The risk of acute arterial events associated with treatment of inflammatory bowel diseases: a nationwide Danish cohort study

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Kirchgesner *et al* recently found that anti-TNF therapy for inflammatory bowel disease (IBD) was associated with a reduced risk of a first acute arterial event (including ischaemic heart disease, cerebrovascular disease, and peripheral artery disease) in a nationwide French cohort (1), while the risk was increased compared to the general population (2). Nevertheless, a cardioprotective effect of thiopurines could not be excluded in the French cohort study as risk estimates were at the limits of statistical significance. The reduction in systemic inflammation following IBD treatment is thought to protect against cardiovascular disease (3,4), as elevated CRP is now considered to be a cardiovascular risk factor (5,6). We sought to establish further evidence regarding cardiovascular risk and IBD treatments by investigating the risk of acute arterial events associated with thiopurines and anti-TNF in a nationwide Danish cohort study.

Using Danish nationwide registers (7,8), we assembled a cohort of IBD patients aged 18 years or older in Denmark, in the period 2005 to 2018 (online Supplementary Methods). We defined current exposure to either anti-TNF (30 days from the date of administration of golimumab or adalimumab, and 60 days for infliximab), or thiopurines (estimated from defined daily doses for azathioprine and tablets dispensed for mercaptopurine). Currently exposed subjects were matched 1:1 with unexposed subjects (who did not receive the treatment modelled) on propensity scores estimated from covariates including basic demographics, IBD subtype and duration, other IBD treatments, IBD-related endoscopy or imaging, comorbidities, and traditional cardiovascular risk factors, all assessed at cohort entry. Thus, we constructed a cohort with subjects matched on propensity scores for exposure to anti-TNF, and another with subjects matched for exposure to thiopurines.

Subjects were followed for their first acute arterial event, specifically, ischaemic heart disease, cerebrovascular disease, and peripheral artery disease. Hazard ratios (HR) for the outcomes associated with either thiopurines or anti-TNF were estimated using Cox models to account for death as a competing risk and adjust for corticosteroid use, IBD-related hospital activity (inpatient admission or surgery), and use of the 'other' treatment (i.e. thiopurines in the anti-TNF cohort, and vice versa) as time-dependent covariates assessed prospectively in follow-up time. HRs were also estimated separately for an induction period (<6 months follow-up) and a maintenance period (≥6 months).

Overall, our nationwide cohort comprised 63,167 patients with IBD. The thiopurine cohort included 7,840 subjects, and the anti-TNF cohort included 6,458 subjects (online Supplemental Tables 1, 2). Follow-up time contributed by each exposure group, number of events, and incidence rates are shown in Table 1.

Table 1. Number of events and incidence rates of acute arterial events in anti-TNF exposed, thiopurine exposed, and unexposed patients matched to each.

Exposure status	Anti-TNF exposed 5,130 PY	Anti-TNF unexposed 10,500 PY	Thiopurine exposed 7,300 PY	Thiopurine unexposed 12,000 PY
Any acute arterial event	28 (5.5)	127 (12.1)	43 (5.9)	175 (14.6)
Cerebrovascular disease	7	15	15	69
Ischaemic heart disease	20	12	25	91
Peripheral artery disease	<5	<5	<5	5

Abbreviations: anti-TNF: tumour necrosis factor inhibitors; PS: propensity score; PY: person-years.

Numbers are events (incidence rates [events/1000 PY]). Number of events fewer than five are suppressed due to data protection laws. Incidence rates for subtypes of acute arterial events are not given to prevent back-calculation of the number of events.

Current use of thiopurines was associated with a significantly reduced risk of acute arterial events (HR 0.39; 95% CI 0.24-0.65), which was greater during the induction period than the maintenance period (HR 0.14; 95% CI 0.05-0.39 and HR 0.56; 95% CI 0.32-0.99, respectively), relative to unexposed patients. Anti-TNF was also associated with a significantly reduced risk (HR 0.41; 95% CI 0.24-0.71), which differed little between the induction and the maintenance period (Figure 1). The risks of subtypes of acute arterial events were consistent for both treatments, and results were consistent across subgroup analyses by sex, IBD type, and age (online Supplemental Figure 1).

