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Original Article

The Incidence and Characteristics of Venous Thromboembolisms in Paediatric-Onset Inflammatory Bowel Disease: A Prospective International Cohort Study Based on the PIBD-SETQuality Safety Registry

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Abstract

Background and Aims: Guidelines regarding thromboprophylaxis for venous thromboembolisms [VTEs] in children with inflammatory bowel disease [IBD] are based on limited paediatric evidence. We aimed to prospectively assess the incidence of VTEs in paediatric-onset IBD [PIBD], characterize PIBD patients with a VTE and identify potential IBD-related risk factors.

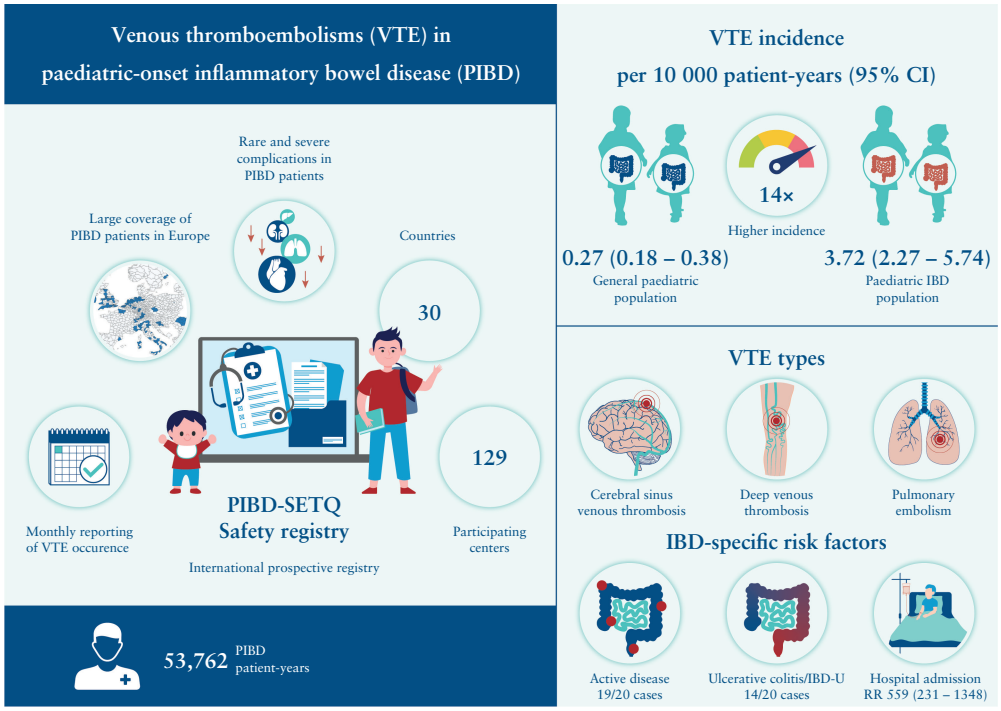
Methods: From October 2016 to September 2020, paediatric gastroenterologists prospectively replied to the international Safety Registry, monthly indicating whether they had observed a VTE case in a patient <19 years with IBD. IBD details [type, Paris classification, clinical and biochemical disease activity, treatment] and VTE details [type, location, treatment, outcome] were collected. To estimate VTE incidence, participants annually reported the number of PIBD patients, data source and catchment area of their centre. A systematic literature review and meta-analysis was performed to calculate the VTE incidence in the general paediatric population.

Results: Participation of 129 PIBD centres resulted in coverage of 24 802 PIBD patients. Twenty cases of VTE were identified [30% Crohn's disease]. The incidence of VTEs was 3.72 (95% confidence interval [CI] 2.27–5.74) per 10 000 person-years, 14-fold higher than in the general paediatric population (0.27 [95% CI 0.18–0.38], $p < 0.001$). Cerebral sinus venous thrombosis was most frequently reported [50%]. All but one patient had active IBD, 45% were using steroids and 45% were hospitalized. No patient received thromboprophylaxis, whereas according to current PIBD guidelines, this was recommended in 4/20 patients.

Conclusion: There is an increased risk of VTEs in the PIBD population compared to the general paediatric population. Awareness of VTE occurrence and prevention should be extended to all PIBD patients with active disease, especially those hospitalized.

Key Words: Crohn's disease; ulcerative colitis; paediatric; complication; extra-intestinal manifestation

Graphical Abstract



1. Introduction

A venous thromboembolic event [VTE] is a severe complication that may occur in paediatric patients with inflammatory bowel disease [IBD]. It includes deep venous thrombosis [DVT] of the upper and lower extremity or central vasculature, pulmonary embolism [PE], cerebral sinus venous thrombosis [CSVT] and renal vein thrombosis. Population-based studies in the general paediatric population have reported annual incidences of 0.07–0.49 per 10 000 children, with higher incidences in neonates and adolescents.[1–6] In hospitalized children this incidence may be increased, with reported incidences of 19–58 per 10 000 admissions.[5,7–10] VTE in children is associated with high mortality[2,5,6] and may result in significant morbidity, such as persistent or recurrent thrombosis, post-thrombotic syndrome or persistent neurological deficits due to CSVT.[11] In addition, VTE in hospitalized children with IBD is associated with an increased likelihood of intensive care unit stay and accompanied by increased adjusted total costs.[12]

Population-based studies have shown that adults with IBD are at increased risk of developing VTEs.[13–16] Few studies have reported an increased risk of VTE development in children with IBD, especially in those hospitalized.[15,17–21] However, most studies are based on retrospective studies involving billing or hospital databases, or report limited paediatric data.

Risk factors are present in over 90% of paediatric VTE cases, including a central venous catheter [CVC], surgery, immobility and infection.[5,22–25] In adult patients with IBD, active disease, fistulizing or stenosing disease behaviour, extensive colonic involvement, *Clostridium difficile* infection, corticosteroid use, surgery and recent hospitalization are associated with increased VTE risk.[14–16,26–30] Interestingly, hospitalized adult patients with IBD have a 1.5–2-fold higher VTE risk than hospitalized adult patients without IBD.[14,27] However, little is known about the IBD-related risk factors associated with VTEs in paediatric IBD [PIBD] patients.

