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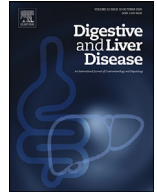
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Incidence and risk factors for thromboembolic events in pediatric-onset inflammatory bowel disease: A French population-based study

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ABSTRACT

Introduction: Patients with inflammatory bowel disease (IBD) are at higher risk of thromboembolic events (TE). In pediatric-onset IBD, more data on incidence and risk factors of venous (VTE) and arterial events (ATE) at the population level are needed to guide thromboprophylaxis.**Methods:** All patients aged ≤ 16 years diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) between 1988 and 2011 in the prospective EPIMAD population-based registry were followed until 2013. Every TE occurring during the follow-up period was included.**Results:** A total of 1,344 patients were included: 1,007 with CD and 337 with UC, and a median diagnosis age of 14.3 years. After a median follow-up of 8.3 years, 2 (0.15 %) ATE and 15 (1.1 %) VTE occurred at median age of 20.4 years. The global incidence rate of thromboembolic events was 1.32 per 1000 person-years. Periods of active disease (HR=8.4, $p = 0.0002$), the 3-month-period following surgery (HR=16.4, $p = 0.0002$) and hospitalization (HR=21.7, $p < 0.0001$) were found to be associated with an increased risk of VTE. A lower rate of VTE was found in patients treated with 5-aminosalicylates (HR=0.1, $p = 0.002$).**Conclusion:** The risk of TE was low in this population. VTE were strongly associated with active disease, surgery and hospitalization.© 2024 The Author(s). Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

1. Introduction

In adults, inflammatory bowel disease (IBD) is associated with an increased risk of thromboembolism (TE) and particularly of venous TE (VTE), despite significant variability in findings across dif-

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ferent publications [1–9]. A meta-analysis enrolling >200 000 IBD patients, revealed that the risk of VTE in IBD patients was approximately double that of the general population [1]. Similarly a modest increase of the risk of arterial TE (ATE) was reported, especially in women and young patients [10]. Despite a growing body of literature on this subject and the development of guidelines for thromboprophylaxis in IBD, the incidence of VTE has been decreasing only slowly in the United States. In the meantime, hospitalizations related to VTE in IBD patients have been on the rise [11,12].

Compared to the general population, the relative risk of TE is higher in younger patients with a six-fold increase before 20 years

old [2]. Nevertheless, none of the existing cohort studies have reported on ATE, and the only available data in this regard is derived from the adult population of IBD patients [1,13–15]. Moreover, in pediatric-onset IBD patients, data on VTE incidence and risk factors are limited and primarily based on small observational retrospective cohorts [16,17]. As a result, the application of thromboprophylaxis in this population is inconsistent [18]. Current guidelines from ECCO recommend thromboprophylaxis only for children with severe acute colitis who have at least one additional risk factor [19]. In 2022, a RAND panel emphasized the need to re-evaluate of the role of thromboprophylaxis in future guidelines [18]. Therefore, gaining a better understanding of VTE risk factors in pediatric-onset IBD patients is essential.

In 2023, a meta-analysis comprising 107 studies involving 216 cases of VTE in pediatric IBD found associations with ulcerative colitis, steroid use, central venous catheters, and the first year of IBD diagnosis [16]. Recently, a large international study involving 129 centers reported, based on a questionnaire, that the incidence of venous thromboembolism (VTE) in pediatric inflammatory bowel disease (IBD) was 3.72 per 10,000 person-years, with cerebral sinus venous thrombosis occurring in half of these cases [20]. Nevertheless, this non-population-based study is a likely to present selection bias. Population-based observational cohort studies evaluate an entire population in a defined geographic area during an extended period of time. They avoid selection biases associated with referral center studies and are ideal to inform on natural history of disease. The largest population-based studies relied on administrative data, which are susceptible to information bias, yielding to heterogeneous results with a seven-fold difference in incidence rates of VTE among them [21–23]. Parallely, administrative data or non-dedicated data bases do not provide a precise description of the IBD phenotype, location or activity. In addition, these studies primarily focused on the increased risk of VTE caused by IBD itself, rather than delving into the risk factors for VTE in pediatric IBD.

Consequently, there is a pressing need for high-quality cohort studies to expand our understanding of TE in pediatric IBD [17]. Hence, our objective was to investigate the risk of TE in pediatric-onset IBD through a population-based study.

