1)	3884 (8.9)	3460 (13.1)	10607 (6.0)
Hospitalization related to IBD >24h	11 608 (9.6)	10 625 (24.2)	8929 (33.8)	26 896 (15.1)
Comorbidities, n (%)				
Chronic pulmonary disease	2099 (1.7)	471 (1.1)	313 (1.2)	2767 (1.6)
Chronic kidney disease	738 (0.6)	245 (0.6)	165 (0.6)	1098 (0.6)
Cirrhosis	601 (0.5)	188 (0.4)	188 (0.7)	922 (0.5)
Rheumatic disease	3371 (2.8)	1268 (2.9)	3065 (11.6)	7087 (4.0)
HIV	288 (0.2)	46 (0.1)	27 (0.1)	349 (0.2)
Cancer	7350 (6.1)	1395 (3.2)	1084 (4.1)	9437 (5.3)
Serious infections	4512 (3.7)	1934 (4.4)	1650 (6.2)	7373 (4.1)
Venous thromboembolism	1163 (1.0)	433 (1.0)	323 (1.2)	1783 (1.0)
Atherosclerosis	760 (0.6)	120 (0.3)	68 (0.3)	922 (0.5)
Cardiovascular risk factors, n (%)				
Hypertension	22 596 (18.7)	4585 (10.4)	2469 (9.3)	28 667 (16.1)
Diabetes	6165 (5.1)	1371 (3.1)	729 (2.8)	7957 (4.5)
Dyslipidemia	13 334 (11.0)	2741 (6.2)	1349 (5.1)	16 837 (9.5)
Obesity	1535 (1.3)	505 (1.2)	404 (1.5)	2275 (1.3)
Smoking behavior	3603 (3.0)	1941 (4.4)	1570 (5.9)	6411 (3.6)
Alcohol use disorder	1185 (1.0)	319 (0.7)	243 (0.9)	1653 (0.9)
Exposure to Antiplatelet Drugs, n (%) [c]	3566 (2.9)	593 (1.4)	263 (1.0)	4312 (2.4)

[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 three months before cohort entry (except for corticosteroids [within one month] and inflammatory bowel disease assessment [within one year]). Abbreviation: SD; Standard deviation.

Table 2. Incidence of acute arterial events according to medication exposure

	Total 773 405 PY	Unexposed to thiopurines or anti-TNFs 613 697 PY	Exposed to thiopurines 103 735 PY	Exposed to anti-TNFs 66 057 PY
All acute arterial events	4145 (5.4)	3609 (5.9)	363 (3.5)	196 (2.9)
Ischemic heart disease	2155 (2.8)	1881 (3.1)	188 (1.8)	98 (1.5)
Myocardial infarction	766 (1.0)	663 (1.1)	67 (0.7)	42 (0.6)
Cerebrovascular disease	1326 (1.7)	1157 (1.9)	110 (1.1)	67 (1.0)
Stroke	970 (1.3)	847 (1.4)	87 (0.8)	43 (0.7)
Peripheral artery disease	664 (0.9)	571 (0.9)	65 (0.6)	31 (0.5)

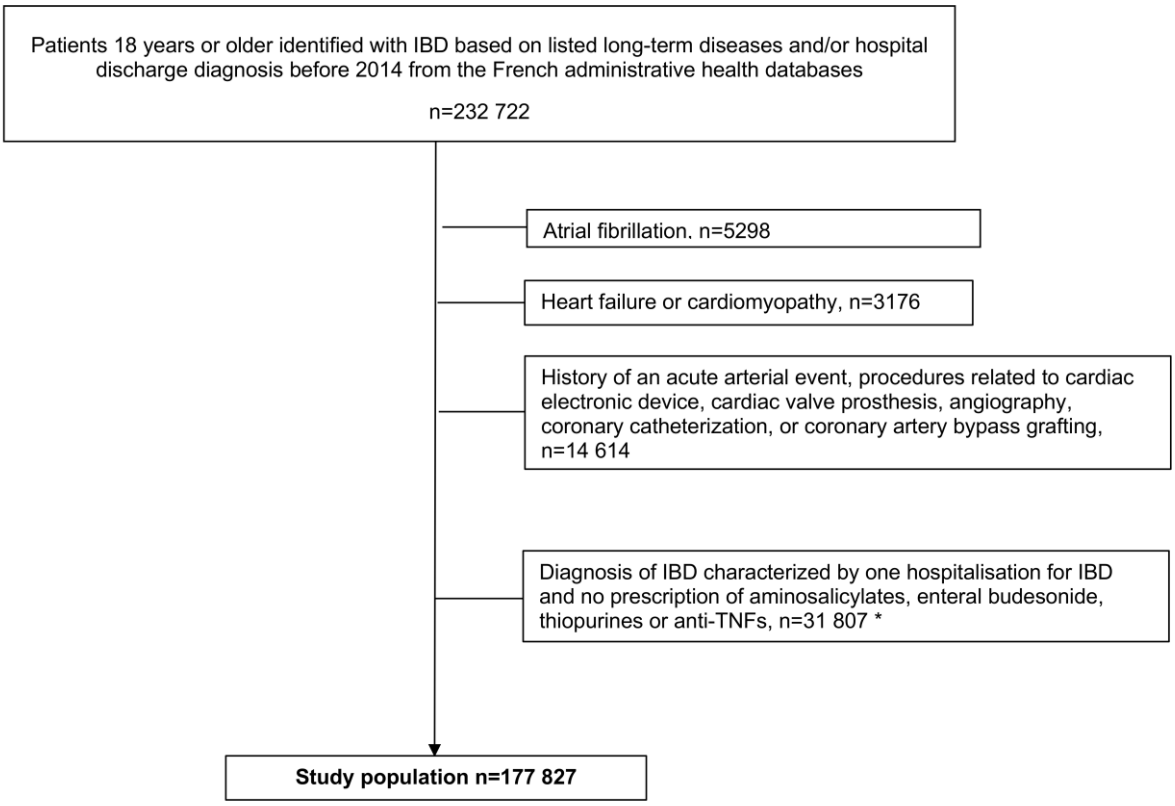
Abbreviation: PY, person-years. Numbers are n (incidence rates/1000 person-years)