There are conflicting recommendations regarding thromboprophylaxis in current guidelines for adults and children with IBD, as summarized in Supplementary Table 1.[31–38] The ESPGHAN guideline only recommends thromboprophylaxis for hospitalized children with acute severe colitis [ASC], with at least one additional VTE risk factor.[31] By contrast, this is not supported by the consensus statements of the Canadian Association of Gastroenterology, which recommends against VTE prophylaxis in hospitalized children with IBD, even if hospitalizations are related to severe IBD flares.[34] No recommendations exist for children with Crohn's disease [CD]. For adults with IBD, VTE prophylaxis is recommended during all hospitalizations according to some guidelines,[34,35] whereas it is recommended only in hospitalized patients with ASC according to others.[36–38] These conflicting recommendations demonstrate that convincing evidence regarding incidence and risk factors of VTEs and safety and efficacy of thromboprophylaxis in paediatric IBD patients is lacking.

We aimed to establish the first international prospective cohort study of VTEs in paediatric IBD patients, allowing us to examine and quantify the incidence of VTEs in this population, for comparison with the general paediatric population. We aimed to examine the clinical phenotype and risk factors in cases reported. We hypothesized there would be an increased incidence of VTEs in PIBD with active disease as the most likely risk factor.

2. Methods

2.1. PIBD-SETQuality Safety Registry

The PIBD-SETQuality Safety Registry is an international, prospective, electronic registry of rare and severe complications in children and adolescents with IBD, established by PIBD-NET. A list of ten rare but severe complications, including VTE, was established based on current literature and clinical

expertise by a team of PIBD experts [Supplementary Table 2]. In October 2016, the registry was initiated in the Netherlands and the UK and in following years extended to other countries. Every month, participating physicians are requested via an electronic invite [E-card] to report whether any of the listed complications occurred in a PIBD patient under their care in the last month. Participants were asked to actively report the absence of a complication. To minimize the risk of selection bias, participants who did not respond to the survey received a maximum of nine reminders in 3 months. In addition to the monthly E-card, participants annually received a survey to collect information including: the number of PIBD patients under their care, whether this number was based on a local database or estimated, and at what age children with IBD were transferred to adult care. In this annual survey, participants also reported the catchment area for referrals, based on well-defined geographical regions [Supplementary Methods].[39] Based on these defined geographical regions, overlap in claimed areas could be examined.

For each complication a follow-up form was designed and sent out automatically following the report of a complication to collect information on the IBD and the complication. IBD characteristics collected included year of diagnosis, IBD type (CD, ulcerative colitis [UC] or IBD unclassified [IBD-U]), Paris classification, clinical and biochemical disease activity, and treatment [details in Supplementary Methods].

2.2. Venous thromboembolisms

For VTEs specifically, inclusion criteria were: [1] diagnosis of IBD according to the revised Porto criteria,[40] [2] age <19 years at VTE diagnosis, and [3] occurrence of a first VTE between September 2016 and August 2020. A VTE was defined as a radiologically confirmed thromboembolism and categorized as extremity DVT [upper or lower], CSVT, renal vein thrombosis or right intra-cardiac thrombosis. For each case the following additional information was collected: VTE type and location, presenting symptoms, history of VTEs, presence of thrombophilia and VTE risk factors, anti-thrombotic treatment and prophylaxis, and outcome [details in Supplementary Methods].

2.3. Data extraction

Data were extracted from the online registry on September 30, 2020. Duplicates were excluded by checking responder, centre, sex, year and month of birth, and date of VTE diagnosis. All data were anonymously collected using unique electronic links for each participant. The data were submitted by the participants using the REDCap electronic data capture system and stored on secured Queen Mary University of London servers.

2.4. Incidence data

Incidence was calculated by the total number of IBD patients who developed a VTE divided by the number of PIBD patient-years in the registry [Supplementary Methods]. If participants did not respond to the E-card over three consecutive months, they were considered inactive during that time period and this period was thus not included in the calculation of patient-years. To account for possible inaccuracies in reporting of the PIBD population, we performed a sensitivity analysis including only those centres using robust local databases. We also performed a sensitivity analysis where we included the inactive months of participants. Since some centres had more than one reporting physician, the incidence calculations were done on a centre level.

2.5. Meta-analysis on the incidence of VTEs in the general paediatric population

A systematic literature review was performed to identify studies examining the incidence rate of VTE in the general paediatric population. Databases searched were Ovid Medline and Embase. A detailed search strategy and inclusion criteria are provided in the Supplementary Methods. Titles and abstracts were screened by two independent reviewers [M.A. and R.K.] and inconsistencies on inclusion were resolved by consensus. Extracted data included VTE incidence rate, sample size, total VTE number, duration of follow-up and number of patient-years. Studies were included in the meta-analysis if the number of patient-years was reported or could be calculated based on sample size and duration of follow-up. A random effects model was used to compensate for heterogeneity [I^2] across studies.[41]

2.6. Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]), rates as percentages (95% confidence interval [CI]). Proportions were compared using Chi square tests or Fisher's exact tests for smaller samples. Medians between groups were compared with the Mann–Whitney U test. For the meta-analysis, the heterogeneity between studies was assessed with the I^2 statistic. The incidence and 95% CIs were calculated based on the total number of VTE cases and patient-years using the normal approximation to the binomial distribution.

To estimate the relative risk of VTE development in the hospitalized compared to the non-hospitalized PIBD patients, we calculated the rate of VTE events in the two groups individually. The denominator for the hospitalized group is the number of inpatient days while for the non-hospitalized group it is the number of outpatient days. The expected number of inpatient days for the PIBD population in our study is a product of the total study population [in patient-days] and the inpatient days rate. This inpatient days rate was calculated using the PIBD population in the USA as a reference. The reported prevalence rates of PIBD by Ye *et al.*[42] and the total number of children [3–17 years] registered in the USA in 2020[43] were used to estimate that the total PIBD population in the USA is 47 319 patients. This corresponds to 17 283 113 patient-days annually. Based on the length of stay and number of PIBD admissions in the USA,[44] the total annual inpatient PIBD days in the USA is 25 281. Therefore, according to the US literature, a PIBD patient is expected to spend 1.46 in every 1000 days in the hospital [0.146%].

The proportions of UC/IBD-U and CD patients within the VTE cohort were compared to the proportions of UC/IBD-U and CD patients in the general PIBD population with a one-sample proportion test, using the EUROKIDS cohort, a representative large international cohort study, as a reference.[45] All test statistics were two-sided and a p-value <0.05 was considered statistically significant. Data analyses were performed with IBM SPSS version 25 [Armonk, NY, USA] or R version 4.0.2.