2. Methods

2.1. Study population

All patients from the prospective EPIMAD registry with a diagnosis of IBD between January 1988 and December 2011 younger than 17 years at diagnosis were included. The EPIMAD registry covers a large area of Northern France with almost 6 million inhabitants representing 9.3 % of the entire French population. The methodology of the EPIMAD registry has been previously described in detail [24]. Briefly, all patients consulting for the first time for symptoms compatible with IBD are reported since 1988 by adult ($n = 250$) and pediatric ($n = 12$) gastroenterologists, regardless of their type of practice (hospital [$n = 94$] or private [$n = 168$]). Only patients who are residents in Northern France at the time of diagnosis are included. Interviewing practitioners collect data for each new case from medical records using a standardized questionnaire including age, sex, year of diagnosis, clinical, radiological, endoscopic, and histologic findings at the time of diagnosis. A final diagnosis of CD, UC, or IBD—unclassified is made by 2 expert gastroenterologists according to previously defined criteria.

2.2. Study design and data collection

This study was part of the INSPIRED (impact of therapeutic strategies on the natural history of pediatric IBD) project whose

methodology has already been presented in detail [25]. Briefly, additional data were collected from the medical charts by trained research assistants, and each file was further audited by 2 independent expert gastroenterologists. Baseline characteristics collected were type of IBD, age at diagnosis, gender, IBD phenotype and location according to Paris classification [26], smoking status at baseline, and extraintestinal manifestations. During follow-up, smoking status was updated, and intercurrent medical events were collected. At each visit, the location and behavior of IBD as well as the smoking status were recorded. Dates of initiation, withdrawal, dosage and reason for withdrawal of the following medications were recorded for each patient: oral 5-aminosalicylic acid (5-ASA), oral and intravenous corticosteroids, immunosuppressants (IS) (azathioprine, 6-mercaptopurine, and methotrexate) and anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, golimumab, and certolizumab). Patients were followed from diagnosis to December 31, 2013, date of loss to follow-up, or date of death.

2.3. Definitions and outcomes

Every thromboembolic event, both venous and arterial, occurring during the follow-up period were included. A VTE was defined as a radiologically confirmed thromboembolism and categorized as deep venous thrombosis (DVT), pulmonary embolism, and other location according to the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification [27]. Arterial thrombosis consisted of the following: ischemic heart disease, myocardial infarction, stroke, peripheral artery disease and mesenteric ischemia. For each case the following additional information was collected: thrombosis type and location, history of thrombosis, presence of thrombophilia and thrombosis risk factors, and outcome.

Active disease was defined by the presence of at least one of the following criteria: (1) clinical flare defined by a Harvey-Bradshaw index \geq to 4 in CD patients or by partial Mayo Score \geq 3 in UC, and/or (2) active luminal inflammation in endoscopy defined by a Mayo endoscopic subscore greater than or equal to 2 in UC or by the presence of ulcerations in CD, and/or (3) radiological features related to disease activity. Inflammation was considered as present on CT or MRI if the radiologist's report described ileitis or colitis.

2.4. Statistics

Quantitative data were described with their median and interquartile range (Q1-Q3) and categorical data by frequencies and percentages. Incidence rates were calculated by dividing the number of events by the person-time of follow-up, and 95 % confidence intervals (95 % CI) were calculated using a Poisson distribution. Cumulative incidence rates and cumulative incidence curves were estimated by the Kaplan-Meier method. Univariable Cox proportional hazard models with hazard ratio (HR) and 95 % CI were used to analyze impact of different patient and disease characteristics on VTE occurrence: patient's characteristics at diagnosis (sex, age, type of IBD, extraintestinal manifestations and period of diagnosis), tobacco smoking, disease activity, drug therapy (IS, anti-TNF, systemic steroids and systemic 5-ASA), and some events within the last 3 months (surgery, hospitalization and hospitalization without surgery). All variables studied were treated as time dependent [28] (Supplementary Table 1) except for patient's characteristics at diagnosis. In order to take into account only immobilization of at least 72 h, only hospitalizations \geq 3 days were considered in this analysis. In addition, a sensitivity analysis was done for hospitalization, considering all these events, except scheduled hospitalization for check-up. At last, bivariable Cox proportional hazard model was used to analyze joint impact of disease activity and 5-ASA use on VTE occurrence. The threshold for statistical significance was set

Table 1
Characteristics of the population.