Table 3. Multivariable adjusted hazard ratios for acute arterial event according to medication exposure between exposed and unexposed patients [a]

	Exposed to thiopurines versus unexposed to thiopurines or anti-TNFs	Exposed to anti-TNFs versus unexposed to thiopurines or anti-TNFs
	HR (95% CI)	**HR (95% CI)**
All acute arterial events	0.93 (0.82-1.05)	0.79 (0.66-0.95)
Ischemic heart disease	0.91 (0.76-1.08)	0.80 (0.61-1.05)
Myocardial infarction	0.90 (0.66-1.23)	0.83 (0.54-1.30)
Cerebrovascular disease	0.84 (0.68-1.04)	0.83 (0.61-1.13)
Stroke	0.91 (0.72-1.16)	0.74 (0.51-1.09)
Peripheral artery disease	1.15 (0.83-1.61)	0.69 (0.45-1.05)

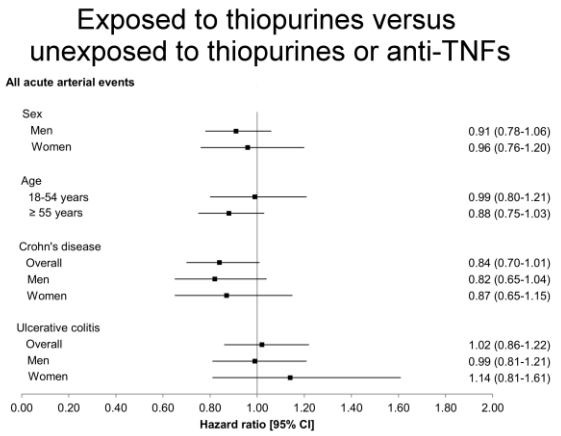
Abbreviation: HR, hazard ratio. [a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.

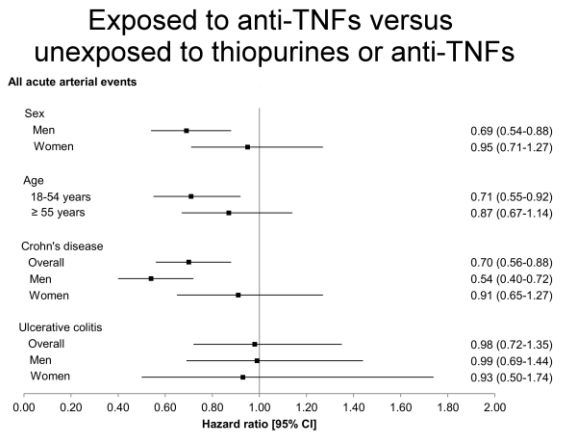
Figure 1: Study Population Flowchart



*Considered in sensitivity analyses

Figure 2: Multivariable adjusted hazard ratios for any acute arterial event according to medication exposure between exposed and unexposed patients: subgroup analysis according to sex, age and IBD subtype





SUPPLEMENTAL MATERIAL

Supplementary table 1: Codes used to define exclusion criteria and covariates

Supplementary table 2: Outcomes

Supplementary table 3: Patients characteristics at cohort entry according to having an acute arterial event or not during follow up.