2.7. Ethical statement

This study was first approved by the ethics committee of Erasmus Medical Centre in the Netherlands and then

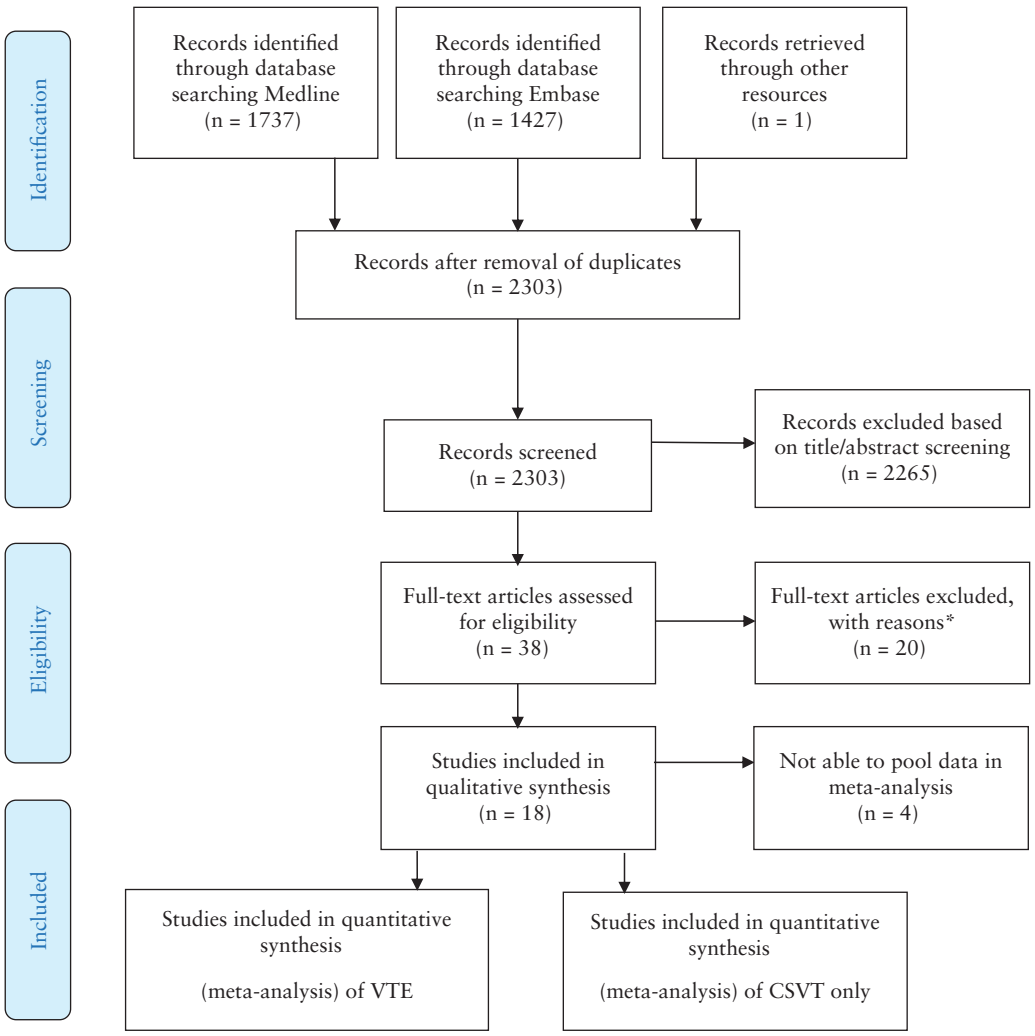


Figure 1. PRISM flow chart. Flow diagram of the systematic literature search on the incidence of venous thromboembolism in the general paediatric population. *Reasons for exclusion included: did not report on a pediatric population [n = 4]; did not provide data to calculate incidence rates [n = 5]; no population-based study [e.g. only hospital-associated VTE] [n = 2]; incidence rates reported per number of hospital admissions [n = 3]; no original article [n = 4]; not available in full-text [n = 2].

conducted as required by local ethics committees. Data security agreements were signed with participating centres if required by national legislation.

3. Results

3.1. Cohort description and denominator data

The PIBD-SETQuality Safety Registry currently has active participation of 149 PIBD specialists from 129 centres in 30 different countries [Supplementary Table 3].The PIBD population under their care is 24 802 patients. The median duration of active participation in the Safety Registry was 2.2 years per participating centre [IQR 0.92–3.70]. The continuously increasing covered population in combination with the duration of each centre's participation resulted in 53 762 PIBD patient-years of follow-up.

3.2. Systematic review and meta-analysis of VTE incidence in children

Electronic search results are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [PRISMA] diagram [Figure 1]. Study characteristics of 14 included studies are presented in Supplementary Table 4. Meta-analysis of ten studies including VTEs in general resulted in a pooled incidence rate of 0.27 [95% CI 0.18–0.38, I^2 99.7%] per 10 000 person-years in the general paediatric population [Figure 2]. Data of six studies specifically describing CSVT resulted in a pooled incidence rate for CSVT of 0.045 [95% CI 0.025–0.070, I^2 94.1%] per 10 000 person-years in the general paediatric population [Figure 3].

3.3. Incidence of VTEs in PIBD patients

During the period of follow-up, 21 cases of first VTE diagnosis in PIBD patients were reported. One case of a CSVT was excluded, because there was too little information to exclude duplicate reporting. We identified no other duplicates. The 20 remaining cases resulted in an incidence of 3.72 per 10 000 patient-years [95% CI 2.27–5.74]. The VTE incidence in the PIBD population included in this study is thus 13.8 times higher [95% CI 8.8–21.7] than the pooled incidence rate in the general paediatric population [3.72 vs 0.27; $p < 0.001$]. Ten cases were CSVTs, resulting in an incidence of 1.86 per 10 000 patient-years [95% CI 0.71–3.01], 41.3 times higher [95% CI 20.8–82.0] than the pooled incidence

