The Incremental Rate of Thromboembolic Events in Patients With Inflammatory Bowel Disease Compared to Patients Without Immune-mediated Diseases

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BACKGROUND

- Inflammatory bowel diseases (IBD) are linked to an increased risk of thromboembolic events, potentially due to the close relationship between systematic inflammation and hypercoagulability
- Thromboembolic events include venous events, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial events, such as ischemic stroke (IS) and myocardial infarction (MI)
- Previous studies confirm that patients with IBD are at an approximately two-fold increased risk for venous thromboembolic events compared to the general population or to patients without IBD; similarly, studies have shown that patients with IBD are at an increased risk for arterial thromboembolic events, albeit to a lesser degree than for venous events[1,2,3]
- As the management of IBD has changed dramatically and several novel IBD therapeutic agents have been approved, there is a need to systematically assess the association between IBD and thromboembolic events in the current era
  - Such an assessment will also serve as a baseline reference for newer agents for IBD, such as Janus kinase (JAK) inhibitors

OBJECTIVE

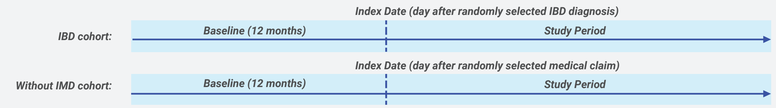
- To assess the incremental rate of thromboembolic events in patients with IBD compared to patients without immune-mediated diseases (IMD)
  - Thromboembolic events included DVT, PE, IS, and MI
  - IMD included ankylosing spondylitis, atopic dermatitis, IBD, multiple sclerosis, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, and systemic lupus erythematosus

METHODS

DATA SOURCE

- This study was a retrospective cohort study of IBM MarketScan® Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits Databases: 2014-2018
  - These databases include both employer-paid (e.g., active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act [COBRA] continues, and dependents) and employer-sponsored Medicare supplemental healthcare encounters
  - Data contain enrollment history, dates of service, claims for medical (e.g., professional and institutional services) and pharmacy services, and some demographic variables (e.g., age, sex, and geographic region)

Figure 1. Study Design



Baseline

- The baseline period was defined as the 12-month period prior to the index date

Index Date

- *IBD cohort*: the index date was defined as the day after a randomly selected date of a medical claim with an IBD diagnosis to capture patients at different points in their disease spectrum, i.e., with different severities and treatment profiles; if the first IBD diagnosis was chosen, then the sample would be a group of predominantly newly diagnosed patients
- *Without IMD cohort*: the index date was defined as the day after a randomly selected date of a medical claim

Study Period

- The study period was defined as the time from the index date until the earliest of patient death, end of continuous eligibility, or end of data
- Patients were required to have at least 30 days of continuous eligibility following the index date, and were followed for up to four years

BASELINE

- The following characteristics were assessed during the baseline period and compared between patients with IBD and patients without IMD:
  - Demographics (e.g., age at index date, sex)
  - Index year
  - History of thromboembolic events
  - Conditions of interest (e.g., comorbidities, pregnancy)
  - Common classes of drug use (e.g., oral contraceptives, hormone replacement therapy, biologics, non-biologic immunomodulators, etc.)
- Statistical comparisons for matched samples were conducted using Wilcoxon signed-rank tests for continuous variables and McNemar tests for categorical variables

STATISTICAL ANALYSIS

- For each cohort, incidence rates (IR) of thromboembolic events (overall and separately for DVT, PE, IS, and MI) were calculated as the total number of thromboembolic events divided by the total patient-years during the study period
- Unadjusted and adjusted incidence rate ratios (IRRs) were used to compare the IR of thromboembolic events between patients with IBD and without IMD
  - IRRs, 95% confidence intervals, and *P*-values were estimated using generalized linear models with a Poisson distribution and a sandwich (robust) variance estimator
    - An offset was used to account for varying lengths of follow-up time
  - The adjusted IRRs controlled for baseline IBD status (yes/no), age at index date, gender (female), baseline comorbidities, baseline medications (excluding IMD treatments), and history of thromboembolic event of interest during baseline
    - IMD treatments were not adjusted for because many of them have no or low utilization in the without IMD cohort; furthermore, these factors could be considered mediators for the IBD to thromboembolic event pathway

RESULTS

Table 1. Comparison of Demographics and Clinical Characteristics Between IBD Patients and Patients Without IMD During the Baseline Period

