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# Cardiac arrhythmia in patients with inflammatory bowel disease: a retrospective, population-based cohort study in Manitoba, Canada

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## ABSTRACT

**Objective** We aimed to characterise the association between inflammatory bowel disease (IBD) and IBD medications and risk of cardiac arrhythmia.

**Design, setting and participants** In a retrospective population-based study using the University of Manitoba IBD Epidemiology Database (Manitoba, Canada) from 1984 to 2018, we identified 10 992 IBD cases and 102 875 matched controls.

**Analysis** Arrhythmia risk in IBD was adjusted for the presence of comorbidities of the Charlson Comorbidity Index. The effect of IBD medications on the development of arrhythmia was assessed in a nested cohort study of individuals with IBD. Cases were censored at the date of first database identification of a diagnosis of heart failure or myocardial infarction.

**Results** The cohort was 48.5% Crohn's disease and 51.5% ulcerative colitis, and 80.5% were incident cases. The median age of incident cases at IBD diagnosis was 35 (IQR, 25 to 49). The median age at arrhythmia diagnosis for persons with IBD was 69 years (IQR, 59 to 77) and for controls 69 years (IQR, 59 to 78). Persons diagnosed with IBD were more likely than controls (HR 1.51; 95% CI, 1.30 to 1.76) to develop arrhythmia. Persons within their sixth decade or younger had increased risk of arrhythmia. When controlling for comorbidities, the significant association between IBD and arrhythmia remains. Medications including 5-aminosalicylates, thiopurines and tumour necrosis factor-α inhibitors were not associated with arrhythmia.

**Conclusions** Persons with IBD have a higher risk of arrhythmia prior to a diagnosis with heart disease. Use of IBD medications was not associated with risk of arrhythmia.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A major strength of our study pertains to its relatively large population obtained from a large Canadian provincial administrative health database, which allows for adjustment for multiple demographic variables including socioeconomic status and number of healthcare visits.
⇒ Another strength of the study is the assessment of the risk of supraventricular and ventricular arrhythmias in inflammatory bowel disease (IBD).
⇒ A further strength is the determination as to whether medications used to treat IBD impact the risk of arrhythmia incidence.
⇒ A primary study limitation is the observational and retrospective nature of its design.
⇒ Another study limitation is the inability to determine IBD activity or severity at the time of the arrhythmia diagnosis.

## INTRODUCTION

Inflammatory immune conditions have been linked to cardiovascular diseases. Chronic inflammation is a hallmark of inflammatory bowel disease (IBD), which has systemic effects beyond the gastrointestinal tract. We have previously shown that IBD, comprising Crohn's disease (CD) and ulcerative colitis (UC), is associated with an increased risk of venous and arterial thromboembolic events.[1 2]

Cardiac arrhythmia, particularly atrial fibrillation (AF), has been linked to IBD.[3] Several mechanisms for systemic inflammation-mediated arrhythmia have been proposed including pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukins (IL), which promote endothelial dysfunction, myocardial injury (eg, fibrosis or remodelling) and oxidative stress.[4–6] Autonomic dysfunction can also contribute to abnormal heart rate variability and baroreflex sensitivity and thus an arrhythmogenic substrate to atrial or ventricular arrhythmias.[7 8]

Recognising the prevalence of arrhythmia in IBD is paramount in the comprehensive management of patients with IBD to reduce the burden of arrhythmic complications and improve long-term cardiovascular outcomes. To date, few studies have focused on the risk of AF in IBD, and data are lacking as to

the risk of other arrhythmias in IBD.[9–11] Further, little is known about the association of IBD medications and arrhythmia.[12 13]

In this population-based cohort study, we aimed to determine the risk of arrhythmia (AF, other supraventricular tachycardia (SVT), and ventricular tachycardia (VT)) in IBD prior to the development of heart disease (HD), defined as myocardial infarction (MI) or congestive heart failure (CHF). In secondary analysis, we also sought to compare the risk of arrhythmia associated with IBD medications, including 5-aminosalicylates (5-ASA), thiopurines and TNF-α inhibitors.

## METHODS

The risk of arrhythmia (defined as AF, other SVT or VT) was determined in a historical cohort study using population-based data sources. The effect of immunomodulatory medication use in IBD on the development of arrhythmia was assessed in a nested cohort study of individuals with IBD. The construction of the University of Manitoba IBD Epidemiology Database (UMIBDED) and the use of it for clinical studies was approved by the University of Manitoba Research Ethics Board (#HS11468 (H2009:217)) and by the Health Information Privacy Committee of Manitoba Health (MH) (HIPC #2009/2010–23).