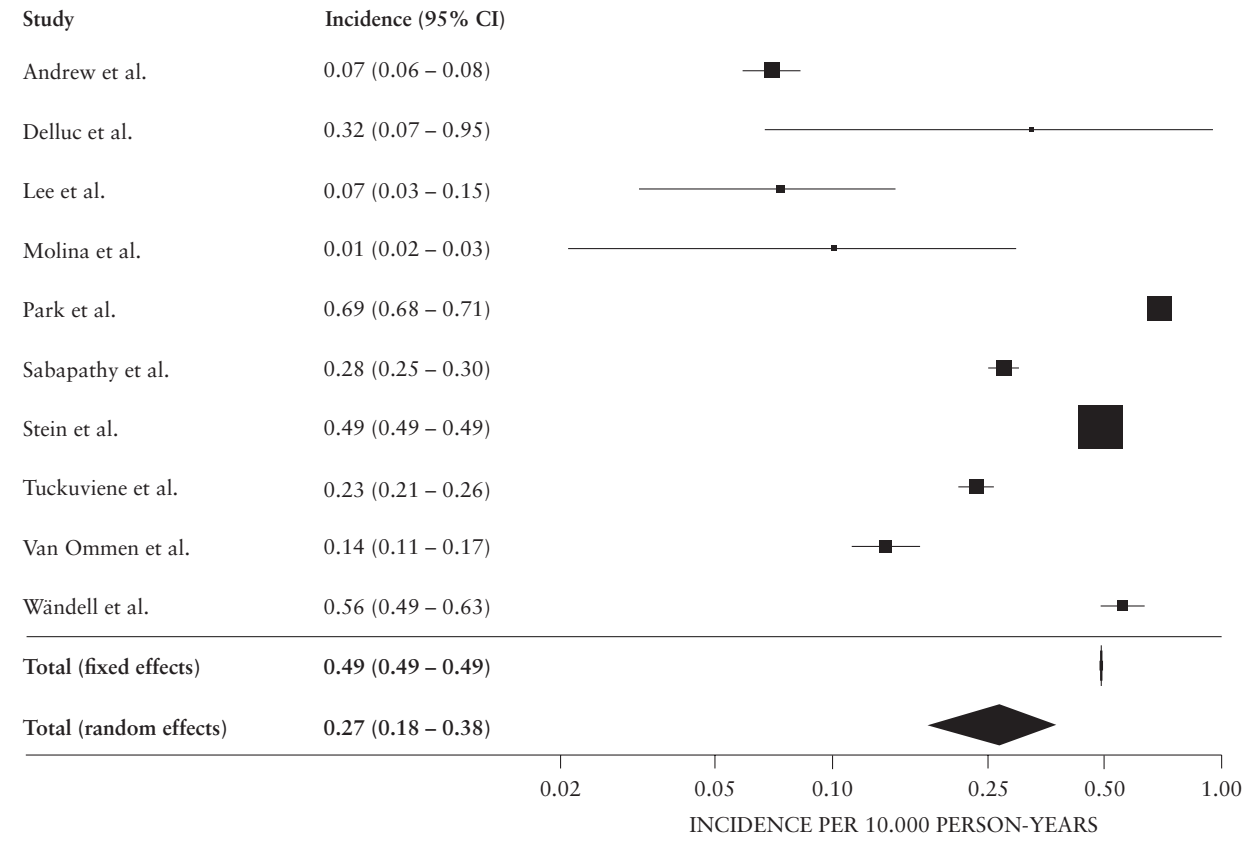


Figure 2. Meta-analysis of the incidence of VTEs in the general paediatric population. VTE: venous thromboembolism.

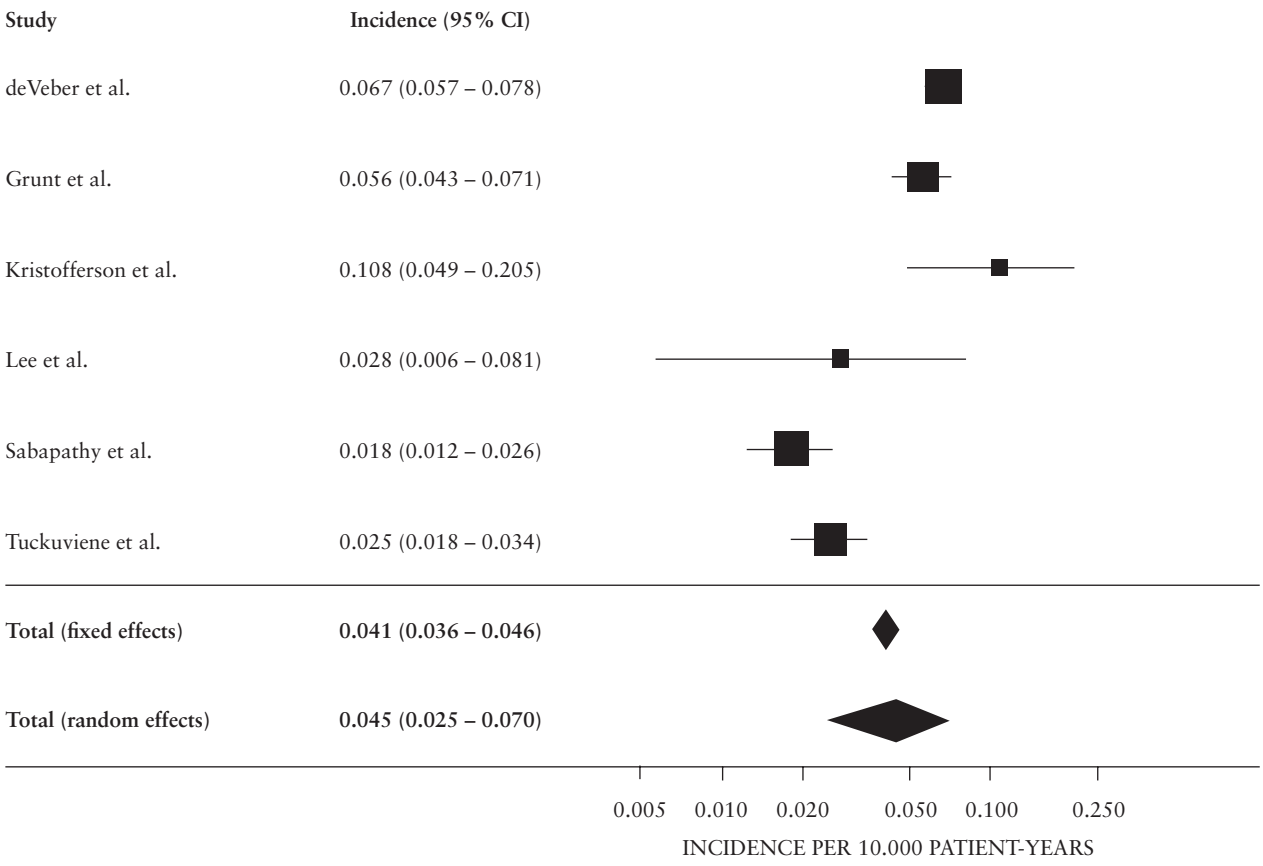


Figure 3. Meta-analysis of the incidence of CSVT in the general paediatric population. CSVT: cerebral sinus venous thrombosis.

