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ORIGINAL ARTICLE

Direct oral anticoagulants in pediatric venous thromboembolism: Experience in specialized pediatric hemostasis centers in the United States

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Abstract

Background: Before the official US Food and Drug Administration approval in 2021, pediatric hematologists across the United States have used direct oral anticoagulants (DOACs) "off-label" and based on extrapolation from labeling for adults with venous thromboembolism (VTE) and interim results of pediatric-specific DOAC clinical studies.

Objectives: The American Thrombosis and Hemostasis Network 15 (ATHN 15) study aimed to characterize the use of DOACs from 2015 to 2021 at 15 specialized pediatric hemostasis centers in the United States, with emphasis on safety and effectiveness.

Methods: Eligible participants were those aged 0 to 21 years who had a DOAC included as part of their anticoagulation regimen for the treatment of acute VTE or secondary prevention of VTE. Data were collected for up to 6 months after initiation of the DOAC.

Results: A total of 233 participants were enrolled, with a mean age of 16.5 years. Rivaroxaban was the most commonly prescribed DOAC (59.1%) followed by apixaban (38.8%). Thirty-one (13.8%) participants reported bleeding complications while on a DOAC. Major or clinically relevant nonmajor bleeding events occurred in 1 (0.4%) and 5 (2.2%) participants, respectively. Worsening menstrual bleeding was reported in 35.7% of females aged >12 years and occurred more frequently in those using rivaroxaban (45.6%) compared with apixaban (18.9%). The recurrent thrombosis rate was 4%.

Conclusion: Pediatric hematologists at specialized hemostasis centers in the United States have been using DOACs for the treatment and prevention of VTEs, primarily in adolescents and young adults. Reported DOAC use showed adequate safety and effectiveness rates.

KEYWORDS
children, direct oral anticoagulants, pediatric, venous thromboembolism, VTE

[9] A list of the ATHN 15 Study Investigators appears in Appendix 1.

Hemostasis Network (ATHN) (grant number: ATHN 15) and The Children's Hospital of Philadelphia.

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Essentials

- The use of direct oral anticoagulants (DOACs) in specialized pediatric centers in the United States was investigated.
- DOACs were mostly used in adolescents and young adults for the treatment/prevention of blood clots.
- Rivaroxaban and apixaban were the most commonly prescribed DOACs.
- DOACs were found to be safe and effective.

1 | INTRODUCTION

The incidence of venous thromboembolism (VTE) in children has significantly increased over the last 2 decades [1,2]. This is attributed, in part, to improved survival rates in children with chronic medical conditions and advances in the medical care of pediatric patients presenting with life-threatening events. Identified pediatric prothrombotic risk factors include age (peaks observed in early infancy and adolescence), concomitant medical comorbidities (ie, congenital heart defects, solid organ transplant, and cancer), and the increased use of central venous catheters (CVCs) in the pediatric setting. Besides improvements in radiologic detection, there is also increased awareness of the potential for VTE events to occur in children [3].

There is a lack of evidence-based approaches for the management of VTE in children. Guidelines are primarily extrapolated from adult studies [4,5]. These recommendations directly influence the use of specific anticoagulants for the acute treatment and secondary prevention of pediatric VTE. Unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), and vitamin K antagonists remain the mainstay of pediatric anticoagulation. Besides dalteparin, which was approved for pediatric use in the United States by the Food and Drug Administration (FDA) in 2021, none of these agents have a pediatric labeling [6].

Traditional anticoagulants have important limitations when used in children. Because the mechanism of action of UFH, and to a lesser extent of LMWH, depends on adequate plasma antithrombin concentration, therapeutic levels are difficult to achieve in neonates and children due to physiologic or acquired antithrombin deficiencies [7]. Vitamin K antagonists have multiple food and drug interactions affecting their metabolism. Most importantly, traditional anticoagulants are only available as parenteral and oral (tablet) formulations and mandate frequent laboratory monitoring of therapeutic target levels. Newer anticoagulants are required for children.

