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
1. Introduction

A venous thromboembolic event [VTE] is a severe complication that may occur in pediatric 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 pediatric 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 mortality2,5,6 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 pediatric VTE cases, including a central venous catheter [CVC], surgery, immobility and infection.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.26,27 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 pediatric 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]. 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, [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 [F] across studies.

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 F 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. and the total number of children [3–17 years] registered in the USA in 2020 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, 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 EUROLIDS cohort, a representative large international cohort study, as a reference. 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
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
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Study Incidence (95% CI)
Andrew et al. 0.07 (0.06 – 0.08)
Delluc et al. 0.32 (0.07 – 0.95)
Lee et al. 0.07 (0.03 – 0.15)
Molina et al. 0.01 (0.02 – 0.03)
Park et al. 0.69 (0.68 – 0.71)
Sabapathy et al. 0.28 (0.25 – 0.30)
Stein et al. 0.49 (0.49 – 0.49)
Tuckuviene et al. 0.23 (0.21 – 0.26)
Van Ommen et al. 0.14 (0.11 – 0.17)
Wändell et al. 0.56 (0.49 – 0.63)
Total (fixed effects) 0.49 (0.49 – 0.49)
Total (random effects) 0.27 (0.18 – 0.38)

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

Study Incidence (95% CI)
deVeber et al. 0.041 (0.036 – 0.046)
Grunt et al. 0.056 (0.043 – 0.071)
Kristofferson et al. 0.108 (0.049 – 0.205)
Lee et al. 0.028 (0.006 – 0.081)
Sabapathy et al. 0.018 (0.012 – 0.026)
Tuckuviene et al. 0.025 (0.018 – 0.034)
Total (fixed effects) 0.045 (0.025 – 0.070)
Total (random effects) 0.045 (0.025 – 0.070)

Figure 3. Meta-analysis of the incidence of CSVT in the general paediatric population. CSVT: cerebral sinus venous thrombosis.
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 outside the hospital, which was only a fraction of the patient-days reported by the centres. The estimated VTE risk ratio 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 \( p = 0.03 \).
| 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 |
|------|--------------------------------------------------|-----|----------|---------------------------|------------------|--------------|---------------|--------------|------------------------|--------------|------------------------|---------------------------------------------------------------|
| 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     | None                   | 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     | None                   | 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     | None                   | 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     | None                   | 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] |
| 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 | 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 guidance on prophylaxis in CD                               |
| 15   | Left posterior tibial vein                        | F   | UC       | 13.3                      | 13.8             | Kurdish      | No            | None         | No                     | None         | No additional risk factors, so prophylaxis not recommended    | No guidance on prophylaxis in CD                               |
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 discharged from an IBD-related hospital admission for 2 days at the time of VTE diagnosis.

\|This patient was diagnosed with an arterial thrombosis in the middle cerebral artery branches 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.
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 x 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].

### 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, regardless of IBD type. A Danish population-based study showed that the relative risk is higher in children and adolescents and decreases with increasing age. 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 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 per 10 000 person-years. This is almost ten times higher than in our study. However, the absolute number of VTE cases in

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

| Patient Characteristics | CD (n = 6 [30%]) | UC/IBD-U (n = 14 [70%]) | Total (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] | 438 [261–468]  | 436 [268–679]          | 438 [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.39 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.40 A large study in adults with IBD found a 1.32 times greater prevalence among UC patients than CD patients.72 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.13 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%].30–32

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.14,25,31 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.34 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.36–39 Interestingly, three cases involved VTEs at multiple locations, supporting the theory that systemic in addition to local factors contribute to thrombus formation.40

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, parental nutrition and an identified hypercoagulable condition as risk factors, without further defining the term hypercoagulable 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%].64,65 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.63,66 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.33 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.74 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.v.O. 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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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.

References
1. Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. J Pediatr 2004;145:563–5.
2. Sabapathy CA, Djouonang TN, Kahn SR, Platt RW, Tagalakis V. Incidence trends and mortality from childhood venous thromboembolism: a population-based cohort study. J Pediatr 2016;172:175–80.e1.
3. Park ES, Choi HS, Lee KS, Kim SW, Lee JM. Venous thromboembolism in children and young adults in Korea: analysis of the Korean Health Insurance Review and Assessment Service Database. J Korean Med Sci 2019;34:e316.

4. van Ommen CH, Heijboer H, Buijler HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr 2001;139:676–81.

5. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood 1994;83:1251–7.

6. Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen N. Pediatric venous and arterial noncerebral thromboembolism in Denmark: a nationwide population-based study. J Pediatr 2011;159:663–9.

7. Wright JM, Watts RG. Venous thromboembolism in pediatric patients: epidemiologic data from a pediatric tertiary care center in Alabama. J Pediatr Hematol Oncol 2011;33:261–4.