Table 1. Patient characteristics depicted per IBD diagnosis

Patient characteristics	CD	UC/IBD-U	Total	p-value*
	n = 6	*n* = 14	*n* = 20	
Sex [*n*, % male]	1 [16.7]	7 [50.0]	8 [40.0]	0.01
Body mass index SDS [median, IQR]	0.38 [–0.85 to 0.55]	–0.44 [–2.3 to 0.49]	–0.43 [–1.7 to 0.53]	0.40
Age at IBD diagnosis, years [median, IQR]	11.6 [8.5–15.1]	12.9 [7.6–14.8]	12.2 [7.8–14.9]	0.90
Age at VTE diagnosis, years [median, IQR]	13.5 [9.1–16.1]	13.7 [9.3–16.3]	13.7 [9.6–16.1]	1.00
IBD disease duration prior to VTE diagnosis, months [median, IQR]	1.7 [0.2–28.7]	9.6 [1.9–23.8]	8.4 [0.4–20.5]	0.32
Paris classification at latest assessment				
Location/extent	L1: 0	E1: 0		
	L2: 2	E2: 0		
	L3: 4	E3: 0		
	L4a/4b: 2	E4: 14		
Behaviour	B1: 6	n/a		
	B2/B3: 0	n/a		
Perianal disease	0	n/a		

Comparisons between CD and UC/IBD-U patients were performed with the Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables.
*p-values are for the comparison of CD vs UC/IBD-U. SDS: standard deviation score; IBD: inflammatory bowel disease; VTE: venous thromboembolism; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: IBD unclassified; DVT: deep venous thrombosis; SVC: superior vena cava; IVC: inferior vena cava; CSVT: cerebral sinus venous thrombosis; n/a: not applicable.

rate of CSVT in the general paediatric population [1.86 vs 0.045; $p < 0.001$].

3.4. Sensitivity analysis

Sensitivity analysis only using cases [*n* = 13] and denominator data [*n* = 26 611] from centres that reported the total number of PIBD patients under their care based on robust local databases resulted in an estimated incidence of 4.89 per 10 000 patient-years [95% CI 2.60–8.35]. When calculating the patient-years without excluding the inactive period of at least three consecutive months, the number of patient-years was 55 001. Using this denominator data, the estimated VTE incidence is 3.6 per 10 000 patient-years [95% CI 2.22–5.62] and the estimated CSVT incidence is 1.82 per 10 000 patient-years [95% CI 0.87–3.34].

3.5. VTE risk ratio in outpatient vs hospitalized patients

After applying the expected inpatient days rate [0.146%] on our study population of 53 762 patient-years, we estimated that the Safety Registry patients would have spent 28 723 out of the 19 636 571 patient-days in the hospital. Given that nine VTE events occurred during admission and 11 outside the hospital, the estimated VTE incidence for hospitalized PIBD patients is 1144 [95% CI 523–2173] per 10 000 patient-years while the estimated VTE incidence for outpatient PIBD patients is 2.05 [95% CI 1.02–3.66] per 10 000 patient-years. Therefore, the estimated relative risk of developing a VTE in inpatients compared to outpatients is 559 [231–1348].

3.6. Patient characteristics

In all cases, detailed patient characteristics and disease specifics were available. The median age at VTE occurrence was 13.6 years [IQR 9.6–16.1], with eight children [40%] diagnosed at <12 years of age. The median IBD duration was 7.9 months [IQR 0.3–20.5] [Table 1]. Eight VTEs [38%] presented within 2 months of IBD diagnosis of which six [30%] were at the time of first diagnosis. Fourteen out of 20 cases occurred in children with UC/IBD-U, all with pancolitis. All CD patients had colonic or ileocolonic disease. There were no statistically significant differences between patients with CD and UC/IBD-U concerning age at IBD diagnosis, age at VTE diagnosis or IBD duration prior to VTE diagnosis. Compared to the percentage of UC patients in a large European cohort characterizing PIBD patients [EUROKIDS study] [32%], the percentage of UC patients within the VTE cohort [55%] was significantly higher [$p = 0.03$].

3.7. VTE specifics

In 50% of cases [*n* = 10] a CSVT was reported, mostly involving multiple dural venous sinuses [Table 2]. Presenting symptoms of CSVT included headache [*n* = 8], seizures [*n* = 3] and hemiparesis [*n* = 2]. Extremity DVTs were the second most reported VTE type [*n* = 7]. Three patients had a PE [two with a lower extremity DVT]. One patient had a simultaneous cerebral arterial thrombosis and DVT.

3.8. Risk factors

No patient had a medical or family history of VTEs. Both hereditary and acquired thrombophilia were tested in 70% of cases, but none was identified. In 65% of cases, one or more non-IBD risk factors were identified [Table 2]. These included: steroids [45%, *n* = 9], immobility [15%, *n* = 20], central venous catheter [15%, *n* = 3], parenteral nutrition [10% *n* = 2] and surgery [10%, *n* = 2]. Nine out of 20 patients [45%] were diagnosed with the VTE during hospital admission, including eight IBD-related hospitalizations.