	CD N = 1007	UC N = 337	Total N = 1344
Gender [n (%)]			
Male	556 (55.2)	144 (42.7)	700 (52.1)
Female	451 (44.8)	193 (57.3)	644 (47.9)
Age at diagnosis (years) [median [IQR]]	14.5 [12.0, 16.1]	14.0 [11.2, 15.8]	14.3 [11.7, 16.0]
Year of IBD diagnosis [n (%)]			
1988–1993	167 (16.6)	58 (17.2)	225 (16.7)
1994–2000	260 (25.8)	87 (25.8)	347 (25.8)
2001–2011	580 (57.6)	192 (57.0)	772 (57.4)
Follow-up (years) [median [IQR]]	8.8 [4.6–14.2]	7.2 [3.8–13.0]	8.3 [4.3, 13.9]
CD location [n (%)] – 12 missing			
L1	215 (21.6)	–	–
L2	234 (23.5)	–	–
L3	546 (54.9)	–	–
CD behavior [n (%)] – 3 missing			
B1	827 (82.4)	–	–
B2	145 (14.4)	–	–
B3	32 (3.2)	–	–
UC location [n (%)] – 4 missing			
E1	–	79 (23.7)	–
E2	–	107 (32.1)	–
E3	–	40 (12.0)	–
E4	–	107 (32.1)	–
Smoking [n (%)]	92 (9.1)	19 (5.6)	111 (8.3)
Hypertension	3 (0.3)	1 (0.3)	4 (0.3)
(at any point during the follow-up period) [n (%)]			
Obesity	24 (2.4)	7 (2.1)	31 (2.3)
(at any point during the follow-up period) [n (%)]			
Diabetes mellitus	2 (0.2)	1 (0.3)	3 (0.2)
(at any point during the follow-up period) [n (%)]			
Thrombophilia [n (%)]	3 (0.3)	1 (0.3)	4 (0.3)
Surgery during follow-up [n (%)]	470 (46.7)	61 (18.1)	531 (39.5)
Therapeutics during follow-up			
5-ASA [n (%)]	887 (88.1)	316 (93.8)	1203 (89.5)
Steroids [n (%)]	718 (71.3)	237 (70.3)	955 (71.1)
Immunosuppressant [n (%)]	711 (70.6)	155 (46.0)	866 (64.4)
Biologics [n (%)]	482 (47.9)	83 (24.6)	565 (42.0)
None [n (%)]	12 (1.2)	18 (5.3)	30 (2.2)

Location is given at diagnosis according to Paris classification. 5-ASA, 5-aminosalicylates; CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; UC, ulcerative colitis.

to P value < 0.05 in all tests. Data were analyzed with R v4.0.3, using the 'survival' and 'mstate' packages. The study protocol was approved by the French Ministry of Health according to the regulation of the registries in general population (Number n°14.519 for CCTIRS and 915,476 for the CNIL). Authors vouch for the accuracy of reported data. The data of this article cannot be shared publicly to ensure the privacy of patients.

3. Results

3.1. Population

Among the 1344 patients diagnosed with IBD between 1988 and 2011, 1007 (74.9 %) patients were diagnosed with CD and 337 (25.1 %) with UC. Demographic and clinical characteristics of this population are depicted in Table 1. The follow-up stopped in 2013 and overall median of follow-up was 8.3 IQR[4.3, 13.9] years. The median age at diagnosis was 14.3 [11.7, 16.0] years. One hundred-eleven patients (8.3 %) were smoker at diagnosis. Thrombophilia was known in 4 (0.3 %) patients and 37 (2.8 %) had cardiovascular risk factor including hypertension, diabetes mellitus or obesity. During follow-up 1069 IBD-related surgery were performed in 531 (39.5 %) patients and 837 (62.3 %) were hospitalized during at least 3 days.

3.2. Incidence rate of thromboembolic events

During follow-up, 17 thromboembolic events, 15 venous and 2 arterial events, were observed among 1344 patients. No patients were excluded from the analysis. The cumulative incidence of TE was 0.2 % 95 %CI [0.0 %, 0.5 %] at one year, 0.7 % [0.2 %, 1.2 %] at five years and 1.5 % [0.6 %, 2.4 %] at ten years (Fig. 1A). The global incidence rate of thromboembolic event was 1.32 per 1000 person-years, [0.77 - 2.11]. The median age at the thromboembolic event was 21.3 [16.7, 26.8] years (Fig. 2).

The incidence rate of VTE was 1.16 per 1000 person-years, [0.65 - 1.92]. The cumulative incidence of VTE was 0.2 % [0.0 %, 0.5 %] at one year and 0.7 % [0.2 %, 1.2 %] at five years (Fig. 1B). In patients with CD, the incidence of VTE was 1.41 per 1000 person-years, [0.77 - 2.37], whereas it stood at 0.33 per 1000 person-years, [0.01 - 1.85], in those with UC. No cases of death linked to thromboembolic event was reported.

