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

Short title: Venous thromboembolisms in paediatric-onset IBD

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Abbreviations:

CD - Crohn's disease

CRP - C-reactive protein

CSVT - cerebral sinus venous thrombosis

CVC - central venous catheter

DVT - deep venous thrombosis

ESR - erythrocyte sedimentation rate

IBD - inflammatory bowel disease

IBD-U - IBD-unclassified

LMWH - low molecular weight heparin

PE - pulmonary embolism

PGA - physician’s global assessment

PIBD - paediatric-onset inflammatory bowel disease

PUCAI - paediatric ulcerative colitis activity index

UC - ulcerative colitis

VTE - venous thromboembolism

wPCDAI - weighted paediatric Crohn’s disease activity index

ABSTRACT

Background & Aims

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

Methods

From October 2016 till 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 the VTE incidence, participants annually reported the number of PIBD patients, data source and catchment area of their center. A systematic literature review and meta-analysis was performed to calculate the VTE incidence in the general paediatric population.

Results

Participation of 129 PIBD centers resulted in coverage of 24,802 PIBD patients. Twenty cases of VTE were identified (30% Crohn's disease). The VTE incidence was 3.72 [95%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% 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 VTE 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.

INTRODUCTION

Background

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 to 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 to 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 neurologic deficits due to CSVT[11]. In addition, VTE in hospitalized children with IBD is associated with increased likelihood of intensive care unit stay and accompanied with increased adjusted total costs[12].

Population-based studies have shown adults with IBD are at increased risk of developing VTE[13-16]. Few studies reported an increased risk for development of VTE 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 central venous catheter (CVC), surgery, immobility and infection[5,22-25]. In adult patients with IBD, active disease, fistulising 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 to 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 VTE in paediatric IBD (PIBD) patients.

There are conflicting recommendations regarding thromboprophylaxis in current guidelines for adults and children with IBD, as summarized in Supplemental Table 1[31-33]. The ESPGHAN guideline only recommends thromboprophylaxis for hospitalized children with acute severe colitis (ASC), with at least one additional VTE risk factor. Contrarily, 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 according to other guidelines only in hospitalized patients with ASC[36-38]. These conflicting recommendations demonstrate that convincing evidence regarding incidence and risk factors of VTE and safety and efficacy of thromboprophylaxis in paediatric IBD patients is lacking.

We aimed to establish the first international prospective cohort study of VTE in paediatric IBD patients, allowing us to examine and quantify the incidence of VTE 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 VTE in PIBD with active disease as the most likely risk factor.

METHODS

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 (Supplemental Table 2). In October 2016, the registry was initiated in the Netherlands and the United Kingdom 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 three 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 (Supplemental 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 Supplemental Methods).

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, 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), cerebral venous sinus thrombosis (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 VTE, presence of thrombophilia and VTE risk factors, antithrombotic treatment and prophylaxis and outcome (details in Supplemental Methods).

Data extraction

Data were extracted from the online registry on the 30th of September 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 was submitted by the participants using REDCap electronic data capture system and stored on secured Queen Mary University of London servers.

Incidence data

The incidence was calculated by the total number of IBD patients that developed a VTE divided by the number of PIBD patient-years in the registry (Supplemental Methods). If participants did not respond to the E-card 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 centers using robust local databases. We also performed a sensitivity analysis where we included the inactive months of participants. Since some centers had more than one reporting physician, the incidence calculations were done on a center level.

Meta-analysis on incidence of VTE in 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 Supplemental Methods. Titles and abstracts were screened by two independent reviewers (MA and RK) 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].

Statistical analysis

Continuous variables are presented as median (IQR), rates as percentages (95%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-square statistic. The incidence and 95% confidence intervals 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 US 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 US in 2020[43] were used to estimate that the total PIBD population in the US 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 US[44], the total annual inpatient PIBD days in the US 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.

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 ethical committees. Data security agreements were signed with participating centers if required by national legislation.

RESULTS

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 (Supplemental 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 center (IQR 0.92-3.70). The continuously increasing covered population in combination with the duration of each center's participation, resulted in 53,762 PIBD patient-years of follow-up.

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 fourteen included studies are presented in Supplemental Table 4. Meta-analysis of ten studies including VTE 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).

Incidence of VTE in PIBD patients

During the time 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 rate of CSVT in the general paediatric population (1.86 vs. 0.045; p<0.001).

Sensitivity analysis

Sensitivity analysis only using cases (n=13) and denominator data (n=26,611) from centers 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).

VTE risk ratio in outpatient versus 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 9 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).

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) of which 8 children (40%) were diagnosed <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 6 (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).

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.

Risk factors

No patient had a medical or family history of VTE. Both hereditary and acquired thrombophilia were tested in 70% of cases, but none were 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.

IBD characteristics

Most VTEs (90%) occurred during active disease. Of these 15/17 had moderate (n=7) or severe (n=8) disease activity (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 two months prior to the VTE, the other had a faecal calprotectin level of 194 and presented with a CVC-related upper extremity DVT (Supplemental 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 ESR >20 mm/hour or a CRP level >5 mg/L. Median platelet count was 458 x 10^9/L (IQR 268 – 637).

IBD treatment

Five (25%) patients were not receiving any IBD-related medication at the time VTE was diagnosed. 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.