### Study design and population

Individuals with IBD were identified from the UMIBDED, which was previously created using the MH administrative databases, a publicly funded health insurance agency providing universal health insurance to all residents in Manitoba. The MH databases have been described in detail elsewhere.[14] Using each study subject's 9-digit personal health identification number as assigned by MH, longitudinal health service use and outcomes can be defined by deterministic linkage of health use files. To preserve patient confidentiality, all linkages were performed using scrambled personal health identification numbers. Outpatient visits and hospitalisations dating back to 1984 and all prescription drugs supplied outside hospital dating back to April 1995 were tracked until 31 March 2018. Persons with IBD in the UMIBDED were matched 1:10 to randomly selected members of the general population with no history of IBD by age, sex and postal area of residence. This control cohort was extracted from the population registry of MH. Matched controls were selected based on the date of IBD diagnosis. Additionally, relative rates analyses included a comparison of participants based on Socioeconomic Factor Index (SEFI) at IBD diagnosis. The socioeconomic status (SES) of the study subjects was assigned based on their neighbourhood of residence on the date of IBD diagnosis (for both individuals with IBD and their matched control subjects) using the SEFI.[15] A lower SEFI score indicates a more favourable SES.

The case definition of IBD in UMIBDED includes individuals with at least five separate physician contacts or hospitalisations with an IBD diagnosis (≥3 contacts for those residing in Manitoba for ≤2 years). This case definition has been validated previously, with a sensitivity and specificity of approximately 90% in comparison with both patients' self-report and chart review.[16] The specificity of 90% refers to the specificity among those with at least one physician or hospital claim for the diagnosis of IBD. The data used in this study begin in 1984. IBD cases identified between 1984 and 1986 are considered prevalent, and their date of IBD diagnosis cannot be considered as accurate as later data. There is a possibility that subjects were incorrectly excluded because the first arrhythmia diagnosis predates the first recorded IBD diagnosis spuriously. Subjects identified in 1987 onward are considered incident IBD cases.

### Assessment of exposures and outcomes

CD was identified by International Classification of Diseases-9th revision - Clinical Modification (ICD-9-CM) code 555.xx and ICD-10th revision (ICD-10) code K50. UC was identified by ICD-9-CM code 556.xx and ICD-10 code K51. ICD codes for arrhythmias included ICD9 427.31 (AF), 427.0 (SVT), 427.1 (VT); ICD10 I48 subcodes .0,.1,.2,.91 (AF), I47.1 (SVT) and I47.2 (VT).

Our primary outcome was the diagnosis with incident arrhythmias. We excluded persons diagnosed with arrhythmia prior to the index date of IBD diagnosis. Follow-up started on the index date until arrhythmia diagnosis, emigration out of the province of Manitoba, death, or 31 March 2018, and in some analyses, development of HD — MI or CHF as defined for the Charlson Comorbidity Index (CCI).

### Nested cohort study

In a nested cohort study, we created case-control data sets to study the association between use of IBD medications (specifically, 5-ASA preparations, thiopurines and TNF-α inhibitors) and risk of arrhythmia in IBD subjects. All subjects were drawn from IBD cases diagnosed after 1 April 1995, when the drug database became available. Of note, only post-2001 sets were used for TNF-α inhibitor analysis, as this is when TNF-α inhibitors became available in the MH drug database. Cases were selected with arrhythmia first diagnosed after IBD diagnosis and before MI and/or CHF diagnoses. All participants were censored at diagnosis of MI or CHF per the CCI definitions. These diagnoses were obtained from hospital discharge summaries or physician claim forms. The set date was defined as the first diagnosis date of arrhythmia in the case for each case-control set. The analysis set consisted of one case and one to four controls matched by sex, disease (CD or UC), year of IBD diagnosis and age ±5 years. All controls were free of arrhythmia and HD at the set date. A subject may appear multiple times as a control for different cases, and a case may appear as a control for another case.

### Statistical analysis

Comparative descriptive statistics were calculated using the Fisher's exact test and median ages with interquartile ranges (IQR) were compared using the Wilcoxon rank-sum test.