The incidence rate of ATE was 0.15 cases per 1000 person-years, [0.19–0.56]. Two ATE occurred 18.1 and 20.8 years after the diagnosis of IBD.

3.3. Clinical characteristics of venous thromboembolic events

During follow-up, 15 venous thromboembolisms were observed (Table 2) with a median age at diagnosis of 20.4 [16.6 - 24.5] years. The minimal age of occurrence was 14.8 years. Specifically, 5 of

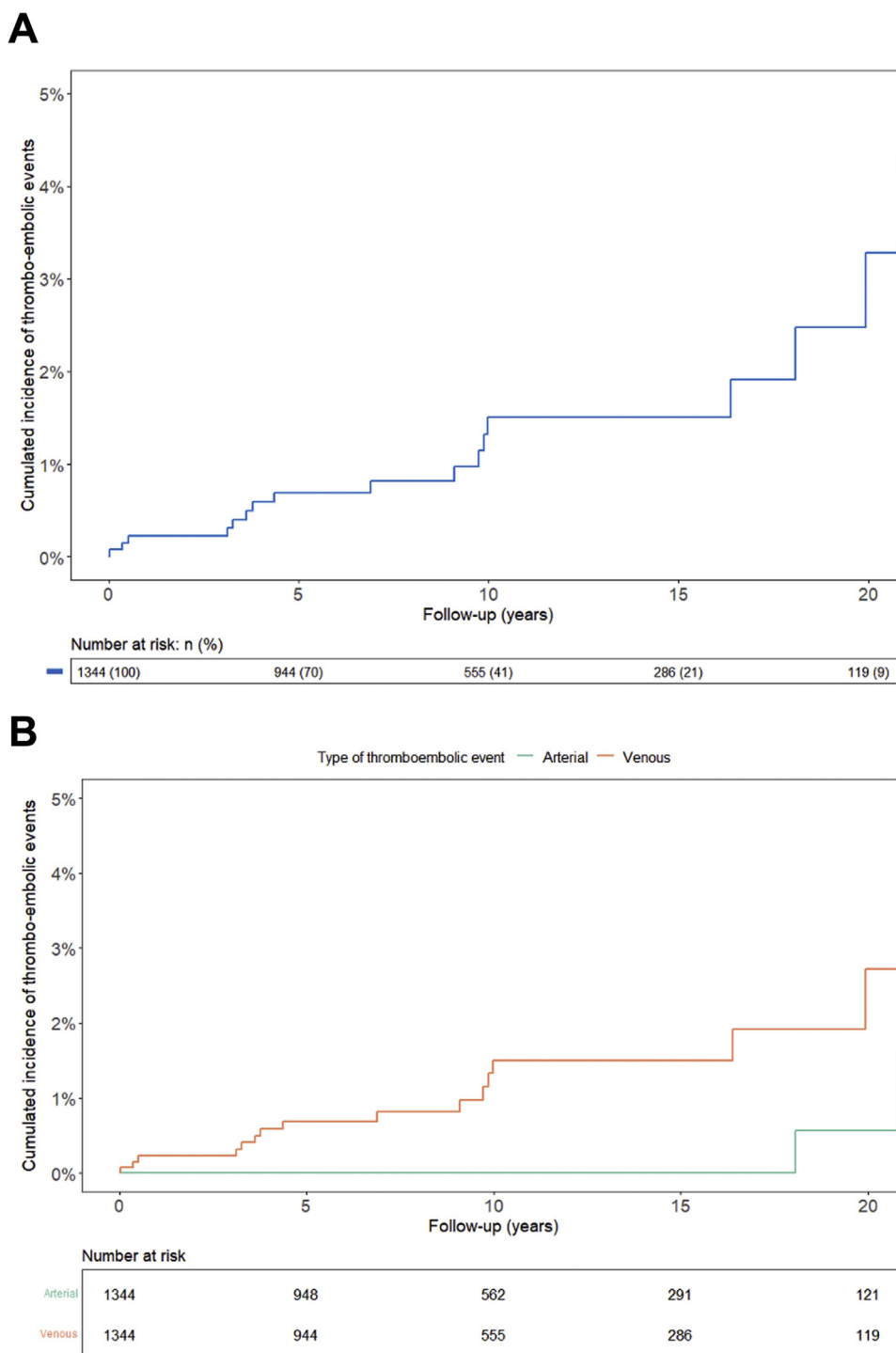


Fig. 1. Global cumulative incidence rate of thromboembolic event [A] and cumulative incidence rates of venous and arterial thromboembolic events, separately [B] in the 1344 patients population-based cohort (Kaplan-Meier curves).