3.9. IBD characteristics

Most VTEs [90%] occurred during active disease. Of these, 15/17 had moderate [*n* = 7] or severe [*n* = 8] disease activity

Table 2. Type of venous thromboembolism and presence of risk factors

Case	VTE location	Sex	IBD type	Age at IBD diagnosis. years	Age at VTE. years	Ethnic origin	Thrombophilia	Risk factors	VTE during admission	Comorbidities	Prophylaxis prior to VTE	Considerations regarding prophylaxis according to ECCO/ESPGHAN guidelines
	Intracranial, *n* = 11											
1	*Multiple venous sinuses and left internal jugular vein*	M	UC	7.6	7.6	White	No	None	No[¥]	None	No	No guidance on prophylaxis in UC that is not ASC
2	*Superior sagittal sinus*	F	UC	14.7	14.7	White	No	None	No	None	No	Does not fit criteria for consideration of prophylaxis [no additional risk factors]
3	*Multiple venous sinuses*	M	CD	9.3	10.2	White	No	Steroids	No	None	No	No guidance on prophylaxis in CD
4	*Multiple venous sinuses and proximal internal jugular vein*	F	IBD-U	14.1	15.8	White	Unknown	Steroids	No	None	No	No guidance on prophylaxis in UC that is not ASC
5	*Multiple venous sinuses*	F	CD	15.0	15.3	White	No	Steroids	No	None	No	No guidance on prophylaxis in CD
6	*Multiple venous sinuses*	M	UC	2.1	2.3	SEA	No[#]	None	Yes	None	No	Does not fit criteria for consideration of prophylaxis [no additional risk factors]
7	*Dural venous sinus, unspecified*	F	CD	11.6	18.3	White/ SEA	Unknown	Steroids	No	None	No	No guidance on prophylaxis in CD
8	*Multiple venous sinuses*	M	UC	16.7	16.7	White	No	Surgery	Yes	None	No	No guidance on prophylaxis in UC that is not ASC
9	*Superior sagittal sinus and right femoral vein*	F	CD	6.0	5.9	White/ SEA	Unknown	None	Yes	None	No	No guidance on prophylaxis in CD
10	*Posterior sagittal sinus*	M	UC	12.7	13.6	Mixed	Unknown	Steroids	Yes	None	No	Does not fit criteria for consideration of prophylaxis [no additional risk factors]
	Lower extremity, *n* = 8[‡]											
11	*Proximal medial gastrocnemius veins*	F	CD	15.4	15.4	White	No	None	Yes	None	No	No guidance on prophylaxis in CD
12	*Common femoral vein to popliteal vein*	F	UC	8.4	11.2	White	No	Steroids, immobility	No	Recent severe anaemia	No	Prophylaxis *should be* considered [adolescent girl with 1 risk factor]
13	*Lower IVC, common iliac, femoral, superficial femoral vein*	M	UC	15.0	16.2	White	No	None	No	None	No	No guidance on prophylaxis in UC that is not ASC
14	*Femoral and popliteal vein*[*]	F	CD	11.6	11.6	White	Unknown	CVC, steroids, myocarditis	Yes	None	No	No guidance on prophylaxis in CD
15	*Left posterior tibial vein*	F	UC	13.3	13.8	Kurdish	No	None	No	Spherocytosis, chronic haemolysis	No	No additional risk factors, so prophylaxis not recommended

Table 2. Continued

Case	VTE location	Sex	IBD type	Age at IBD diagnosis. years	Age at VTE. years	Ethnic origin	Thrombophilia	Risk factors	VTE during admission	Comorbidities	Prophylaxis prior to VTE	Considerations regarding prophylaxis according to ECCO/ESPGHAN guidelines
	Upper extremity, *n* = 1											
16	*Right basilic vein*	F	IBD-U	2.9	13.5	White	No	CVC, surgery, parenteral nutrition	Yes	Primary dysmotility	No	No guidance on prophylaxis in UC that is not ASC
	Pulmonary, *n* = 3											
17	*Subsegmental pulmonary embolus left lower lobe*	M	UC	13.0	17.0	Black	Unknown	Trauma, immobility	No	G6PD deficiency, PSC	No	Prophylaxis *should be* considered [adolescent boy with 1 additional risk factors]
18	*Proximal left pulmonary vein and IVC*	F	UC	8.7	9.4	White	No	Steroids, sepsis, immobility	Yes	None	No	Prophylaxis *should be* considered [prepubertal girl with 2 additional risk factors]
19	*[Sub]segmental bilateral lower lobe, left posterior tibial, peroneal and popliteal veins*	M	UC	16.6	17.2	White	No	Obesity, dehydration, hypovolemia	No	None	No	No guidance on prophylaxis in UC that is not ASC
	Other, *n* = 1											
20	*Right cardiac chamber*	F	IBD-U	7.5	9.2	Hispanic/ Latino	No[**]	CVC, steroids, immobility, parenteral nutrition	Yes	None	No	Prophylaxis *may be* considered [prepubertal girl with 2 additional risk factors]

The column thrombophilia includes hereditary and acquired thrombophilia.
[#]Hereditary thrombophilia was not tested.
[**]Acquired thrombophilia was not tested.
[‡]Three patients had a lower extremity DVT occurring together with another VTE type.
[*]This patient was diagnosed with an arterial thrombosis in the middle cerebral artery branches at the time of VTE diagnosis.
[¥]This patient was discharged from an IBD-related hospital admission for 2 days at the time of VTE diagnosis.
VTE: venous thromboembolism; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: IBD unclassified; G6PD: glucose-6-phosphate dehydrogenase; CVC: central venous catheter; PSC: primary sclerosing cholangitis; IVC: inferior vena cava; SEA: South East Asian.

[Table 3]. Only two VTEs occurred while the patient's disease was in clinical remission; one was receiving a steroid course and had a faecal calprotectin level of >6000 µg/g 2 months prior to the VTE, while the other had a faecal calprotectin level of 194 µg/g and presented with a CVC-related upper extremity DVT [Supplementary Table 5]. In all other patients, faecal calprotectin levels around VTE diagnosis were >500 µg/g [median 2100 µg/g, IQR 995–5615]. Blood results around VTE diagnosis show active inflammation in most patients: 12/17 patients had an erythrocyte sedimentation rate [ESR] >20 mm/h or a CRP level >5 mg/L. Median platelet count was 458 × 10^9/L [IQR 268–637].

3.10. IBD treatment

Five [25%] patients were not receiving any IBD-related medication at the time of VTE diagnosis. In four of those, the IBD was diagnosed around the time of VTE diagnosis [Table 3]. Nine patients [45%] were on steroids, in some cases combined with other IBD-related treatments.