All outcomes of incident arrhythmias in IBD were reported as hazard ratios (HR) with 95% confidence intervals (CI) based on a proportional hazard regression model stratified by case-control group. Any subject with arrhythmia diagnosed before IBD diagnosis (or IBD diagnosis of associated case if the subject was a control) was excluded from the study. Subjects were censored when HD was diagnosed.

In a nested cohort study, the effects of immunosuppressive medications (primarily thiopurines and TNF-α inhibitors) on the risk of arrhythmias in the cohort of individuals diagnosed with IBD were evaluated using logistic regression analysis, with the predictor being drug status. In this model, controls were matched for sex and age at IBD diagnosis. Persons with arrhythmia prior to IBD were excluded from this data set. Drug use was treated as a time-dependent variable in the regression model, with subjects becoming medication users on receipt of their first prescription and qualified as users by getting at least two prescriptions for the medication during their time in the study. Subjects lost their medication user status after two years without a prescription.

All analyses were conducted using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). A two-sided $p \leq 0.05$ was considered statistically significant.

### Patient and public involvement

None.

## RESULTS

The baseline characteristics of the study cohort are provided in table 1. A total of 10 992 patients with IBD (53.4% female; 48.5% CD; 51.5% UC) were age-matched with 102 875 controls. Incident cases of IBD represented 80.6% of the IBD cohort. The median age of incident cases at IBD diagnosis was 35 (IQR, 25 to 49) years. The median age at arrhythmia diagnosis for patients with IBD was 69 (IQR, 59 to 77) years and of controls 69 (IQR, 59 to 78) years. The median SEFI score was -0.31 (IQR, -0.98 to +0.63). IBD cases had a median of 14 (IQR, 11 to 21) ambulatory care visits annually versus 11 (IQR, 7 to 16) visits annually for controls. All comorbidities of the CCI were more common in persons with IBD than controls except for HIV/AIDS (online supplemental table 1).

Over a median follow-up of 15.4 years, 2.05% of patients with IBD developed arrhythmia compared with 1.25% of controls without IBD ($p<0.0001$). Figure 1 displays survival to first arrhythmia diagnosis. Of note, 12.2% of patients with IBD patients developed HD, compared with 9.6% of controls ($p<0.0001$). Interestingly, patients with UC had more HD than those with CD (11.22% vs 8.8%, $p<0.001$), but the UC sample was also older than the CD one (median age 71 vs 68 years, respectively, $p=0.0007$).

Censoring at HD diagnosis, the risk of any arrhythmia was significantly raised in persons with IBD (HR 1.51; 95% CI, 1.30 to 1.76), as well as in each of CD and UC (table 2). Of all arrhythmias, VT had the highest HR of 2.57 (95% CI, 1.43 to 4.61). Within the UC cohort, AF was the only arrhythmia of elevated risk as compared with controls. Persons within their sixth decade or younger had increased risk of arrhythmia (table 3). Persons with IBD in their seventh decade did not have a significantly increased risk of arrhythmia compared to controls, but persons with IBD in their eighth decade did have a significantly increased risk (table 3). The risk of arrhythmia in patients with IBD following HD diagnosis was higher than prior to HD diagnosis. In online supplemental table 2, we report on differences by sex. Females with CD had a higher likelihood of any arrhythmias, AF or VT compared with men with CD. This pattern is somewhat reversed in UC where men have a higher risk for arrhythmias.

Comorbidities were added as a time-dependent predictor in the analysis of all arrhythmias. Subjects became part of the comorbidity group at the first relevant diagnosis. Peripheral vascular disease (PVD), chronic obstructive pulmonary disease, connective tissue disease, diabetes, chronic kidney disease and cancers all independently raised the risk of arrhythmia overall. Cerebrovascular disease and dementia increased the risk of arrhythmia in CD. PVD increases the risk in UC subjects. When adjusting for the presence of each of the CCI comorbidities, the significant association between IBD and risk of arrhythmia remains (online supplemental table 1).

In a nested cohort study, we sought to determine the association between IBD medication use and risk of arrhythmia. We analysed 156 data sets with 642 matched controls for history of 5-ASA preparations or thiopurine use, and 130 datasets with 532 matched controls for TNF-α inhibitor use. IBD medication exposure did not predict arrhythmia in a proportional hazards regression analysis stratified by set. Within the overall IBD cohort, 5-ASA, thiopurine and TNF-α inhibitor use was not associated with arrhythmia diagnosis, with odds ratios (OR) of 0.99 (95% CI, 0.68 to 1.45), 1.06 (95% CI, 0.57 to 1.97) and 0.90 (95% CI, 0.31 to 2.61), respectively. Similar findings are reported for CD and UC as per table 4, where the described numbers of cases represent users of the IBD medication at the date of arrhythmia diagnosis.