8. Raffini L, Huang YS, Wittmer C, Feudtner C. Dramatic increase in venous thromboembolism in children’s hospitals in the United States from 2001 to 2007. Pediatrics 2009;124:1001–8.

9. Takemoto CM, Sohi S, Desai K, et al. Hospital-associated venous thromboembolism in children: incidence and clinical characteristics. J Pediatr 2014;164:332–8.

10. Setty BA, O’Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic disease. Pediatr Blood Cancer 2012;59:258–64.

11. Goldenberg NA, Bernard TJ. Venous thromboembolism in children. Hematol Oncol Clin North Am 2010;24:151–66.

12. Chien KA, Cooley V, Prixtitha F, Gorinspan ZM, Gerber LM, Kucine N. Health and financial burdens associated with venous thrombosis in hospitalized children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2021;72:748–51.

13. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost 2001;85:430–4.

14. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet 2010;375:657–63.

15. Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut 2011;60:937–43.

16. Michels W, Reinisch W, Valic E, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? Gut 2004;53:542–8.

17. Zitomersky NL, Levine AE, Atkinson BJ, et al. Risk factors, morbidity, and treatment of thrombosis in children and young adults with active inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2013;57:343–7.

18. Nylund CM, Goudie A, Garza JM, Crouch G, Denson LA. Venous thrombotic events in hospitalized children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2013;56:485–91.

19. McKie K, McLoughlin RJ, Hirsh MP, Cleary MA, Aidlen JT. Risk factors for venous thromboembolism in children and young adults with inflammatory bowel disease. J Surg Res 2019;233:173–9.

20. Barclay AR, Keightley JM, Horrocks I, Garrick V, McGrogan P, Russell RK. Cerebral thromboembolic events in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2010;16:677–83.

21. Kuenzig ME, Bitton A, Carroll MW, et al. Inflammatory bowel disease increases the risk of venous thromboembolism in children: a population-based matched cohort study. J Crohns Colitis 2021;15:2031–2040.

22. Jaffray J, Mahajerin A, Young G, et al. A multi-institutional registry of pediatric hospital-acquired thrombosis cases: the Children’s Hospital-Acquired Thrombosis (CHAT) project. Thromb Res 2018;161:67–72.

23. Mahajerin A, Branchford BR, Amanwah EK, et al. Hospital-associated venous thromboembolism in pediatrics: a systematic review and meta-analysis of risk factors and risk-assessment models. Haematologica 2015;100:1045–50.

24. Massicotte MP, Dix D, Monagle P, Adams M, Andrew M. Central venous catheter related thrombosis in children: analysis of the Canadian Registry of Venous Thromboembolic Complications. J Pediatr 1998;133:770–6.

25. Kuhle S, Massicotte P, Chan A, et al. Systemic thromboembolism in children. Data from the 1-800-NO-CLOTS Consultation Service. Thromb Haemost 2004;92:722–8.

26. Bhandari S, Mohammed Abdul MK, Dhakal B, Kreuzberger LB, Saetien K, Stein D. Increased rate of venous thromboembolism in hospitalized inflammatory bowel disease patients with Clostridium difficile infection. Inflamm Bowel Dis 2017;23:1847–52.

27. Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. Am J Gastroenterol 2008;103:2272–80.

28. Papay P, Micheler W, Tilg H, et al. Clinical presentation of venous thromboembolism in inflammatory bowel disease. J Crohns Colitis 2013;7:723–9.

29. Solem CA, Loftus EV, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. Am J Gastroenterol 2004;99:97–101.

30. Weng MT, Park SH, Matsuoka K, et al. Incidence and risk factor analysis of thromboembolic events in East Asian Patients with inflammatory bowel disease, a multinational collaborative study. Inflamm Bowel Dis 2018;24:1791–800.

31. Turner D, Ruemmele FM, Oralski-Meyer E, et al. Management of paediatric ulcerative colitis, part 2: acute severe colitis—an evidence-based consensus guideline from the European Crohn’s and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;67:292–310.

32. Turner D, Ruemmele FM, Oralski-Meyer E, et al. Management of paediatric ulcerative colitis, part 1: ambulatory care—an evidence-based guideline from European Crohn’s and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;67:257–91.

33. van Rheenen PF, Aloï M, Assa A, et al. The medical management of paediatric Crohn’s disease: an ECCO-ESPGHAN guideline update. J Crohns Colitis 2021;15:171–94.

34. Nguyen GC, Bernstein CN, Bitton A, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology, Gastroenterology 2014;146:835–48.e6.

35. Harbord M, Annese V, Vavricka SR, et al.; European Crohn’s and Colitis Organisation. The First European Evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis 2016;10:239–54.

36. Lichtenstein GR, Loftus EV, Isaacs KL, Requeiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: management of Crohn’s disease in adults. Am J Gastroenterol 2018;113:481–517.

37. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: ulcerative colitis in adults. Am J Gastroenterol 2019;114:384–413.

38. Lamb CA, Kennedy NA, Raine T, et al.; IBD guidelines eDelphi consensus group. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1–s106.

39. Eurostat. Nomenclature of territorial units for statistics (NUTS) maps. https://ec.europa.eu/eurostat/web/nuts/nuts-maps. Accessed August 17, 2021.

40. Levine A, Koletzko S, Turner D, et al.; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr 2014;58:795–806.
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56. Knight-Perry J, Branchford BR, Thornhill D, Martiniano SL, Sagel Danese S, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M. Inflammatory bowel disease and risk of venous thromboembolism: a meta-analysis. *J Crohns Colitis* 2018;12:489–98.

57. Walker AJ, Grainge MJ, Carol TR, West J, Ranta S, Ludvigsson JF. Venous thromboembolism in children and cancer: a population-based cohort study. *Thromb Res* 2014;133:340–4.

58. Carpenter SL, Goldman J, Sherman AK, *et al.* Clinical variables and *Staphylococcus aureus* virulence factors associated with venous thromboembolism in children. *Thromb Res* 2016;138:69–73.

59. Bouchoucha S, Bengchame F, Trifa M, *et al.* Deep venous thrombosis associated with acute hematogenous osteomyelitis in children. *Orthop Traumatol Surg Res* 2010;96:890–3.

60. Branchford BR, Carpenter SL. The role of inflammation in venous thromboembolism. *Front Pediatr* 2018;6:142.

61. Sarlos P, Szemes K, Hegyi P, *et al.* Steroid but not biological therapy elevates the risk of venous thromboembolic events in inflammatory bowel disease: a meta-analysis. *J Crohns Colitis* 2018;12:489–98.

62. Dlamin N, Billington L, Kirkham FJ. Cerebral venous sinus (sinovenous) thrombosis in children. *Neurosurg Clin N Am* 2010;21:511–27.

63. Lazzerini M, Bramuzzo M, Maschio M, Martelossi S, Ventura A. Thromboembolism in pediatric inflammatory bowel disease: systematic review. *Inflamm Bowel Dis* 2011;17:2174–83.

64. Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen SR. Paediatric arterial ischaemic stroke and cerebral venous thrombosis in Denmark 1994–2006: a nationwide population-based study. *Acta Pediatr* 2011;100:543–9.

65. Ranta S, Tuckuviene R, Makipernaa A, *et al.* Cerebral sinus venous thromboses in children with acute lymphoblastic leukaemia – a multicentre study from the Nordic Society of Paediatric Haematology and Oncology. *Br J Haematol* 2015;168:547–52.

66. Ghanei KM, Dhayni RM, Al-Ardi C, *et al.* Cerebral sinus venous thrombosis during childhood acute lymphoblastic leukemia therapy: risk factors and management. *Pediatr Blood Cancer* 2017;64:e26694.

67. Branchford BR, Gibson E, Manco-Johnson MJ, Goldenberg NA. Sensitivity of discharge diagnosis ICD-9 codes for pediatric venous thromboembolism is greater than specificity, but still suboptimal for surveillance and clinical research. *Thromb Res* 2012;129:662–3.

68. Chien KA, Hammad HT, Gerber I, Sheith S, Sockelow R, Kucine N. Pediatric Gastroenterologists’ approach to venous thromboembolism prophylaxis in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2018;66:286–8.

69. Faye AS, Hung KW, Cheng K, *et al.* Minor hematochezia decreases use of venous thromboembolism prophylaxis in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2020;26:1394–400.

70. Klaassen ILM, Sol JJ, Suijker MH, Fijnvandraat K, van de Wetering MD, Heleen van Ommen C. Are low-molecular-weight heparins safe and effective in children? A systematic review. *Blood Rev* 2019;33:33–42.

71. Ra G, Thanabal R, Ratneswaran S, Nguyen GC. Predictors and safety of venous thromboembolism prophylaxis among hospitalized inflammatory bowel disease patients. *J Crohns Colitis* 2013;7:479–85.

72. Shen J, Ran ZH, Tong JL, Xiao SD. Meta-analysis: the utility and safety of heparin in the treatment of active ulcerative colitis. *Aliment Pharmacol Ther* 2012;36:204–17.

73. Monagle P, Lensing AWA, Thelen K, *et al.*; EUROKIDS Porto IBD Investigators. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm, phase 2 studies. *Lancet Haematol* 2019;6:e500–9.

74. Hansen R, Meade S, Beattie RM, *et al.* Adaptations to the current ECCO/ESPGHAN guidelines on the management of paediatric acute severe colitis in the context of the COVID-19 pandemic: a RAND appropriateness panel. *Gut* 2021;70:1044–52.