Characteristic	IBD cohort (N = 34,687)	Without IMD cohort (N = 34,687)	*P*-value
Age at index date (years)			
Mean ± SD	49.0 ± 16.1	49.0 ± 16.1	0.1406
Sex, n (%)			
Male	15,807 (45.6%)	15,807 (45.6%)	-
Female	18,880 (54.4%)	18,880 (54.4%)	-
Index year			
2015	9,422 (27.2%)	9,422 (27.2%)	-
2016	9,282 (26.8%)	9,282 (26.8%)	-
2017	7,945 (22.9%)	7,945 (22.9%)	-
2018	8,038 (23.2%)	8,038 (23.2%)	-
History of thromboembolic events, n (%)	1,613 (4.7%)	887 (2.6%)	<0.0001
Deep vein thrombosis	810 (2.3%)	326 (0.9%)	<0.0001
Ischemic stroke	443 (1.3%)	327 (0.9%)	<0.0001
Pulmonary embolism	355 (1.0%)	144 (0.4%)	<0.0001
Myocardial infarction	306 (0.9%)	212 (0.6%)	<0.0001
Conditions of interest, n (%)			
Cancer	3,412 (9.8%)	2,318 (6.7%)	<0.0001
Cardiovascular diseases	15,474 (44.6%)	14,622 (42.2%)	<0.0001
Atherosclerosis	2,415 (7.0%)	2,005 (5.8%)	<0.0001
Atrial fibrillation	1,253 (3.6%)	895 (2.6%)	<0.0001
Heart failure	963 (2.8%)	687 (2.0%)	<0.0001
Hyperlipidemia	10,336 (29.8%)	10,350 (29.8%)	0.8975
Hypertension	11,266 (32.5%)	10,582 (30.5%)	<0.0001
Chronic kidney disease	1,313 (3.8%)	843 (2.4%)	<0.0001
Chronic obstructive pulmonary disease	1,596 (4.6%)	1,043 (3.0%)	<0.0001
Diabetes			
Type 1	457 (1.3%)	405 (1.2%)	0.0752
Type 2	3,782 (10.9%)	3,937 (11.4%)	0.0519
Fracture (hip or leg)	224 (0.6%)	221 (0.6%)	0.8861
Peripheral vascular disease	1,797 (5.2%)	1,096 (3.2%)	<0.0001
Pregnancy[1]	855 (4.5%)	1,077 (5.7%)	<0.0001
Common classes of drug use, n (%)			
Non-IMD drugs			
Hormone replacement therapies[1]	1,424 (7.5%)	1,199 (6.4%)	<0.0001
Testosterone replacement therapies[1]	448 (2.8%)	327 (2.1%)	<0.0001
Oral contraceptives[1]	2,570 (13.6%)	2,133 (11.3%)	<0.0001
IMD drugs			
Biologics	4,089 (11.8%)	2 (0.0%)	-
TNF inhibitors	3,835 (11.1%)	2 (0.0%)	-
Interferon beta-1a	13 (0.0%)	0 (0.0%)	-
Interleukin inhibitors	194 (0.6%)	0 (0.0%)	-
Other biologics	152 (0.4%)	0 (0.0%)	-
Glucocorticoids	13,058 (37.6%)	5,730 (16.5%)	<0.0001
JAK inhibitors	19 (0.1%)	1 (0.0%)	-
Non-biologic immunomodulators	6,695 (19.3%)	180 (0.5%)	-
Methotrexate	797 (2.3%)	15 (0.0%)	-
S1P-receptor modulators	5 (0.0%)	0 (0.0%)	-
Other non-biologic immunomodulators	6,078 (17.5%)	170 (0.5%)	-
NSAIDs	5,864 (16.9%)	6,556 (18.9%)	<0.0001
5-aminosalicyclic-acid derivative agents	15,811 (45.6%)	23 (0.1%)	-

Notes: [1]The proportions of patients with pregnancy, hormone replacement therapies, and oral contraceptives were reported out of the total number of women in each group. The proportion of patients with testosterone replacement therapies was reported out of the total number of men in each group.
Abbreviations: IBD, inflammatory bowel disease; IMD, immune-mediated disease; JAK, Janus kinase; NSAID, nonsteroidal anti-inflammatory drugs; S1P, sphingosine-1-phosphate; SD, standard deviation; TNF, tumor necrosis factor.