## DISCUSSION

This study examined the risk of arrhythmia in a provincial cohort of 10 992 patients with IBD and 102 875 matched controls. We found that IBD was associated with an increased risk of arrhythmia, including AF, other SVT and VT, independent of the presence of HD, comorbidities as per the CCI and other demographic confounding variables as described. Interestingly, IBD medications such

**Table 1** Baseline characteristics

| | IBD | | CD | | UC | |
|---|---|---|---|---|---|---|
| | Case | Control | Case | Control | Case | Control |
| N | 10 992 | 102 875 | 5335 | 50 359 | 5657 | 52 532 |
| Male (%) | 46.6 | 47 | 42.5 | 42.8 | 50.4 | 51 |
| Any arrhythmia (%) | 2.1 | 1.3 | 2.2 | 1.2 | 1.9 | 1.3 |
| P value | <0.0001 | | <0.0001 | | 0.0002 | |
| First arrhythmia diagnosis (%) | | | | | | |
| Atrial fibrillation | 1.6 | 1 | 1.7 | 0.9 | 1.5 | 1.1 |
| P value | <0.0001 | | <0.0001 | | 0.0034 | |
| Supraventricular tachycardia | 0.3 | 0.2 | 0.3 | 0.2 | 0.3 | 0.2 |
| P value | 0.008 | | 0.069 | | 0.052 | |
| Ventricular tachycardia | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 |
| P value | 0.0029 | | 0.0045 | | 0.16 | |
| Heart disease (%) | 12.2 | 9.6 | 11.4 | 8.8 | 13.1 | 10.3 |
| P value | <0.0001 | | <0.0001 | | <0.0001 | |
| Age at arrhythmia diagnosis | | | | | | |
| Median (IQR) | 69 (59 to 77) | 69 (59 to 78) | 68 (58 to 76) | 67 (58 to 78) | 71 (59 to 78) | 71 (60.5 to 78) |
| P value | 0.38 | | 0.58 | | 0.64 | |
| Age at heart disease diagnosis | | | | | | |
| Median (IQR) | 69 (58 to 78) | 68 (58 to 78) | 67 (56 to 75) | 67 (57 to 77) | 70 (59 to 79) | 69 (58 to 79) |
| P value | 0.78 | | 0.14 | | 0.34 | |
| SEFI | | | | | | |
| Median (IQR) | −0.31 (−0.98 to +0.63) | −0.31 (−0.98 to +0.63) | −0.30 (−0.96 to +0.69) | −0.31 (−0.97 to +0.64) | −0.34 (−1.02 to +0.58) | −0.32 (−0.99 to +0.62) |
| P value | 0.95 | | 0.11 | | 0.15 | |
| Annual healthcare contact rate during all follow-up after IBD diagnosis for those with arrhythmia, median (IQR) | | | | | | |
| Inpatient | 0.34 (0.21 to 0.71) | 0.22 (0.11 to 0.42) | 0.40 (0.27 to 0.74) | 0.21 (0.10 to 0.39) | 0.40 (0.27 to 0.74) | 0.21 (0.10 to 0.39) |
| P value | <0.0001 | | <0.0001 | | <0.0001 | |
| Outpatient | 0.31 (0.17 to 0.48) | 0.13 (0.06 to 0.24) | 0.26 (0.13 to 0.45) | 0.12 (0.06 to 0.24) | 0.26 (0.13 to 0.45) | 0.12 (0.06 to 0.24) |
| P value | <0.0001 | | <0.0001 | | <0.0001 | |
| Ambulatory | 14 (11 to 21) | 11 (7 to 16) | 16 (11 to 23) | 11 (7 to 16) | 16 (11 to 23) | 11 (7 to 16) |
| P value | <0.0001 | | <0.0001 | | <0.0001 | |

DAD visit definitions are as follows: inpatient is at least one night in hospital, outpatient is admission and discharge on the same day (on a date not recorded as inpatient) and ambulatory is per physician claim that is in person or remote (on a date without an inpatient or outpatient claim).
CD, Crohn's disease; DAD, discharge abstract database; IBD, inflammatory bowel disease; SEFI, Socioeconomic Factor Index; UC, ulcerative colitis.