3.11. VTE prophylaxis

No patients were using anti-thrombotic prophylaxis prior to the event. In retrospect, based on the most recent ESPGHAN guidelines, only 4/20 cases would have fulfilled the criteria for thromboprophylaxis [Table 2].[31–33]

3.12. VTE treatment

The majority of patients [80%] were treated with low-molecular-weight heparin [LMWH] [Supplementary Table 6]. One CSVT patient with a haemorrhagic stroke received no anti-thrombotic therapy. Anti-thrombotic treatment complications were reported in four patients and were all IBD-related gastrointestinal bleeds: two non-major bleedings and two minor bleedings. Following the VTE event, 8/20 patients received long-term anti-thrombotic prophylaxis after anti-thrombotic therapy was ceased.

3.13. VTE outcome

Sixteen out of 20 patients fully recovered from their VTE. Two CSVT patients died [Supplementary Table 6]. One CSVT patient, who needed a craniotomy, experienced mild neurological impairment after recovery. One patient had a post-thrombotic syndrome with persisting leg swelling a few weeks after the VTE, but was lost to follow-up after 2 months. Two patients had recurrent VTEs reported. One patient developed a DVT in the right femoral vein 2 weeks after the CSVT and a third VTE in the right popliteal vein 1 year after the first event, both while on anti-thrombotic prophylaxis. The other patient had a second and third DVT around 6 and 10 months, respectively, after the first DVT.

4. Discussion

This is the first prospective, international cohort study reporting data on VTEs in paediatric IBD. With a cohort of almost 25 000 patients, this study covered a larger population than any previous study. The set-up of this study enabled us to collect data on rare events from multiple countries in a homogeneous manner, resulting in 20 well-described VTE cases.

The results show that PIBD patients have a nearly 14-fold higher VTE risk compared to the general paediatric population. Previously, studies in adults have reported a 1.5- to 3-fold increased incidence in IBD patients,[15,46–48] regardless of IBD type.[46] A Danish population-based study showed that the relative risk is higher in children and adolescents and decreases with increasing age.[15] This study found an incidence rate of 8.9 per 10 000 person-years in IBD patients within the age group 0–20 years and a relative risk of 4.5 [1.7–12.0] compared to non-IBD patients. A recently published Canadian population-based study demonstrated that the 5-year incidence of VTE in PIBD patients was 31.2 [23.7–41.0] per 10 000 person-years.[21] This is almost ten times higher than in our study. However, the absolute number of VTE cases in

Table 3. IBD-related characteristics at time of VTE diagnosis

	CD	UC/IBD-U	Total
	n = 6 [30%]	*n* = 14 [70%]	*n* = 20
Physician's global assessment			
None/remission	1	1	2
Mild	1	1	2
Moderate	3	4	7
Severe	1	7	8
Faecal calprotectin, µg/g [median, IQR]	4050 [2100–6000]	1637 [985–5433]	2100 [995–5615]
ESR, mm/h [median, IQR]	55 [3–68.5]	23 [18.5–49.5]	27.0 [18.0–56.0]
CRP, mg/L [median, IQR]	8.9 [1.8–49.0]	27.0 [12.0–84.0]	23.0 [3.9–60.0]
Haemoglobin, mmol/L [median, IQR]	5.7 [4.5–6.7]	5.7 [5.0–6.7]	5.7 [4.9–6.7]
Platelet count, ×10^9/L [median, IQR]	458 [261–468]	436 [268–679]	458 [268–637]
Leukocyte count, ×10^9/L [median, IQR]	10.2 [7.6–13.1]	12.3 [6.0–16.8]	11.7 [7.4–15.6]
IBD treatment at time of VTE			
Corticosteroid use	4 [67%]	5 [36%]	
Anti-TNF agent use	0	4 [29%]	
Immunomodulator use	3 [50%]	3 [21%]	

Missing values for each variable were: PGA *n* = 1; Fcal *n* = 10; ESR *n* = 7; CRP *n* = 5; Haemoglobin *n* = 5; Platelet count *n* = 4; Leukocyte count *n* = 4. IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: IBD unclassified; PGA: physician's global assessment; ESR; erythrocyte sedimentation rate; CRP: C-reactive protein.

their study is not reported and they only included newly diagnosed IBD patients, who are probably those most at risk, as supported by the fact that the 1-year incidence was 81.2 per 10 000 person-years. Despite these differences in incidence between the studies, all suggest an increased risk of VTEs in PIBD patients.

In another study, Nylund *et al*. used the inpatient billing codes in the USA to assess the risk of developing a VTE and reported an absolute risk of 117.9 per 10 000 hospitalizations for children with IBD compared to 50.4 per 10 000 hospitalizations for children without IBD.[18] Similarly, we show that the risk in the hospitalized PIBD population is 559 times higher than in the outpatient PIBD population. It should be noted that this relative risk was calculated using hospitalization data from the USA, which could be different from hospitalization rates in Europe.

An interesting finding considering the larger proportion of CD patients within the PIBD population is the majority of UC/IBD-U cases in our cohort.[45] A large study in adults with IBD found a 1.32 times greater prevalence among UC patients than CD patients.[27] Saleh *et al*. also found that the relative risk [RR], compared to non-IBD patients, was higher in UC [RR 1.13] than in CD patients [RR 1.08].[47] By contrast, the Danish population-based study reported a higher risk in patients with CD than those with UC.[15] However, the proportion of UC patients [71%] within their IBD population was remarkably high, which may contribute to their high reported incidence. Disease location in CD was not described in their study, but based on our findings colonic disease may play a role in the VTE risk of those patients.

Although thrombophilia may be a risk factor of VTE in adult IBD patients, it does not appear to be an important one in children.[49] None of the patients in our cohort had acquired or hereditary thrombophilia. This is in contrast to a retrospective study in PIBD patients describing thrombophilia in four out of nine [44%] VTE cases.[17] Studies investigating the prevalence of inherited thrombophilia in children with VTE also reported lower rates [12–15%].[50–52]

In our study all but one patient had active inflammation. Studies in adult IBD patients showed that the risk of VTEs is increased at the time of a disease flare.[14,29,53] Although the aetiology of VTE in patients with IBD is likely to be multifactorial, accumulating evidence exists that the presence of systemic inflammation triggers a hypercoagulable state.[54,55] This is supported by the fact that some other pro-inflammatory conditions are more commonly associated with the development of hospital-acquired VTE in paediatric patients, such as cystic fibrosis, childhood cancer and systemic infection.[56–59] Interestingly, three cases involved VTEs at multiple locations, supporting the theory that systemic in addition to local factors contribute to thrombus formation.[60]