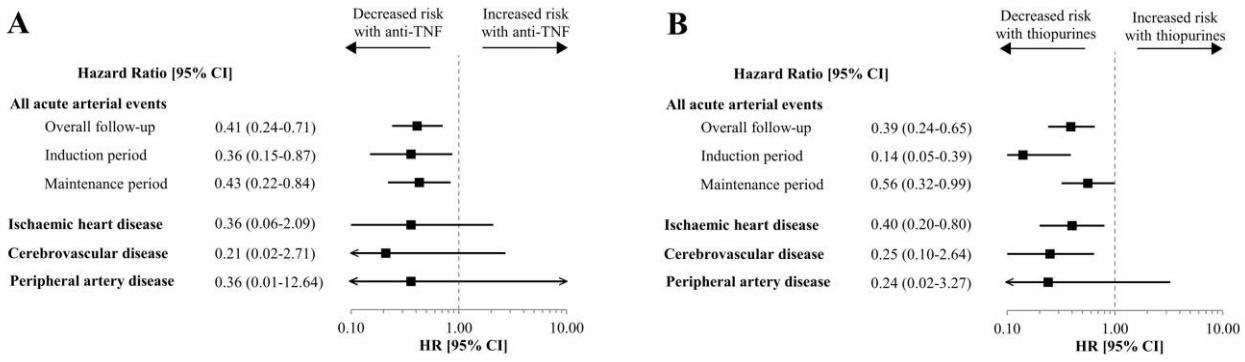

Figure 1. Hazard ratios for acute arterial events associated with anti-TNF (A) and thiopurines (B), stratified by acute arterial event type. Abbreviations: anti-TNF: tumour necrosis factor inhibitors; CI, confidence interval; IBD: inflammatory bowel disease.

In addition to the previous nationwide French cohort study (1), our nationwide Danish cohort study provides evidence of a cardioprotective effect of both thiopurine and anti-TNF therapy for IBD (online Supplementary Discussion). The association of both treatments with a reduced risk suggests that immunosuppressives may protect against arterial thrombosis via multiple mechanisms. Prevention of acute arterial events should be considered in the benefit-risk assessment of treatment with anti-TNF and thiopurines in patients with IBD.

Competing interests

Julien Kirchgesner received lecture fees from Pfizer and consulting fees from Roche, Pfizer, and Gilead. Laurent Beaugerie received consulting fees from BMS, Janssen, and Mylan; lecture fees from Abbvie, BMS, Janssen, MSD, Ferring, and Takeda; research support from Abbvie, Celltrion, Ferring Pharmaceuticals, Hospira-Pfizer, Janssen, MSD, Mylan, Takeda and Tillots. Daniel Ward, Mikael Andersson, Nynne Nyboe Andersen, Kristine Højgaard Allin, and Tine Jess disclose no conflicts.

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Supplementary material

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Supplementary Methods
Study population and data sources

The study population included all patients aged 18 years or older with Crohn's disease (CD) and ulcerative colitis (UC) in Denmark identified in the Danish National Patient Registry (1), a nationwide register of hospital episodes, diagnoses, and treatments indexed by International Classification of Diseases 8 and 10 codes (ICD-8 and -10). We used a unique identifying number to link individual-level data with the Danish National Prescription Registry, a register of prescriptions indexed by Anatomical Therapeutic Chemical (ATC) code, dispensed at retail pharmacies (2). Patients were followed from 1 January 2005, or the date of first health care episode relating to IBD if occurring later, until 31 December 2018. Patients with an acute arterial event, heart failure, atrial fibrillation, cardiomyopathy, or related surgical or medical procedures before the start of follow-up were excluded. Additionally, all patients exposed to anti-TNF and thiopurines prior to the start of follow-up were excluded to ensure a new user approach.

Supplementary Table 1. Characteristics and standardised differences for the cohort by thiopurine exposure, at baseline and after PS matching (1:1).