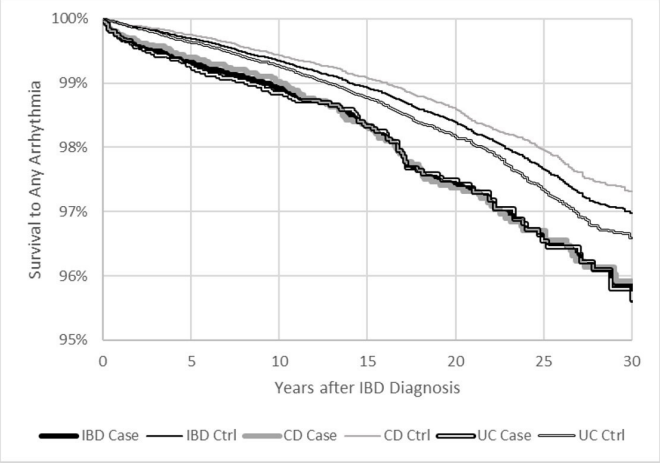


**Figure 1** Kaplan-Meier curve depicting time to first arrhythmia diagnosis following index IBD diagnosis. CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

as 5-ASA preparations, thiopurines and TNF-α inhibitors were not associated with arrhythmia.

Our study corroborates findings of previous literature reporting a higher risk of AF in patients with IBD.[11 17–19] In a retrospective study of medical records of persons with IBD hospitalised or seen in gastroenterology clinic, the prevalence of AF in 141 patients with IBD was 11.3% compared with the 0.9% AF prevalence reported in the US general population (nearly 1.9 million).[18] Additionally, the higher prevalence of AF remained significant across different age categories, including those younger than 59 years.[18] In a population-based study, Choi and colleagues reported a 36% increase in risk of AF in patients with IBD compared with controls; a higher risk for AF was maintained in younger age groups, as well as in the absence of cardiovascular risk factors.[17] Another registry-based study from Denmark described increased incidence of IBD-associated AF with an incidence rate ratio (IRR) of 1.26 (95% CI, 1.16 to 1.36), which was primarily driven by higher incidence of the arrhythmia during periods of disease flares or persistent activity; whereas the risk of AF was not significantly increased during periods of disease remission.[11] In a more recent Danish study the adjusted HR for tachyarrhythmia risk in CD was 1.15 (95% CI, 1.09 to 1.21), and in UC was 1.14 (95% CI, 1.10 to 1.18). However, they did not assess the role of IBD-associated medications and arrhythmia risk.[6]

One novel aspect of our study is reporting on the risk of other SVT and VT in IBD. Beyond AF, we also reported significantly higher risks of other SVT and VT in all patients with IBD, most pronounced in patients with CD and not in UC. Adjusted analyses from data collected from a US national inpatient sample (NIS) database interestingly demonstrated a lower likelihood of arrhythmia diagnoses (including AF, VT and SVT) in patients with IBD with an OR of 0.87 (95% CI, 0.85 to 0.88).[20] The argument made for these findings pertained to the generally younger age of patients with IBD being protective against other cardiovascular risks.[20] Another study using the US NIS database from 2015 to 2017 reported a 9% incidence of AF in hospitalised patients with IBD; this group had a mean age of 73.2 years, compared with a mean age of 50.8 years in patients with IBD without AF.[21] Patients with IBD with AF also happened to have more cardiovascular risk factors and heart failure, as well as higher incidence of in-hospital mortality, sepsis and longer hospital stays.[21] Also using the NIS, Kichloo and colleagues assessed IBD hospitalisations from 2018 and reported an adjusted OR of 2.05% for in-hospital mortality in IBD hospitalisation with AF versus 0.24% for those without AF.[22]

In our study, of all arrhythmias, VT had the highest HR. Within the UC cohort, the only arrhythmia with an elevated risk compared with controls was AF. There was not a linear effect of age on arrhythmia risk. For persons with IBD, arrhythmia risk was increased in their sixth decade or younger, and in their eighth decade. Persons with IBD in their seventh decade did not have a significantly increased risk of arrhythmia compared to controls. While we cannot explain why the risk of arrhythmias in persons in their seventh decade was not increased compared with controls, perhaps the increased risk of VT suggests that it is more susceptible to systemic inflammation than other arrhythmias assessed, and that CD is associated with more systemic inflammation than UC.