Direct oral anticoagulants (DOACs) offer the potential for providing pediatric-specific formulations without the need for laboratory monitoring. There are currently 5 FDA-approved DOACs for the acute treatment and prevention of VTE in adults, and 2 DOACs, dabigatran and rivaroxaban, have been approved for use in children in 2021 [8,9]. We previously demonstrated that between 2010 and 2019, 16% of pediatric and young adults with VTE included in the American Hemostasis and Thrombosis Network's (ATHN's) database—the ATHNdataset—had a DOAC prescribed either as their only anticoagulant or as part of their anticoagulation regimen [10].

The primary objective of the ATHN 15 study "Characterizing the Real-World Use of DOACs in Pediatric Thrombosis Patients" was to further investigate the use of DOACs in 15 different ATHN-affiliated specialized pediatric hemostasis centers, with an emphasis on safety and effectiveness.

2 | METHODS

ATHN 15 was developed in collaboration with ATHN, a nonprofit organization that partners with over 145 hemophilia treatment centers and provides infrastructure and opportunities for national and regional research and public health surveillance [11]. The ATHNdataset is a deidentified Health Insurance Portability and Accountability Act–compliant dataset that includes demographic and clinical information from patients with bleeding and clotting disorders. All participants or their parents or guardians sign an authorization or informed consent per the local institutional review board guidelines for the ATHNdataset and associated research studies.

The ATHN 15 study was conducted at 15 ATHN-affiliated pediatric sites throughout the United States (Supplementary File) from January 2015 to June 2021. Because most pediatric centers in the United States treat patients up to 22 years of age, the eligibility criteria included participants aged 0 to 21 years, at the time of DOAC treatment, who received anticoagulation for the management of an acute VTE or secondary VTE prevention and had a DOAC as part of their treatment regimen (commercial product or within a clinical trial). Participating sites submitted information only on eligible participants who previously provided authorization or signed informed consent for the ATHNdataset.

The participants were divided into 2 cohorts. The retrospective cohort included participants who completed treatment with a DOAC at least 6 months before study enrollment. The prospective cohort included participants who started a DOAC at the time of enrollment.

Data collected, from the start of DOAC and up to 6 months from the initiation of this therapy, were entered into project-specific electronic case-report forms in the secure ATHN Systems infrastructure.

Analyzed data included demographic characteristics (date of birth, sex assigned at birth, weight, height, self-reported ethnicity, self-reported race, and health insurance coverage), baseline medical history including but not limited to diagnoses, comorbidities, surgeries/procedures, VTE medical risk factors, anticoagulation therapy, and DOAC selected therapy. To identify a congenital thrombophilia condition, cutoff determinations for reporting protein C, protein S, and antithrombin deficiencies were left to the discretion of each investigator. Hormonal therapy data, defined as the use of any combined estrogen and progestin oral or transdermal contraceptives within 4 weeks before VTE onset, were also captured.

Safety and effectiveness outcomes, including VTE progression and recurrence, treatment-related bleeding, and mortality status, were assessed through chart review at 3 months and at 6 months from the start of the DOAC therapy. Treatment-related bleeding events were classified as major, clinically relevant nonmajor bleeding (CRNMB), or minor, in accordance to previously published guidelines [12]. A major bleeding event was defined as a composite of fatal bleeding, clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL in a 24-hour period and/or bleeding that was retroperitoneal, pulmonary, intracranial, or in the central nervous system, or bleeding that required surgical intervention in an operating room. CRNMB was a composite of any overt bleeding for which a blood product was administered, not directly attributable to the patient's underlying medical condition and that required a medical or surgical intervention, to restore hemostasis, other than in an operating room. Minor bleeding was defined as any overt or macroscopic evidence of bleeding that does not fulfill criteria for either major bleeding or CRNMB. Participant self-reported and physician-perceived worsening of heavy menstrual bleeding (HMB) in females, aged >12 years, after the initiation of DOAC therapy, and specific interventions required for their management, were also captured.