In addition to active disease, the most common risk factors in our PIBD cohort were steroid use and presence of a CVC. Nylund *et al*. performed a multivariate analysis in patients aged 5–20 years and identified older age, CVC, parenteral nutrition and an identified hypercoagulable condition as risk factors, without further defining the term hypercoaguable condition.[18] Notably, steroid use was not included in this analysis. Findings from a meta-analysis showed that systemic corticosteroid use was associated with a 2.2 times higher rate of VTE compared to IBD patients without steroid medication.[61]

Remarkably, 50% of VTE cases in our study concerned a CSVT, resulting in a 46-fold higher incidence than in the general paediatric population. This is of particular interest considering the 20% mortality rate in children with CSVT in our cohort and known high rates of persisting neurological deficits [17–79%] of CSVT in children.[62] In a systematic review by Lazzerini *et al*., 50/92 cases of arterial and venous thromboembolisms in children with IBD were cerebral.[63] This is higher than the CSVT rate in adult IBD patients [4.5%] or the general paediatric population [10.8%].[6,64] A possible contributing factor to the large proportion of CSVT in our cohort could be corticosteroid use, as this is also a contributory factor in children with acute lymphatic leukaemia, who have a 2–6% risk of CSVT.[65,66] However, as only 45% of CSVT patients in our cohort were on corticosteroids, the aetiology behind the specific cerebral location remains unexplained.

An important strength of our study is the reporting by the physicians themselves, which led to solid and detailed information about every patient who developed a VTE. Another strength is the prospective set-up in which physicians report cases within the month of occurrence of the VTE. Physicians need to actively report the absence of a VTE case every month. The risk of selection bias in case reporting is further minimized by actively chasing participants who did not respond to the monthly survey. We are the first to report an incidence of VTEs in children and adolescents with IBD based on a prospective registry. Available studies in children thus far have reported increased incidences based on retrospective billing databases or ICD-9 and ICD-10 coding, which has limitations.[67] Reporting by the physicians themselves led to solid and detailed information about every patient who developed a VTE. Although the collection of denominator data via the reporting physician could have led to less precise estimates of the denominator, as registries of new and current IBD patients might not be up to date in every hospital, and the sensitivity analysis we performed confirmed the higher incidence rate compared to the general paediatric population. Moreover, given the large number of participating centres, we expect any inaccuracies in over- or under-reporting to level out, thereby not influencing our findings significantly.

One of the limitations of our study is that our data do not include full coverage of entire countries, but rely on clearly defined geographical catchment areas reported by the local investigators. This could have introduced heterogeneity, as depending on the country or region patients might be referred from other centres to tertiary centres for specialized care and there could be overlap in patients covered by each centre. A second limitation is the transition from paediatric to adult care between 14 and 19 years of age in some centres, which could explain the relatively young age of our VTE cohort. This could have resulted in less precise estimates, as we expect the incidence to be higher with increasing age. However, the majority of centres [68%] treat their patients up to the age limit of 18 years. A third limitation of this study is the inability to perform a multivariate analysis on the risk factors of developing a VTE. Despite the large cohort, the small number of patients with a VTE and the lack of a control group prevents such an analysis. Considering this low number of cases was found after 3 years of international case collection, including a large coverage of 24 802 children and adolescents with IBD, this shows that the absolute number of VTE cases in paediatric IBD patients is low.

According to the ECCO guideline, prophylaxis is recommended in adult IBD patients if they are hospitalized, regardless of indication.[35] In our cohort, 11/20 patients

developed a VTE while not hospitalized. A survey among 162 paediatric gastroenterologists showed that physicians are hesitant to provide thromboprophylaxis for children with IBD because of a lack of clear paediatric guidelines.[68] Safety concerns, specifically the presumed bleeding risk, are the main reason for paediatric and adult gastroenterologists to be cautious about prescribing prophylactic anticoagulation.[68,69] A systematic review assessing the safety and efficacy of thromboprophylaxis in children showed that major bleeding events occurred in only 0.6% of children [some in neonates].[70] Studies in children are lacking, but in adults with IBD thromboprophylaxis with LMWH has been shown to be safe, even in patients who initially present with rectal bleeding.[71,72] In future, direct oral anticoagulants may replace the use of LMWH as thromboprophylaxis in children with a VTE, because of the advantage of oral over subcutaneous administration and fewer bleeding complications.[73]

The current treatment guideline for children with ASC suggests administering VTE prophylaxis only in pubertal children with at least one other risk factor and in prepubertal children with two other risk factors.[31] This age discrimination is suggested because of limited data on the safety and efficacy of thromboprophylaxis in prepubertal children,[31] not on differences in VTE risk. In our cohort, 40% of the reported cases occurred in children below 12 years of age, indicating that prepubertal children are at least equally at risk.

Interestingly, the findings from a recent British panel of gastroenterologists in the context of the COVID-19 pandemic show that prophylactic anticoagulation was deemed appropriate in all paediatric patients with ASC, thus fitting the guidance of an extra risk factor.[74] We found that four cases should have received prophylaxis if following the recently published paediatric ASC guideline.[31] However, in seven other UC cases, despite the presence of ASC in some, prophylaxis was not suggested because of the absence of extra risk factors.

With this increased risk of VTEs in paediatric IBD patients, especially in those hospitalized, and potentially negative outcomes in paediatric IBD patients, we would advise considering thromboprophylaxis for all hospitalized patients with active UC/IBD-U, regardless of age or presence of additional VTE risk factors, and for all hospitalized children with moderate-to-severe CD with at least one additional VTE risk factor. Further prospective studies are necessary to assess the safety of prophylaxis in paediatric IBD patients, especially in outpatients with active disease.

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Conflict of Interest

All authors declare no conflicts of interest.

Author Contributions

L.dR., N.M.C. and F.M.R. contributed to the study concept and design. M.A.A., R.C.W. and P.K. had full access to the data in the trial and take responsibility for the integrity of the data and the accuracy of the data analysis. M.A.A., R.C.W. and P.K. contributed to the statistical analysis. All authors contributed to acquisition and interpretation of the data. M.A.A., R.C.W., P.K., L.dR., N.M.C. and C.vO. contributed to drafting of the manuscript. L.dR. and N.M.C. supervised the study. All members of the PIBD-VTE group contributed to data collection, critically revised the manuscript and provided important intellectual content. All authors approved the final version of the manuscript.

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Patient and Public Involvement

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

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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