There is growing awareness that chronic inflammation associated with IBD may be a harbinger for the generation of cardiac arrhythmias. Although the mechanisms are poorly understood, it is well appreciated that excessive production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 alter ion channel expression and

**Table 2** Risk of arrhythmia in IBD versus controls preceding heart disease diagnosis

| | IBD | | CD | | UC | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Any arrhythmia | 1.51 (1.3 to 1.76) | <0.0001 | 1.71 (1.38 to 2.12) | <0.0001 | 1.34 (1.08 to 1.67) | 0.0079 |
| Atrial fibrillation | 1.44 (1.21 to 1.71) | <0.0001 | 1.62 (1.27 to 2.08) | 0.0001 | 1.28 (1 to 1.64) | 0.047 |
| Other supraventricular tachycardia | 1.57 (1.07 to 2.31) | 0.022 | 1.6 (0.92 to 2.78) | 0.0967 | 1.54 (0.9 to 2.64) | 0.11 |
| Ventricular tachycardia | 2.57 (1.43 to 4.61) | 0.0016 | 3.57 (1.65 to 7.75) | 0.0013 | 1.73 (0.7 to 4.32) | 0.24 |

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Table 3 Risk of arrhythmia by decade of life in incident IBD versus controls preceding HD diagnosis

| | IBD | Control | CD | Control | UC | Control |
|---|---|---|---|---|---|---|
| Age <50 years | | | | | | |
| Total N | 8281 | 79 139 | 4229 | 40 551 | 4052 | 38 588 |
| With arrhythmia | 34 | 148 | 17 | 75 | 17 | 73 |
| IBD vs control - HR (95% CI) (p value) | 1.91 (1.30 to 2.80) (0.0009) | | 1.94 (1.13 to 3.34) (0.016) | | 1.88 (1.10 to 3.23) (0.022) | |
| Age 50–59 years | | | | | | |
| Total N | 5101 | 39 262 | 2408 | 18 260 | 2693 | 21 002 |
| With arrhythmia | 33 | 164 | 20 | 80 | 13 | 84 |
| IBD vs control - HR (95% CI) (p value) | 1.69 (1.15 to 2.47) (0.0072) | | 2.13 (1.29 to 3.51) (0.003) | | 1.27 (0.71 to 2.30) (0.42) | |
| Age 60–69 years | | | | | | |
| Total N | 3547 | 26 155 | 1614 | 11 913 | 1933 | 14 242 |
| With arrhythmia | 47 | 265 | 26 | 129 | 21 | 136 |
| IBD vs control - HR (95% CI) (p value) | 1.27 (0.93 to 1.75) (0.13) | | 1.40 (0.91 to 2.14) (0.13) | | 1.15 (0.72 to 1.84) (0.55) | |
| Age 70–79 years | | | | | | |
| Total N | 1923 | 12 627 | 823 | 5324 | 1100 | 7303 |
| With arrhythmia | 68 | 279 | 33 | 112 | 35 | 167 |
| IBD vs control - HR (95% CI) (p value) | 1.78 (1.35 to 2.35) (<0.0001) | | 2.18 (1.46 to 3.27) (0.0002) | | 1.51 (1.04 to 2.21) (0.031) | |
| Age >80 years | | | | | | |
| Total N | 741 | 3516 | 282 | 1362 | 459 | 2154 |
| With arrhythmia | 43 | 168 | 19 | 71 | 24 | 97 |
| IBD vs control - HR (95% CI) (p value) | 1.05 (0.71 to 1.56) (0.79) | | 1.02 (0.57 to 1.83) (0.94) | | 1.08 (0.63 to 1.86) (0.77) | |

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

function resulting in abnormal depolarisation and repolarisation currents in cardiomyocytes.[23] For example, changes in either potassium currents or L-type calcium channel activity have been reported by elevated systemic TNF-α and IL-6, which increase the propensity for arrhythmogenesis. In addition, inflammatory cytokines can also disrupt normal ion channel activity through reactive oxygen species generation, which directly impair channel function, leading to re-entrant currents that are substrates for atrial and ventricular tachyarrhythmias, as well as long QT syndromes.[23]