Characteristic	Baseline unexposed n (%) N=62,991	Baseline exposed n (%) N=10,363	Baseline standardised difference	Matched unexposed n (%) N=3,920	Matched exposed n (%) N=3,920	Matched standardised difference
Age, mean (SD)	48.6 (17.9)	39.8 (15.8)	0.52	41.5 (16.5)	41.1 (15.6)	0.03
Female	35,020 (55.6)	5,495 (53.0)	0.51	2,122 (54.1)	2,122 (54.1)	0.03
Crohn's disease	18,998 (30.2)	4,682 (45.2)	0.51	1,460 (37.2)	1,460 (37.2)	0.03
Years with IBD, mean (SD)	8.3 (9.3)	4.1 (6.7)	0.51	4.6 (7.5)	4.4 (6.7)	0.03
Region						
Capital City Region	18,310 (29.1)	2,546 (24.6)	0.13	1,036 (26.4)	942 (24.0)	0.07
Mid Jutland Region	14,579 (23.1)	2,911 (28.1)	-	985 (25.1)	1,076 (27.4)	-
Northern Jutland Region	6,511 (10.3)	1,070 (10.3)	-	413 (10.5)	425 (10.8)	-
Zealand Region	9,556 (15.2)	1,377 (13.3)	-	548 (14.0)	505 (12.9)	-
Southern Denmark Region	14,035 (22.3)	2,459 (23.7)	-	938 (23.9)	972 (24.8)	-
IBD assessment						
IBD endoscopy	19,936 (31.6)	8,582 (82.8)	1.21	3,011 (76.8)	2,962 (75.6)	0.03
IBD imaging	6,644 (10.5)	3,322 (32.1)	0.54	845 (21.6)	889 (22.7)	0.03
IBD drugs						
Methotrexate	426 (0.7)	46 (0.4)	0.03	21 (0.5)	18 (0.5)	0.01
Aminosalicylates	20,968 (33.3)	5,969 (57.6)	0.50	2,250 (57.4)	2,268 (57.9)	0.01
Comorbidities						
Respiratory disease	18,505 (29.4)	2,828 (27.3)	0.05	1,068 (27.2)	1,106 (28.2)	0.02
Kidney disease	515 (0.8)	55 (0.5)	0.04	19 (0.5)	24 (0.6)	0.02
Cirrhosis	497 (0.8)	34 (0.3)	0.06	20 (0.5)	14 (0.4)	0.02
Rheumatic disease	1865 (3.0)	322 (3.1)	0.01	121 (3.1)	116 (3.0)	0.01
HIV	162 (0.3)	5 (0.0)	0.05	<5	<5	0.01
Cancer	5,006 (7.9)	305 (2.9)	0.22	114 (2.9)	99 (2.5)	0.02
Serious Infection	10,633 (16.9)	1,603 (15.5)	0.04	549 (14.0)	620 (15.8)	0.05
Venous thromboembolism	1,614 (2.6)	179 (1.7)	0.06	78 (2.0)	76 (1.9)	0.00
Atherosclerosis	434 (0.7)	29 (0.3)	0.06	11 (0.3)	16 (0.4)	0.02
Cardiovascular risk factors						
Hypertension	20,804 (33.0)	2,334 (22.5)	0.24	973 (24.8)	935 (23.9)	0.02
Diabetes	3,798 (6.0)	404 (3.9)	0.10	150 (3.8)	162 (4.1)	0.02
Dyslipidemia	8,150 (12.9)	906 (8.7)	0.14	367 (9.4)	372 (9.5)	0.00
Obesity	3,045 (4.8)	482 (4.7)	0.01	206 (5.3)	172 (4.4)	0.04
Smoking	1,561 (2.5)	239 (2.3)	0.01	93 (2.4)	91 (2.3)	0.00
Alcohol use disorder	2,338 (3.7)	276 (2.7)	0.06	108 (2.8)	98 (2.5)	0.02
Antiplatelet drugs	3,267 (5.2)	238 (2.3)	0.15	106 (2.7)	93 (2.4)	0.02