these cases were classified as deep vein thrombosis according to the CEAP classification [27], one was a pulmonary embolism, 2 were cerebral venous sinus thrombosis. All these patients had undergone surgery ($n = 4$) or have been hospitalized ($n = 8$) within 3 months prior to VTE occurrence or had active disease ($n = 13$) at the time of VTE. The median delay between clinical flare diagnosis and thromboembolism was 31.0 [8.0 - 50.8] days. Five patients (33 %) received systemic steroid within the last 30 days. A median delay of 23.5 [5.8 - 41.0] days between hospital discharge and VTE occurrence was observed, as well as a median delay of 8.5

[6.8 - 23.5] days between surgery and VTE occurrence. None of the patients with thromboembolism were found to have either thrombophilia or cancer. Lastly, there were no cases of pulmonary hypertension, or postphlebotic syndrome reported at the end of follow-up.

3.4. Clinical characteristics of arterial thromboembolic events

Two arterial thromboembolic events were observed, occurring at the age of 31 and 35 years, including one myocardial infarction

Table 2
Characteristics of venous thromboembolic events.

	Total n = 15
Age at thrombo-embolic event [years] [median [IQR]]	20.4 [16.6, 24.5]
Time since IBD diagnosis [years] [median[IQR]]	4.4 [3.2, 9.8]
Anatomical location [n (%)]	
Deep vein thrombosis	5 (33)
Cerebral venous sinus	2 (13)
Splanchnic vein	2 (13)
Pulmonary embolism	1 (6.7)
Right atrial	1 (6.7)
Basilic vein	1 (6.7)
Superior vena cava	1 (6.7)
Internal jugular vein	1 (6.7)
Unknown	1 (6.7)
Catheter-related thrombosis [n (%)]	4 (26.7)
HBI ≥ 4 or pMS ≥ 3 [n (%)]	9 (60.0)
C-reactive protein before VTE [mg/L] [median [IQR]], n = 4	63.4 (62.0, 82.0)
Biological, endoscopic or radiological signs of IBD activity within 6 months [n (%)]	
Yes	10 (66.7)
No	4 (26.7)
Unknown	1 (6.7)
Type of IBD [n (%)]	
UC	1 (6.7)
CD	14 (93.3)
pMS ≥ 3 [n (%)], n = 1	1 (100)
HBI ≥ 4 [n (%)], n = 14	8 (57)
Hospitalisation within 3 months [n (%)]	8 (53.3)
Admission for IBD	8 (100)
Surgery within 3 months [n (%)]	4 (26.7)
IBD surgery	4 (100)
History of smoking [n (%)]	4 (26.7)
Therapeutics at VTE [n (%)]	
Systemic steroid within the last 30 days	5 (33)
5-ASA	1 (6.7)
Immunosuppressant	7 (46.7)
Biologics	3 (20.0)

5-ASA, 5-aminosalicylates; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; IQR, interquartile range; pMS: partial Mayo Score; UC, ulcerative colitis; VTE, venous thromboembolic event.

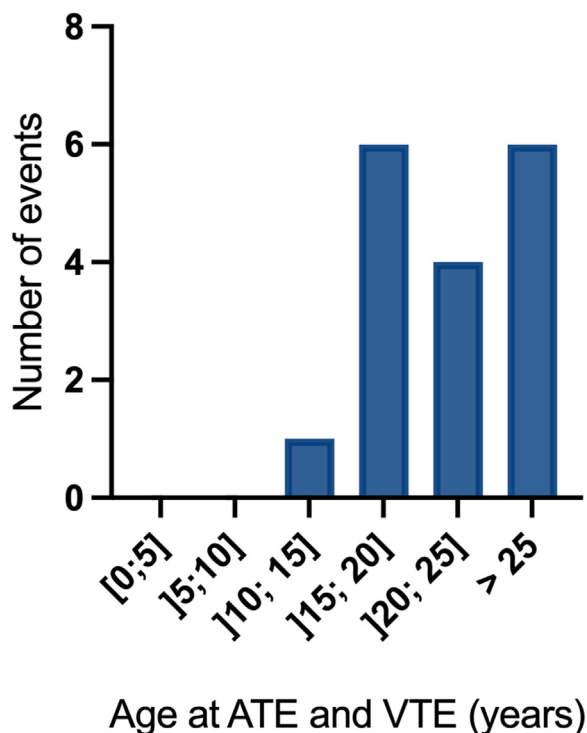


Fig. 2. Number of thromboembolic events according to the age at occurrence.

and one stroke. Notably, there were no biological, radiological, or endoscopic signs of disease activity within the six months preceding the arterial thromboembolic event.