Figure 2. Sample Selection of Patients With IBD and Patients Without an IMD

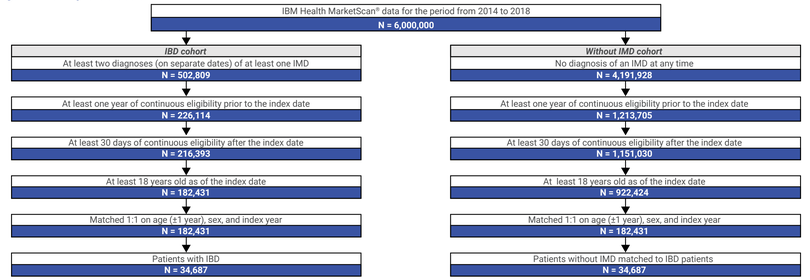


Table 2. Unadjusted and Adjusted Incidence Rates of Thromboembolic Events in Patients With IBD Compared to Patients Without IMD During the Study Period

	Unadjusted				Adjusted	
	IBD cohort (N = 34,687)	Without IMD cohort (N = 34,687)	IRR of IBD vs. without IMD (95% CI)	*P*-value	IRR of IBD vs. without IMD (95% CI)	*P*-value
Total person-years during study period	47,233	44,315	-	-	-	-
Total number of thromboembolic events (any)	9,087	4,186	-	-	-	-
Event rate per year	0.192	0.094	2.04 (1.78, 2.34)	<0.0001	1.49 (1.30, 1.71)	<0.0001
Total number of DVT events	4,188	1,049				
Event rate per year	0.089	0.024	3.75 (3.02, 4.64)	<0.0001	2.44 (2.00, 2.99)	<0.0001
Total number of PE events	2,273	677				
Event rate per year	0.048	0.015	3.15 (2.34, 4.24)	<0.0001	1.90 (1.42, 2.54)	<0.0001
Total number of IS events	2,163	1,535				
Event rate per year	0.046	0.035	1.32 (1.03, 1.69)	0.026	1.15 (0.89, 1.50)	0.278
Total number of MI events	901	1,046				
Event rate per year	0.019	0.024	0.81 (0.59, 1.11)	0.187	0.62 (0.44, 0.88)	0.008

Abbreviations: CI, confidence interval; DVT; deep venous thromboembolism; IBD, inflammatory bowel disease; IMD, immune-mediated disease; IRR, incidence rate ratio; IS, ischemic stroke; MI, myocardial infarction; PE, pulmonary embolism

SUMMARY

Patient Characteristics

- A total of 34,687 matched pairs were analyzed (mean age 49.0 years, 54.4% female) (see **Table 1** and **Figure 2**)
- Patients with IBD generally had higher proportions of comorbidities compared to patients without IMD (e.g., cardiovascular disease [44.6% v 42.2%]; *P* <0.0001) (see **Table 1**)
- A significantly higher proportion of patients with IBD had a history of thromboembolic events during baseline compared to patients without IMD (4.7% v 2.6%, *P* <0.0001) (see **Table 1**)

Incremental rate of thromboembolic events

- Total person-years during the study period were 47,233 and 44,315 for the IBD cohort and the without IMD cohort, respectively (see **Table 2**)
- IBD patients demonstrated a higher incidence rate of experiencing any thromboembolic event compared to patients without IMD (Adjusted IRR: 1.49, *P* <0.0001) (see **Table 2**)
- In both the unadjusted and adjusted analyses, patients with IBD experienced higher rates of venous thromboembolic events compared to patients without IMD (Adjusted IRRs: 2.44 for DVT, 1.90 for PE, both *P* <0.0001) (see **Table 2**)
  - Such increased rates were not observed for the arterial events (Adjusted IRRs: 1.15 for IS, not significant; 0.62 for MI, *P* <0.05) (see **Table 2**)

LIMITATIONS

- Limitations inherent to retrospective observational studies using claims data:
  - Administrative claims data only contain diagnostic and procedure codes recorded for reimbursement purposes and may be subject to coding errors or data omissions
  - Patients may not have used the recorded medication as prescribed after filling a prescription
  - Confounding adjustments can only account for factors that are observable and recorded in the database
    - The impact of omitted variable bias on thromboembolic event outcomes (e.g., HCP's prescribing behaviors, BMI, smoking, immobility, etc.) may not be accounted for in this study, as these variables are not collected in claims data
- Recently approved treatments for IMD may be underrepresented since the data cut spans 2014-2018

CONCLUSIONS

- Patients with IBD had significantly increased rates of DVT and PE compared to patients without IMD, with and without adjustment. Such increased rates were not observed for IS and MI
- This elevated risk of thromboembolic events should be carefully considered when selecting treatment options that may further exacerbate this risk
- The potential association between recent novel IBD therapies approved after 2018 and increasing risk of DVT and PE needs further investigation

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