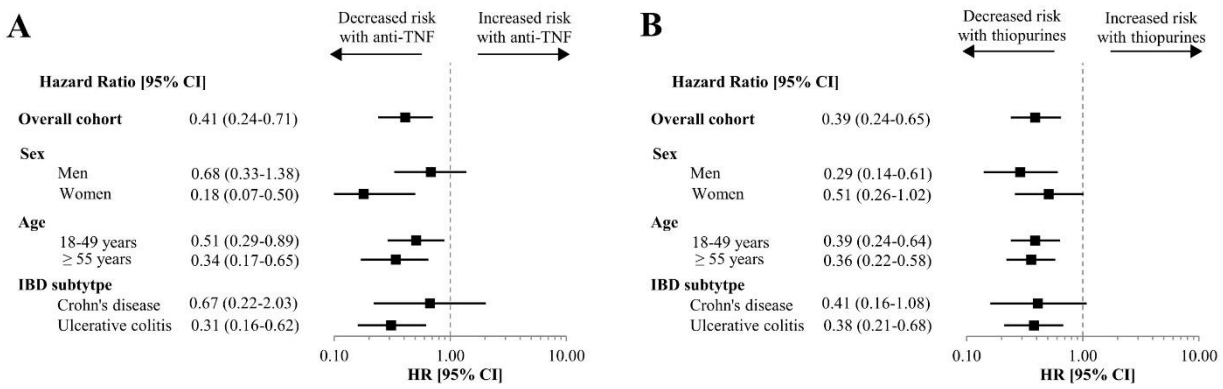
Number are prevalences (number and percentage) and absolute standardised differences, expect where specified otherwise.
Abbreviations: NA, not applicable; HIV, human immunodeficiency virus; IBD inflammatory bowel disease; SD, standard deviation.
Numbers fewr than five suppressed due to data protection laws, percentage not given.

Supplementary Table 2. Characteristics and standardised differences for the cohort by anti-TNF exposure, at baseline and after PS matching (1:1).

Characteristic	Baseline unexposed (%) (n=62,704)	Baseline exposed (%) (n= 7,396)	Baseline standardised difference	Matched unexposed (%) (n=3,229)	Matched exposed (%) (n=3,229)	Matched standardised difference
Age, mean (SD)	49.4 (18.0)	37.9 (14.5)	0.71	39.5 (15.5)	39.4 (14.6)	0.00
Female	34,887 (55.6)	4,013 (54.3)	0.52	1,718 (53.2)	1,718 (53.2)	0.01
Crohn's disease	18,887 (30.1)	3,353 (45.3)	0.51	1,214 (37.6)	1,214 (37.6)	0.01
Years with IBD, mean (SD)	9.2 (9.8)	4.8 (6.9)	0.52	5.2 (8.3)	5.1 (7.1)	0.01
Region						
Capital City Region	18,184 (29.0)	1,821 (24.6)	0.15	806 (25.0)	846 (26.2)	0.03
Mid Jutland Region	14,493 (23.1)	2,148 (29.0)	-	867 (26.9)	848 (26.3)	-
Northern Jutland Region	6,497 (10.4)	735 (9.9)	-	351 (10.9)	341 (10.6)	-
Zealand Region	9,566 (15.3)	1,118 (15.1)	-	492 (15.2)	499 (15.5)	-
Southern Denmark Region	13,964 (22.3)	1,574 (21.3)	-	713 (22.1)	695 (21.5)	-
IBD assessment						
IBD endoscopy	19,007 (30.3)	5,994 (81.1)	1.19	2,443 (75.7)	2,388 (74.0)	0.04
IBD imaging	6,523 (10.4)	2,450 (33.1)	0.57	705 (21.8)	769 (23.8)	0.05
IBD drugs						
Methotrexate	447 (0.7)	277 (3.7)	0.21	41 (1.3)	74 (2.3)	0.08
Aminosalicylates	20,460 (32.6)	3,715 (50.2)	0.36	1,631 (50.5)	1,656 (51.3)	0.02
Comorbidities						
Respiratory disease	19,027 (30.3)	2,092 (28.3)	0.05	901 (27.9)	891 (27.6)	0.01
Kidney disease	573 (0.9)	29 (0.4)	0.06	20 (0.6)	19 (0.6)	0.00
Cirrhosis	538 (0.9)	29 (0.4)	0.06	15 (0.5)	13 (0.4)	0.01
Rheumatic disease	1,998 (3.2)	532 (7.2)	0.18	128 (4.0)	169 (5.2)	0.06
HIV	<5	<5	0.05	<5	<5	0.01
Cancer	5,387 (8.6)	225 (3.0)	0.06	103 (3.2)	100 (3.1)	0.01
Serious Infection	11,111 (17.7)	1,339 (18.1)	0.01	589 (18.2)	549 (17.0)	0.03
Venous thromboembolism	1,737 (2.8)	134 (1.8)	0.06	61 (1.9)	75 (2.3)	0.03
Atherosclerosis	4,71 (0.8)	13 (0.2)	0.08	6 (0.2)	7 (0.2)	0.01
Cardiovascular risk factors						
Hypertension	21,627 (34.5)	1,534 (20.7)	0.31	716 (22.2)	703 (21.8)	0.01
Diabetes	4,089 (6.5)	296 (4.0)	0.11	131 (4.1)	147 (4.6)	0.02
Dyslipidemia	8,833 (14.1)	636 (8.6)	0.17	295 (9.1)	279 (8.6)	0.02
Obesity	3,296 (5.3)	419 (5.7)	0.02	203 (6.3)	173 (5.4)	0.04
Smoking	1,666 (2.7)	227 (3.1)	0.02	82 (2.5)	84 (2.6)	0.00
Alcohol use disorder	2,400 (3.8)	220 (3.0)	0.05	97 (3.0)	99 (3.1)	0.00
Antiplatelet drugs	3,415 (5.4)	114 (1.5)	0.21	53 (1.6)	57 (1.8)	0.01