3.5. Factors associated with venous thromboembolism

Periods of active disease were found to be associated with an increased risk of VTE (HR 8.4 [2.3–30.5], $p = 0.0002$) (Table 3). Similarly, the 3-month-period following surgery or hospitalization exhibited a higher rate of VTE (HR 16.4 [5.2–52.3], $p = 0.0002$ and HR 21.7 [7.5–62.9], $p < 0.0001$, respectively) (Table 3). The periods of hospitalization remained at higher risk of VTE, even when excluding the period in which hospitalization coincides with surgery (HR 10.1 [2.5–40.4], $p = 0.007$) (Table 3). The sensitivity analysis using all hospitalization of any duration (except hospitalization for check-up) provide a similar result. A trend towards a lower rate of thromboembolism in patients with UC was observed (HR 0.2 [0.0–1.8], $p = 0.08$). A lower rate of VTE was found in patients treated with 5-ASA (HR 0.1 [0.0–0.7], $p = 0.002$). Considering both the use of 5-ASA and the disease activity in bivariate analysis, the HR observed remained similar to those observed in univariate analysis (HR 0.1 [0.0–0.7], $p = 0.001$, for the use of 5-ASA and HR 8.8 [2.4–31.9], $p = 0.02$, for disease activity). The risk of thromboembolism did not vary throughout the study period (Table 3). Among patients with VTE, no cases of lupus, cancer, or pregnancy were found. According to the low number of events, no multivariable analysis could be performed [29].

Table 3

Factors associated with venous thromboembolic events.

	Person-years	Number of events	Hazard Ratio [95 %CI]	p value
Gender				0.77
Male	6499	7	1.0 [ref]	
Female	6418	8	1.2 [0.4–3.2]	
Age at diagnosis*				0.38
< age of puberty	6303	7	1.0 [ref]	
≥ age of puberty	6614	8	1.1 [0.4–3.0]	
Type of IBD				0.08
CD	9907	14	1.0 [ref]	
UC	3010	1	0.2 [0–1.8]	
Period of diagnosis				0.84
1988–1993	3903	5	1.0 [ref]	
1994–2000	4534	4	0.7 [0.2–2.9]	
2001–2011	4480	6	1 [0.3–4.1]	
Active tobacco smoking**				0.34
No	10,703	11	1.0 [ref]	
Yes	2214	4	1.8 [0.6–5.9]	
Active disease**				0.0002
No	8898	3	1.0 [ref]	
Yes	4020	12	8.4 [2.3–30.5]	
Treatment**				0.002
5-ASA				
No	7701	14	1.0 [ref]	
Yes	5217	1	0.1 [0.0–0.7]	
Immunosuppressant				0.08
No	9225	8	1.0 [ref]	
Yes	3693	7	2.6 [0.9–7.4]	
Biologics				0.52
No	11,028	12	1.0 [ref]	
Yes	1890	3	1.6 [0.4–5.7]	
Systemic steroids				0.08
No	11,730	11	1.0 [ref]	
Yes	1187	4	3.3 [1.0–10.8]	
Surgery (within 3 months)**				0.0002
No	12,674	11	1.0 [ref]	
Yes	244	4	16.4 [5.2–52.3]	
Hospitalisation**				<0.0001
Up to 3 months after hospitalization				
No	12,390	8	1.0 [ref]	
Yes	528	7	21.7 [7.5–62.9]	
Up to 3 months after hospitalization (excluding surgery related hospitalization)				0.007
No	12,593	12	1.0 [ref]	
Yes	325	3	10.1 [2.5–40.4]	

* the average age of puberty in France is 13 for female and 15 for male⁴¹.

** time-dependant variables

5-ASA, 5-aminosalicylates; IQR, interquartile range; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

4. Discussion

In this population-based study involving patients with pediatric-onset IBD, the risk of VTE was relatively low, occurring in young adults with a median age of 20 years, and showing a cumulative incidence of 0.7 % over five years. The main lesson from these findings is the importance of thrombotic prophylaxis for postpubertal children hospitalized either due to a flare or for digestive surgery.