Descriptive statistics were generated to summarize the demographic characteristics, medical history, and treatment outcomes. A 2-proportion Z-test compared female participants first prescribed apixaban or rivaroxaban who reported worsening menstrual bleeding on at least 1 follow-up form. All statistical reporting and analyses were conducted using R version 4.0.4 (R Core Team, 2021) and RStudio version 1.4.1106 (RStudio Team, 2021).

3 | RESULTS

3.1 | Demographic characteristics

Demographic data are detailed in Table 1. A total of 233 participants were initially enrolled, most retrospectively (184 [79.3%]), and 225 (96.6%) of them submitted at least 1 follow-up form. Of these, 108 (46.4%) participants were male. Most included participants were aged >13 years (209 [89.7%]). The median age at initial VTE was 16.5 years (range, 1-21.4 years; mean, 15.9 years). At the initiation of DOAC therapy, most participants (199 [85.4%]) had a weight of at least 50 kg.

TABLE 1 American Hemostasis and Thrombosis Network 15 study participants' baseline characteristics.

Clinical Characteristics	N (%)
Sex	
Female	125 (53.6)
Male	108 (46.4)
Race	
Asian	8 (3.4)
Black or African American	43 (18.5)
Multiracial[a]	4 (1.7)
White	164 (70.4)
Unknown	14 (6)
Ethnicity	
Hispanic, Latino/a, or Spanish origin	28 (12)
Not Hispanic, Latino/a, or Spanish origin	190 (81.6)
Unknown	15 (6.4)
Patient age(s) at the Start of DOACs, y	
0 to <13	23 (9.9)
13 to <18	164 (70.4)
18-21	45 (19.3)
Unknown	1 (0.4)
Patient weight at the start of DOACs, kg	
<30	8 (3.4)
30 to <50	26 (11.2)
50 to <100	165 (70.8)
≥100	34 (14.6)
Patient insurance information	
Commercial insurance	131 (56.2)
Government-based insurance	84 (36.1)
Other	4 (1.7)
Uninsured	1 (0.4)
Unknown	13 (5.6)

DOAC, direct oral anticoagulant.
[a]Includes 1 self-reported participant as White and Asian and 3 participants self-reporting themselves as White and African American.

Most participants (131 [56.2%]) had medical coverage through commercial insurance, followed by government-based insurance (84 [36.1%]), including Medicaid, Medicare, military health care, and state programs.

3.2 | Thrombosis characteristics

Most participants (194 [83.6%]) did not have a prior history of thrombosis. A total of 269 VTE events were reported, with 32 (13.8%)

TABLE 2 American Hemostasis and Thrombosis Network 15 study: Thrombosis characteristics.

Thrombosis Characteristics	N (%)
Most common VTE location(s)	
Abdominal vein (mesenteric, portal, renal) thrombosis	7 (2.60)
Cerebral sinus venous thrombosis	18 (6.7)
DVT of the lower extremity or pelvis	94 (34.9)
DVT of the upper extremity or upper thorax[a]	49 (18.2)
Pulmonary embolism	80 (29.7)
Superficial vein thrombosis	4 (1.5)
Other locations	17 (6.3)
Most common medical risk factor(s) present at VTE diagnosis	
Antiphospholipid syndrome	6 (2.6)
Autoimmune disorder	12 (5.2)
Cancer (patient undergoing active or palliative therapy)	9 (3.9)
Hospital admission stay (>7 d and within 30 d before the VTE)	26 (11.2)
Obesity	53 (22.7)
Trauma (within 30 d before the VTE, requiring casting or ICU admission)	15 (6.4)
Sepsis (within 7 d before the VTE)	8 (3.4)
Other[b]	47 (20.2)
Most common thrombophilia condition(s) present at VTE diagnosis	
Antithrombin deficiency	6 (2.6)
Factor V Leiden mutation (heterozygous)	22 (9.4)
Factor V Leiden mutation (homozygous)	4 (1.7)
Protein C deficiency	13 (5.6)
Protein S deficiency	12 (5.2)
Prothrombin G20210A mutation (heterozygous)	11 (4.7)
Other[c]	3 (1.3)
Most common drug or environmental risk factor(s) present at VTE diagnosis	
Central venous catheter (within 30 d before VTE)	31 (13.3)
Hormonal therapy (within 4 wks before VTE)	43 (18.5)
Immobility (>72 h and within 30 d before VTE)	24 (10.3)
Smoking	10 (4.3)
Steroids/including anabolic steroids (oral or intravenous used within 30 d before the VTE)	13 (5.6)
Surgical interventions (within 90 d before the VTE and lasting >1 h)	37 (15.9)
Other[d]	30 (12.9)