Further, chronic inflammation promotes fibrosis and structural changes in the atria, which in turn disrupt the normal electrical conduction and increase the risk of arrhythmias like AF.[24] Interatrial and intra-atrial electromechanical delays (EMD) were higher in patients

Table 4 Risk of arrhythmia in IBD, by IBD medication use

| | Cases (%) | Controls (%) | OR | 95% CI | P value |
|---|---|---|---|---|---|
| Thiopurine | | | | | |
| IBD | 156 (10) | 642 (10) | 1.06 | 0.57 to 1.97 | 0.86 |
| CD | 85 (13) | 350 (14) | 1.01 | 0.48 to 2.13 | 0.97 |
| UC | 71 (<8) | 292 (5) | 1.17 | 0.37 to 3.68 | 0.79 |
| 5-ASA | | | | | |
| IBD | 156 (49) | 642 (48) | 0.99 | 0.68 to 1.45 | 0.98 |
| CD | 85 (45) | 350 (38) | 1.24 | 0.74 to 2.07 | 0.42 |
| UC | 71 (54) | 292 (60) | 0.78 | 0.46 to 1.34 | 0.38 |
| TNF-α inhibitor | | | | | |
| IBD | 130 (<5) | 532 (5) | 0.90 | 0.31 to 2.61 | 0.85 |
| CD | 72 (<8) | 303 (7) | 0.64 | 0.17 to 2.52 | 0.53 |
| UC | 58 (<10) | 229 (<3) | 1.88 | 0.30 to 11.73 | 0.50 |

ASA, 5-aminosalicylate; CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumour necrosis factor; UC, ulcerative colitis.

with IBD during active disease compared with those in remission and in controls.[8] These findings were corroborated by Can and colleagues, where interatrial and intra-atrial conduction times were significantly increased in all patients with IBD compared with controls of the same age group; left atrial width was also found to be larger in patients with IBD.[19] Additionally, immune cells like macrophages and T cells infiltrate the heart, exacerbating inflammation and fibrosis, thus enhancing arrhythmia risk.[24] Hence, systemic inflammation in patients with active IBD can play a critical role in the initiation and progression of arrhythmia in affected patients without pre-existing HD.

It has been postulated that arrhythmias in IBD may be increased due to IBD medications, although there are scarce data available on this association. While there is no clear evidence linking IBD treatments like 5-ASA, immunomodulators (eg, azathioprine), or biologics (eg, TNF-α inhibitors) directly to arrhythmias,[25] the anti-inflammatory effects of biological agents (eg, infliximab, adalimumab) have been shown to offer some protection against arrhythmias likely by reducing inflammation and the associated structural ventricular remodelling.[26 27] Therefore, while IBD appears to contribute to arrhythmia risk through inflammation, current treatments, especially anti-inflammatory biologics, may actually reduce the risk of arrhythmias.

Previous registry-based data reported on the potential effect of 5-ASAs on cardiovascular disease, where the risk of coronary artery disease (CAD) was lower in patients with IBD on 5-ASAs (IRR 1.16; 95% CI, 1.06 to 1.26) compared with non-users (IRR 1.36; 95% CI, 1.22 to 1.51).[28] In the same study, the association between TNF-α inhibitors or thiopurines and risk of CAD was unclear.[28] Myocarditis and pericarditis are also rare adverse events associated with the recent start of 5-ASAs that would prompt their immediate discontinuation.[29] In contrast, use of 5-ASAs did not alter the risk of ischemic HD in patients with IBD based on a retrospective British database study in a subset analysis excluding those with HD preceding diagnosis of IBD.[30] TNF-α inhibitors have previously been shown to be associated with reduced incidence of thromboembolic and cardiovascular events, the latter being in comparison to prolonged treatment with corticosteroids.[31 32]

The aforementioned study by Choi and colleagues reported an overall increased risk of AF among patients with moderate to severe IBD, as indicated by their use of immunomodulators, corticosteroids or biological agents; this risk was significant across all medication groups.[17] Other data demonstrated a high risk of AF with TNF-α inhibitors in IBD, whereas stroke risk was comparable to controls.[11] With regards to thiopurines, two case reports describe increased incident AF in patients with UC on azathioprine.[13 33] Our study, notably, did not establish an association between the use of 5-ASAs, thiopurines, or TNF-α inhibitors and risk of arrhythmia. A possible explanation for this may be the small size with stratification of a very select population. Although, these findings may also support the theory of inflammation being the main driver for the development of arrhythmia in IBD, and with the anti-inflammatory effects of these medications, it would be expected that the risk of arrhythmia would decrease.