These data are consistent with a Canadian study that reported a cumulative VTE incidence in children with IBD of 1.69 % after an 11-year follow-up [21]. A non-population-based retrospective study in Germany and Austria recorded a VTE incidence rate of 1.41 per 1000 person-years, close to the incidence rate reported in this study [22]. Likewise, a Danish population-based study found an incidence rate of 0.89 per 1000 person-years in IBD patients within the age group 0–20 years [2]. An international prospective non-population-based study conducted across 129 IBD centers, involving younger patients (10 years at diagnosis in median), reported a lower incidence rate of 0.37 per 1000 person-years [20]. Inversely a Canadian population-based study reported a much higher incidence rate of 3.12 per 1000 person-years

five years after the diagnosis of pediatric-onset IBD [23]. These discrepancies in the literature may be explained by various factors. First, some non-population-based studies might be susceptible to recall and selection biases due to their study design. Second, differences in the age of the studied population play a role, as younger age is associated with a decreased absolute risk of TE [16]. Thus, in two studies, the population studied was younger [2,20], leading to a lower rate of VTE. Accordingly, in the Germano-Austrian study, the age of the population and the incident rate were similar [22]. Nevertheless, the Canadian study, which had the highest incidence, was based on a younger population compared to our study [23]. Third, methodological considerations must be addressed regarding the differentiation between incident and prevalent cases. Hence, administrative data are more likely to discriminate between incident and prevalent cases than studies based on remote questionnaires. Fourth, the diagnosis method used for VTE in the Canadian administrative study with the highest incidence rate may explain part of this difference. Indeed, concerns have been raised regarding the reliability of the ICD codes for the diagnosis of VTE [30,31]. This has led some authors to consider the ICD codes as a preliminary identification tool for TVE before confirming through chart review [31].

Over the study period (1988–2011), the rate of TE remained stable. This observation aligns with data available for the adult population with IBD [11,12]. To our knowledge, this is the first data regarding the evolution of the incidence of TE in pediatric-onset IBD. This stagnation of the incidence rate of TE may result from either the study's insufficient power or a failure to adhere to pediatric IBD guidelines on thromboprophylaxis, with thromboprophylaxis prescriptions being absent in as many as 20 % of pediatric IBD cases [20].

The clinical presentation of VTE was similar to previously published data. In this study, the median age at the diagnosis of VTE was 20.4 years. Previous studies and a scoping review reported a younger age of occurrence (between 13 and 14 years) [16,20,22]. Even though pubertal status was not recorded, the minimum age of VTE occurrence (14.8 years) suggests that these events occurred after puberty. In this study, deep vein thrombosis was the most frequent VTE as previously reported in the Canadian and Danish studies [2,21,23]. Cerebral venous sinus thrombosis was the second most observed type of VTE. In two prior studies, cerebral venous sinus thrombus was the most common VTE type, representing about one third to one half of all VTE cases [16,20,22].

The investigation of risk factors for VTE in pediatric IBD has received limited attention. In this study, VTE occurrence has been associated with at least one risk factor, which was consistent with a prior study [20]. Moreover, a combination of risk factors is likely to amplify the risk of VTE, as established in adults with IBD [32]. Three risk factors linked with VTE were identified in this study: disease activity, recent hospitalization and surgery. Notably, disease activity has not yet been documented as a VTE-associated factor in pediatric IBD, although a population-based study has reported this risk factor in adults with IBD [3]. Recent hospitalization is already a well-established risk factor of VTE in pediatric IBD, albeit with a substantially higher risk ratio (560 versus 21.7 in this study) [22,23]. Similarly, surgery has already been identified as a risk factor for VTE [20] with a VTE rate reaching as high as 4.3 % in pediatric IBD two weeks after colorectal resection [33]. Conversely, a treatment with 5-ASA was associated with a reduction of the risk of VTE. In our study, if disease activity did not seem to impact this association, the low number of thromboembolism events observed necessitates interpreting this result with extreme caution. Moreover, 5-ASA are likely to be prescribed to young patients who are also at low risk of VTE. The effect of 5-ASA on VTE risk is rarely studied, and data are conflicting. One study found a similar result in a nationwide IBD cohort [34], while two other works did not observe any effect of 5-ASA on VTE [35,36]. Recently, a meta-analysis found the risk of VTE to be equivalent in patients with 5-ASA or anti-TNF [37]. Conclusions about the impact of coagulopathy in pediatric IBD cannot be drawn, as this predisposing condition is rarely tested in this young population [16]. Lastly, catheter related thrombosis was frequent in our study, accounting for approximately one-quarter of VTE cases. A similar trend was noted in prior studies [23,33]. On the whole, the risk-increasing factors for VTE in pediatric IBD appeared to align with those described in adults with IBD [3,32,38].