DVT, deep venous thrombosis; ICU, intensive care unit; VTE, venous thromboembolism.
[a]Includes DVTs affecting the upper extremity and thoracic inlet.
[b]Includes congenital heart disease, COVID-19/SARS-CoV-2, inborn errors of metabolism/mitochondrial disease, inflammatory bowel disease, nephrotic syndrome, pregnancy, sickle cell disease, and others.
[c]Includes Prothrombin G20210A mutation (homozygous) and hyperhomocysteinemia.
[d]Includes asparaginase therapy (within 30 days of VTE), cardiac catheterization (within 30 days of VTE), heparin-induced thrombocytopenia, and travel (>4 hours) within 8 weeks before VTE and others.

participants having ≥2 VTEs at the time the DOAC therapy began. The most prevalent location was deep venous thrombosis (DVT) of the lower extremity or pelvis, reported in 94 (34.9%) participants, followed by pulmonary embolism (PE) (80 [29.7%]) and upper extremity/upper thorax DVTs (49 [18.2%]) (Table 2). Upper extremity/upper thorax DVT included any VTE affecting the deep veins of the upper extremity or thoracic inlet. Twenty-two of 49 (44.9 %) participants with an upper extremity or upper thorax DVT reported the presence of a CVC at the time of VTE, or placement or removal within 30 days prior. Cerebral sinus venous thrombosis was less common (18 [6.7%]).

A total of 123 (53%) participants had ≥1 medical risk factors present at the time of VTE diagnosis (Table 2). Obesity and prolonged hospital admission, (hospital stay for >7 days and within 30 days before the VTE) were the most prevalent (53 [22.7%] and 26 [11.2%], respectively). Trauma, within 30 days of the VTE that required casting or intensive care unit admission, and an autoimmune disorder were also reported in 15 (6.4%) and 12 (5.2%) participants, respectively. One or more laboratory risk factor was present in 95 (40.9%) participants. Factor V Leiden heterozygosity was the most frequent congenital thrombophilia condition (22 [9.4%]), followed by protein C and S deficiencies (13 [5.6%] and 12 [5.2%]).

Finally, 134 (53.4%) participants had at least ≥1 prothrombotic environmental risk factor with hormonal therapy and CVC, at the time of VTE development, being the most prevalent of them (43 [18.5%] and 31 [13.3%]).

3.3 | Treatment characteristics

Rivaroxaban was the most commonly prescribed DOAC (137 [59.1%]), followed by apixaban (90 [38.8%]). Dabigatran and edoxaban were rarely used (3 [1.3%] and 2 [0.9%]) (Table 3). During the study, 3 participants transitioned between DOACs (rivaroxaban to apixaban). Sixty-three of 137 (46%) participants who were prescribed rivaroxaban and 56 of 90 (62.2%) participants who were prescribed apixaban

TABLE 3 American Hemostasis and Thrombosis Network 15 study: DOAC treatment characteristics.