In online supplemental table 2, we report on differences in arrhythmia risk by sex. Females with CD had a higher likelihood of any arrhythmias, AF or VT compared with males with CD. This pattern is somewhat reversed in UC, where males have a higher risk for arrhythmias. This may reflect differential impact of sex hormones on arrhythmia risk by disease state, or differential degree of systemic inflammation on arrhythmia risk by sex. More research will be required to better understand differential risks for arrhythmia in males and females and by disease type.

The main strengths of our study pertain to its relatively large population obtained from a large Canadian provincial database, which allows for adjustment for multiple demographic variables including SES and number of healthcare visits. Furthermore, our case definition of IBD is previously validated with high sensitivity and specificity. Adjusting for the presence of HD, as well as other cardiovascular comorbidities of the CCI, in our analyses was key to clearly elucidating the relationship between IBD and arrhythmia. Ours is one of very few studies describing risks of arrhythmia beyond AF, and additionally assessing the association between different IBD medications and arrhythmia.

Several important limitations should be taken into consideration. A primary study limitation is the observational and retrospective nature of its design. Another basic limitation is the use of ICD codes from hospital discharges or physician claims, which can contribute to misclassification bias. Ideally, we would have stratified our analyses by hospitalised patients versus outpatients, and similarly by disease activity, however, we lacked these variables in our database. Like prior studies, we also did not have available to us direct data on the severity of IBD. These variables would be hypothesised to influence the risk of arrhythmia in IBD. We note that prior studies relied on prescriptions with TNF-α inhibitors or biological agents as proxies for the severity of IBD. Additional confounding variables like dietary habits / nutrition status, mental health, or physical activity / fitness levels were also not available in our database. Medication data within our nested cohort study was limited to 5-ASA preparations, thiopurines and TNF-α inhibitors and did not include corticosteroids or other biological agents. We acknowledge that the use of steroids may also influence cardiovascular risks and outcomes.[32]

In conclusion, key findings of our study include a higher risk of AF and other arrhythmias in patients with IBD, independent of the presence of HD or other cardiovascular comorbidities. Additionally, there was no association between the use of IBD medications such as 5-ASAs, thiopurines and TNF-α inhibitors and risk of arrhythmia in IBD. Further large cohort data, ideally collected prospectively, is key to further characterising the direct or

indirect relationship between IBD and/or IBD medications and risk of cardiac arrhythmia.

**Contributors** Study concept and design: CNB, ZN, LK and IR-N. Data analysis and interpretation of the data: CNB, ZN, MN, IR-N and LK. Initial draft of manuscript: MN. Critical revision of the manuscript: CNB, ZN, MN, IR-N, LK. CNB is the guarantor of the article.

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**Competing interests** CNB has served on advisory Boards for AbbVie Canada, Amgen Canada, Bristol Myers Squibb Canada, Celltrion, Eli Lilly Canada, Fresenius Kabi, JAMP Pharmaceuticals, Janssen Canada, Pendopharm Canada, Sandoz Canada, Takeda Canada and Pfizer Canada; Educational grants from AbbVie Canada, Boston Scientific, Bristol Myers Squibb Canada, Ferring Canada, Pfizer Canada, Takeda Canada, Janssen Canada, Organon Canada, Eli Lilly Canada and Amgen Canada. Speaker's panel for AbbVie Canada, Fresenius Kabi, Janssen Canada, Pfizer Canada and Takeda Canada. Received research funding from AbbVie Canada, Amgen Canada, Sandoz Canada, Takeda Canada and Pfizer Canada.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The construction of the University of Manitoba IBD Epidemiology Database (UMIBDED) and the use of it for clinical studies was approved by the University of Manitoba Research Ethics Board (#HS11468 (H2009:217)) and by the Health Information Privacy Committee of Manitoba Health (MH) (HIPC #2009/2010-23). This study includes humans, however, it is an administrative database study and the humans are not identifiable. While each individual has a personal health identification number, the numbers used in this administrative database study are scrambled. No individual gave consent, although the study was approved by the University of Manitoba Heath Research Ethics Board.

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**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. All data that are available are reported in this manuscript.



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