Number are prevalences (number and percentage) and absolute standardised differences, expect where specified otherwise.
Abbreviations: NA, not applicable; HIV, human immunodeficiency virus; IBD inflammatory bowel disease; SD, standard deviation.
Numbers fewer than 5 suppressed due to data protection laws, percentage not given.

Supplementary Figure 1. Hazard ratios for acute arterial events associated with anti-TNF (A) and thiopurines (B), stratified by subjects' sex, IBD type, and age (<55 and ≥55 years old).



Abbreviations: anti-TNF: tumour necrosis factor inhibitors; IBD: inflammatory bowel disease; CI: confidence interval.

Supplementary Discussion

Anti-TNF and thiopurine exposures were consistently associated with reduced risk of acute arterial events, both as induction and maintenance therapy, with a trend for a higher protective effect during the induction period. We would caution against over-interpretation of differences in the estimates between the two periods, as confidence intervals are overlapping, so we cannot conclude that the protective effect is higher during induction compared to maintenance periods. This trend could be related to the effect of inflammatory bowel disease (IBD) treatment on high levels of inflammation during active disease, which we may assume is present at the time of initiating treatment in the treated patients or entering the cohort (at IBD diagnosis) in the unexposed patients, whereas we may assume that inflammation is at a lower level in both groups in follow-up > 6 months (maintenance therapy). However, thiopurines may take up to three months to be effective, which may introduce some doubt to this argument. Also, the new-user design may lead to the inclusion of unexposed patients with high disease activity at cohort entry, and as disease activity is a risk factor for cardiovascular events, the risk in the comparator group may be high in this period.

Prior to this Danish nationwide study, only one population-based study on the effects of IBD treatment on cardiovascular risk has been conducted. In a French nationwide cohort, anti-TNF was associated with a significantly reduced risk of acute arterial events (HR 0.79; 95% CI 0.66-0.95), whereas thiopurines were not (HR 0.93; 95% CI 0.82-1.05) (1). The differences in the estimated effects of treatments between this study and the French one could relate to the baseline rates of acute arterial events and the prevalence of important cardiovascular risk factors. Although the French and Danish cohorts had similar proportions of male subjects and similar ages in the exposed cohorts, factors including hypertension, obesity, and diabetes were more prevalent in exposed patients in the Danish cohort than in the French cohort.

Further, there were important differences in the methods applied in this study compared to the French study. In the present study we used a propensity score matching method to assemble cohorts with closely approximating covariates in exposed and unexposed subjects. The estimated treatment effect with this

model is the average treatment effect in the treated (ATT) (as the comparator population is selected to match the treated population). By contrast, the French study used an inverse probability of treatment weighting (IPTW) method, which estimates the average treatment effect (ATE), interpreted as the effect of applying the treatment to the whole study population compared to the reference (unexposed). The IPTW model was not successful in balancing covariates in the Danish cohort, hence propensity score matching was used. We found a greater protective effect when estimating the effect of treatment in the treated (ATT) than in the whole population (ATE), which might suggest that those selected for treatment benefit more than comparators, as would be expected since treatment was not randomised. These differences in methods, together with the previously mentioned differences in the characteristics of the study populations, may impede any direct comparison of risk estimates between the two nationwide cohorts.

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