Prior studies indicated a higher prevalence of VTE in patients with pediatric-onset UC, although the association was no longer significant when adjusting of demographic characteristics [21–23]. Although our study did not observe this trend, our results are likely to be biased and underpowered due to residual confounding. The extension of the disease, specifically pancolitis, has been suggested to be closely linked to the risk of VTE [22]. In our study, pancolitis represented one-third of UC patients, while in one pediatric-onset UC cohort study, this proportion was over one-half [22] and unknown in a second one [23]. Thus, a lack of power and confounding bias are likely to explain our result as no multivariate analysis has been performed. Indeed, CD patients were three

times more likely to undergo digestive surgery during the follow-up period than UC patients, and the presence of a catheter was not documented in the entire cohort. In adults with IBD, the relationship between IBD subtype and VTE is debated. In a large American study involving hospitalized IBD patients, adults with UC were found to have a heightened risk of VTE [8] whereas two other population-based studies demonstrated a similar risk of VTE between UC and CD [4,7]. Lastly, it should be noted that data regarding obesity status were unavailable for the majority of patients, which represents a limitation of our study. Similarly, while estrogen-based contraceptives are commonly used among young women and are associated with an increased risk of VTE [39], these medications were not included in our study. Currently, ECCO guidelines advocate for thrombotic prophylaxis in adolescent with severe acute colitis associated with at least one other risk factor [19]. These results support the use of thrombotic prophylaxis in postpubertal children aged 14 or older and hospitalized either in context of a flare or digestive surgery. In younger patients with risk factors, we advise a case-by-case discussion.

This study was the first to report the occurrence of ATE in a pediatric-onset IBD population. During the follow-up period, only one case of myocardial infarction was documented. As expected, the incidence of arterial thromboembolic events in this study was considerably lower than the reported myocardial infarction rate in adults with UC (cumulative incidence of about 1.1 % at 5 years) [40] or the prevalence of chronic coronary heart disease (2.2 %) reported in a IBD adult population in Finland [41]. Similarly, only one case of stroke was reported during follow-up, while a Swedish population-based study in adults reported an incidence rate of 3.2 strokes per 1000 person-years [14]. Further case-control studies specifically focused on the pediatric IBD population are necessary to better understand the risk of arterial thromboembolic events in comparison to their peers.

Despite the population-based nature of this work, it is important to acknowledge certain limitations when interpreting our findings. Although we followed >1300 patients with pediatric-onset IBD for 8 years, we observed only 17 cases of TE. This low incidence rate necessitates caution when considering the risk factors we have presented, as (1) some additional risk factors may have been neglected due to limited statistical power and (2) some risk factors, including obesity, cancer, pregnancy, and use of thromboprophylaxis or estrogen-based contraceptives, are missing from analysis. To that extent, the limited number of ATE cases do not allow to draw any conclusion regarding the putative predisposing conditions. Last, while the likelihood of an information bias regarding TE occurrence is low, it remains a possibility. Nevertheless, given the seriousness of such events, it is improbable that they have been missed. Moreover, these results are certainly more applicable to a European population than to an American one, as the obesity rate is higher in the United States and has worsened over the last decade [42]. Likewise, the low number of pancolic UC cases limits the applicability to this specific population. The study time period, which included the last incident cases of IBD in 2011, may introduce bias as standards of care and thromboprophylaxis protocols may have improved in the meantime. However, the follow-up of patients stopped in 2013, and the stable rate of TE advocates for a similar result currently. Moreover, despite the time period of the study, 48 % of CD patients and 24 % of UC patients in our population-based cohort were exposed to anti-TNFs. The major strengths of our study are the use of a large, unselected cohort of pediatric IBD patients included prospectively and consecutively in a population-based registry, and highly detailed data retrieved from patient records by experts rather than from administrative databases.

To conclude, the risk of both arterial and venous thromboembolism was relatively low in this population-based study of

pediatric-onset IBD patients. This data highlights the importance of thromboprophylaxis in hospitalized post-pubertal children with IBD flare or undergoing surgery.

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Conflict of interest

The authors declare the following conflict of interest: M.F. has received lecture/consultant fees from AbbVie, Ferring, Tillotts, MSD, Biogen, Amgen, Fresenius, Hospira, Sandoz, Pfizer, Celgene, Gilead, Boehringer, Galapagos, Janssen, and Takeda. C.D. has received consultant fees from AbbVie. N.R. has received lecture/consultant fees from AbbVie and Takeda. The other authors state that they have no competing interests regarding this work to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.dld.2024.09.005](https://doi.org/10.1016/j.dld.2024.09.005).

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