Supplementary table 4: Multivariable adjusted hazard ratios of any acute arterial event according to medication exposure between exposed and unexposed patients in sensitivity analyses

Supplemental appendix: Methods

Supplementary Table 1. Codes used to define exclusion criteria and covariates

Comorbidity	ICD-10 codes	Anatomical Therapeutic Chemical (ATC) classification system code	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	-	Cerebral angiography with arterial dilation or embolization
Peripheral artery disease	I74	-	Angiography (excluding coronary catheterization and cerebral angiography) with arterial dilation; Peripheral artery bypass
Heart failure	I50	-	-
Atrial fibrillation	I48	-	-
Cardiomyopathies	I42-I43	-	-
Covariates		-	-
Cancer	C0-C9, 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, D63.0, 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
Cirrhosis and portal hypertension	I85; I86.4; I98.2; I98.3; K70.0; K70.3-K70.4; K71.1; K71.7; K72; K74.4-K74.6; K76.6; K76.7;	-	-
Respiratory chronic disease	J40-J44, J47, J96.1	R03AC, R03B	-
Chronic kidney disease	I12, N18, N19, Z49, I13.0, I13.1, Y84.1	-	-
Venus thromboembolism	I26, I80-I82, O22.3, O22.9, O87.1, O88.2	-	-
HIV	B20-B24, C46, R75, Z21, F02.4, O98.7		
Rheumatic disease	M05-M09, M45, M35.1, M35.3		
Serious infections	A00-A99 (except A30, A50, A57-A59, A63-A64, A70-74, A97); B00-B99 (except B03-B04, B07, B16, B18-B19, B20-B24, B85-B94, B98) ; G01-G07 (except G03) ;H00-H01, H03.0-H03.1; H06.1; H10.5; H10.8; H13.1; H19.1-H19.2; J01-J06, J10-J18, J20-J22, J36; J39.0-J39.1, J85-J86; K11.3, K12.2, K23.0, K23.80, K67.3, K75.0, K80.0, K80.3, K80.4, K81.0; K83.0, K87.00, K93.0, K93.820; L00-L01, L04-L05, 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, N71.0, N72, 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		
Atherosclerosis	I70		
Cardiovascular risk factors			
Diabetes	E10-E14, M14.2 , M14.6, N08.3, H28.0, H36.0, G59.0, G63.2, G73.0, G99.0, I79.2	A10	-
Dyslipidemia	E78.0-E78.5	C10	-

Comorbidity	ICD-10 codes	Anatomical Therapeutic Chemical (ATC) classification system code	French Medical Common Procedure Coding System
Alcohol use disorder	E244, F100, F101, F10.20-F10.26, F10.3-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, O35.4, T51, X45, X65, Y15, Z50.2	-	-
Hypertension	I10-I13, I15	C02 C03 C07 C08 C09	-
Smoking behavior	F17, Z71.6, Z72.0, T65.2	-	-
Obesity	E66	-	-
Markers of IBD severity			
IBD-related hospitalization	K50; K51; K56; K60; K61	-	-
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	-	-	HKPA004, HKPA005, HKPA006, HKPA007, HKPA008, HGCA008, HGCC026, HGLA001, HHCA003, HHCC011, HPPA002, HPPC003, ZCJA002, ZCJA004

Supplementary Table 2: Outcomes

Outcomes	ICD-10 codes	French Medical Common Procedure Coding System
Ischemic heart disease	I20-I25	Coronary catheterization with arterial dilation; CABG
Myocardial infarction	I21-I22	Coronary catheterization with arterial dilation; CABG
Cerebrovascular disease	I60-I64 (except I63.6), G45-G46	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 and cerebral angiography and mesenteric angiography) with arterial dilation; Peripheral artery bypass

Abbreviation: CABG, Coronary Artery Bypass Graft Surgery

Supplementary Table 3. Patients characteristics at cohort entry according to having an acute arterial event or not during follow up.