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]

VTE treatment

The majority of patients (80%) were treated with low molecular weight heparin (LMWH) (Supplemental 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 antithrombotic prophylaxis after antithrombotic therapy was ceased.

VTE outcome

Sixteen out of 20 patients fully recovered from their VTE. Two CSVT patients died (Supplemental 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 two months. Two patients had recurrent VTE reported. One patient developed a DVT in the right femoral vein two weeks after the CSVT and a third VTE in the right popliteal vein one year after the first event, both while on antithrombotic prophylaxis. The other patient had a second and third DVT around six and 10 months, respectively, after the first DVT.

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 about 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 10 times higher than in our study. However, the absolute number of VTE cases in their study is not reported and they only included newly-diagnosed IBD patients, which are probably the ones being 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 VTE in PIBD patients.

In another study, Nylund et al. used the inpatient billing codes in the US to assess the risk of developing 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 taken into consideration that this relative risk was calculated using hospitalization data from the United States, which could be different than 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, compared to non-IBD patients, was higher in UC (RR 1.13) than in CD patients (RR 1.08)[47]. Contrarily, 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 VTE risk of those patients.

Although thrombophilia may be a risk factor of VTE in adult IBD patients, it does not seem an important one in children[49]. None of the patients in our cohort had acquired or hereditary thrombophilia. This is in contrast with a retrospective study in PIBD patients describing thrombophilia in 4 out of 9 (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 VTE 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 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 neurologic 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 contributing 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 that 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 VTE 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 data bases 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 that developed a VTE. Although the collection of denominator data via the reporting physician could have led to less precise estimates of the denominator, as not in every hospital registries of new and current IBD patients might be up to date, the sensitivity analysis we performed confirmed the higher incidence rate compared to the general paediatric population. Moreover, given the large number of participating centers, we expect any inaccuracies in over- or underreporting to level out, thereby not influencing our findings significantly.

One of the limitations of our study is that our data does not include full coverage of entire countries, but relies 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 centers to tertiary centers for specialized care and there could be overlap in patients covered by each center. A second limitation is the transition from paediatric to adult care between 14 and 19 years of age in some centers, which could be the explanation of 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 centers (68%) treat their patients up to the age limit of 18. 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 three 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[34]. 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 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 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 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 VTE, because of the advantage of oral over subcutaneous administration and fewer bleeding complications[73].

The current treatment guideline for children with ASC suggests to only administer VTE prophylaxis 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 safety and efficacy of thromboprophylaxis in prepubertal children[74], 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, 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[75]. 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 VTE in paediatric IBD patients, especially in those hospitalized, and potentially negative outcomes in paediatric IBD patients, we would advise to consider 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 safety of prophylaxis in paediatric IBD patients, especially in outpatients with active disease.

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FOOTNOTES

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

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

Contribution: LdR, NMC and FMR contributed to the study concept and design. MAA, RCW and PK 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. MAA, RCW and PK contributed to the statistical analysis. All authors contributed to acquisition and interpretation of the data. MAA, RCW, PK, LdR, NMC and CvO contributed to drafting of the manuscript. LdR and NMC 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 this manuscript.

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FIGURE LEGENDS

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).

Figure 2. Meta-analysis incidence VTE in general paediatric population

Findings of the meta-analysis data regarding the incidence of VTE in the general paediatric population. VTE: venous thromboembolism.

Figure 3. Meta-analysis incidence CSVT in general paediatric population

Findings of the meta-analysis data regarding the incidence of CSVT in the general paediatric population. CSVT: cerebral sinus venous thrombosis.

737 **TABLES**

738 **Table 1. Patient characteristics**

Patient characteristics	**CD** **n=6**	**UC/IBD-U** **n=14**	**Total** **n=20**	**p-value***
Sex (n, % male)	1 (16.7)	7 (50.0)	8 (40.0)	0.01
Body mass index SDS (median, IQR)	0.38 (-0.85-0.55)	-0.44 (-2.3-0.49)	-0.43 (-1.7-0.53)	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 L2: 2 L3: 4 L4a/4b: 2	E1: 0 E2: 0 E3: 0 E4: 14		
Behaviour	B1: 6 B2/B3: 0	n/a n/a		
Perianal disease	0	n/a		

Table 1. Patient characteristics depicted per IBD diagnosis. Comparisons between CD and UC/IBDU 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 comparison of CD vs. UC/IBD-U. IBD: inflammatory bowel disease; VTE: venous thromboembolism; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: IBD unclassified; GI: gastrointestinal; DVT: deep venous thrombosis; SVC: superior vena cava; IVC: inferior vena cava; CSVT: cerebral sinus venous thrombosis; n/a: not applicable.

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

Case	VTE location	Sex	IBD type	Age at IBD diagnosis, y	Age at VTE, y	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
	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)

Table 2. Type of venous thromboembolism and presence of 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 two 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; y: years; G6PD: glucose-6-phosphate dehydrogenase; CVC: central venous catheter; PSC: primary sclerosing cholangitis; IVC: inferior vena cava; SEA: South East Asian.

Table 3. IBD related characteristics at time of VTE diagnosis

	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/hr (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, x 10^9/L (median, IQR)	458 (261 – 468)	436 (268 – 679)	458 (268 – 637)
Leukocyte count, x 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%)	

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