Characteristics	Acute arterial event during follow-up n=4145	No acute arterial event during follow-up n=173 682
Age at cohort inclusion, *y*, mean (SD)	62.3 (14.0)	45.8 (16.2)
Male sex, n (%)	2658 (64.1)	79 058 (45.5)
Complementary universal health insurance, n (%) [a]	306 (7.4)	16 122 (9.3)
Inflammatory bowel disease subtype, n (%)		
Crohn's disease	1863 (44.9)	88 342 (50.9)
Ulcerative colitis	2282 (55.1)	85340 (49.1)
Age at IBD diagnosis, *y*, mean (SD)	54.1 (15.4)	38.8 (15.9)
Disease duration at cohort entry, n (%)		
≥ 10 years	1475 (35.6)	48 972 (28.2)
0-10 years	2087 (50.3)	96 753 (55.7)
Incident patients	583 (14.1)	27 957 (16.1)
Inflammatory bowel disease assessment, n (%) [b]		
Digestive endoscopy	1097 (26.5)	48 968 (28.2)
Radiology tests	506 (12.2)	17 356 (10.0)
Inflammatory bowel disease drugs, n (%) [b]		
Corticosteroids	100 (2.4)	4584 (2.6)
Methotrexate	58 (1.4)	2437 (1.4)
Aminosalicylates	1473 (35.5)	52 727 (30.4)
Complications related to IBD before cohort entry, n (%)		
Surgery related to IBD	224 (5.4)	10 383 (6.0)
Hospitalization related to IBD >24h	602 (14.5)	26 294 (15.1)
Comorbidities, n (%)		
Chronic pulmonary disease	177 (4.3)	2590 (1.5)
Chronic kidney disease	102 (2.5)	996 (0.6)
Cirrhosis	40 (1.0)	882 (0.5)
Rheumatic disease	203 (4.9)	6884 (4.0)
HIV	9 (0.2)	340 (0.2)
Cancer	488 (11.8)	8949 (5.2)
Serious infections	256 (6.2)	7117 (4.1)
Venous thromboembolism	88 (2.1)	1695 (1.0)
Atherosclerosis	196 (4.7)	726 (0.4)
Cardiovascular risk factors, n (%)		
Hypertension	1938 (46.8)	26 729 (15.4)
Diabetes	611 (14.7)	7346 (4.2)
Dyslipidemia	1167 (28.2)	15 670 (9.0)
Obesity	88 (2.1)	2187 (1.3)
Smoking behavior	191 (4.6)	6220 (3.6)
Alcohol use disorder	93 (2.2)	1560 (0.9)
Exposure to Antiplatelet drugs, n (%) [b]	542 (13.1)	3770 (2.2)

[a] Free access to healthcare for people with an annual income <50% of poverty threshold. [b] As registered within three months before cohort entry (except for Corticosteroids [within one month] and inflammatory bowel disease assessment [within one year])

Supplementary Table 4. Multivariable adjusted hazard ratios of any acute arterial event according to medication exposure between exposed and unexposed patients in sensitivity analyses [a]

	Exposed to thiopurines versus unexposed to thiopurines or anti-TNFs	Exposed to anti-TNFs versus unexposed to thiopurines or anti-TNFs
	HR (95% CI)	**HR (95% CI)**
All acute arterial events		
Analysis restricted to incident patients	1.21 (0.84-1.74)	0.67 (0.41-1.09)
Analysis excluding the first treatment sequence (prevalent user)	1.15 (0.96-1.38)	0.77 (0.61-0.99)
Analysis excluding patients only exposed to enteral budesonide and with a single hospital discharge diagnosis of IBD	0.93 (0.82-1.05)	0.79 (0.66-0.95)
Analysis including patients with a non-confirmed IBD diagnosis [b]	0.93 (0.82-1.06)	0.78 (0.65-0.94)

Abbreviation: HR, hazard ratio. [a] For the predictors the multivariable model adjusted for, see the covariates subsection of the Methods section.[b] Patients with only one single hospital discharge IBD diagnosis and no pharmacy claim for any of the following IBD medications: aminosalicylates, enteral budesonide, thiopurines and anti-TNFs were considered to have a non-confirmed diagnosis of IBD

Supplemental appendix: Methods

Under the assumption of no unmeasured confounders, we used marginal structural models to estimate causal effects of thiopurines and anti-TNFs on the risk of acute arterial events.[1] These models, adjusted for time-dependent covariates with inverse probability treatment weights, are appropriate in the presence of time-dependent covariates (such as exposure to corticosteroids and IBD disease activity) that might be associated with both prescription of thiopurines or anti-TNFs and outcomes (time-dependent confounders) and could also be affected by past exposure to thiopurines and anti-TNFs.

The conditional probability of receiving observed treatment was estimated using binomial logistic regression.[2] Covariates included were the baseline and time-dependent covariates (listed in Supplementary Table 1) and past treatment history.

Weights from the exposure selection model were calculated as follows: the numerator was the probability of receiving the treatment actually received after treatment modification 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.

To adjust for potential selection bias from loss to follow-up, we similarly modeled the propensity to be censored. Binary logistic regression was used for the censoring model. 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. After calculation, the weights were truncated at 1st and 99th percentiles to minimize the impact of extreme weights and improve precision. [3,4]
After truncation at the 1st percentile (0.50) and 99th percentile (6.61), mean (SD) of the weights were 1.10 (0.75). There was no tendency for the mean to deviate from 1 after a long period of follow-up.

The outcome model was adjusted for baseline covariates. An interaction term between anti-TNFs and thiopurines exposure was introduced in the outcome model.[2] Robust variance estimators were used to estimate conservative 95% confidence intervals.

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