Treatment Characteristics	N (%)
Initially prescribed DOAC	
Apixaban	90 (38.8)
Dabigatran	3 (1.3)
Edoxaban	2 (0.9)
Rivaroxaban	137 (59.1)
Reasoning for selecting a DOAC therapy	
Physician-related reasons	
Physician recommendation	106 (25.9)
Patient-related reasons	
Subject preference	86 (21)
Subject does not like shots	75 (18.3)
Subject does not want lab draws for monitoring	54 (13.2)
Subject enrolled in a clinical trial studying DOACs	13 (3.2)
Subject lack of adherence with standard anticoagulation	10 (2.4)
Thrombus/treatment-related reasons	
Chronic anticoagulation	30 (7.3)
Inadequate response to other anticoagulation	12 (2.9)
Unprovoked thrombosis	7 (1.7)
Thrombosis progression	1 (0.2)
Other	15 (3.7)
Anticoagulation and thrombolysis regimens used before DOAC therapy (N = 298)	
Catheter-directed thrombolysis	20 (6.7)
Enoxaparin	168 (56.4)
Fondaparinux	10 (3.4)
Heparin	56 (18.8)
Systemic thrombolysis	10 (3.4)
Warfarin	19 (6.4)
Other	15 (5)

DOAC, direct oral anticoagulant.

remained on these therapies for the entire study time. Fifty-seven (25.3%) participants reported having completed anticoagulation at the 3-month follow-up period. Thirty-eight (16.9%) participants reported receiving a DOAC for <3 months. Eleven (4.9%) participants did not report anticoagulation length.

Physician recommendation was the most common reported reason for selecting a DOAC-based therapy (106 [25.9%]). The most common patient-related reason was participant's personal preference (86 [21%]), followed by preference for an oral regimen or one that did not require laboratory monitoring.

Most participants (203 [87.5%]) were initially started on ≥1 standard anticoagulants and/or thrombolytic therapy. In total, there were 298 reported pre-DOAC regimens (Table 3). Enoxaparin was most commonly prescribed (168 [56.4%]), followed by UFH and warfarin (56 [18.8%] and 19 [6.4%], respectively). Of the 30 reported thrombolytic regimens (either catheter-directed or systemic), 29 (96.7%) included at least 1 other standard anticoagulant before a DOAC transition.

Twenty-nine (12.5%) participants used a DOAC as their only anticoagulation regimen. The majority (20 [69%]) were prescribed rivaroxaban. The remaining 9 (31%) participants used apixaban as their selected DOAC. Further analysis of this DOAC-only subgroup revealed that 19 of 29 (65.5%) participants were aged ≤18 years at DOAC initiation. Regarding their VTE location, 11 of 29 (37.9%) participants had a lower extremity or pelvis DVT, and 24.1% (n = 7%) reported an upper extremity/upper thorax DVT. Other reported VTE locations included PE and cerebral sinus venous thrombosis (4 [13.8%] and 1 [3.5%]). Two (6.9%) participants reported concomitant presence of PE and lower extremity or pelvis DVT, and 4 (13.8%) participants reported other VTE locations.

3.4 | DOAC safety

While on a DOAC, 31 of 225 (13.8%) participants with a follow-up form reported a bleeding event for a total of 38 events. Twenty-five (11.1%) participants reported minor bleeding events. Major and CRNMB events occurred in 1 (0.4%) and 5 (2.2%) participants, respectively. Seven participants reported bleeding complications at both the 3-month and 6-month follow-ups (Table 4). One of the 31 (3.2%) participants reported concomitant antiplatelet therapy (aspirin) at the time of bleeding.

Most reported bleeding events (32 of 38 [84.2%]) were categorized as "minor." There were 5 (13.2%) CRNMB events and only 1 (2.6%) "major" bleeding event. Two of 7 participants who reported bleeding events at both time points, initially reported a "minor" bleeding event and CRNMB at the 6-month time point. Another one, first reported CRNMB at 3 months and was reclassified as "minor" bleeding afterward. The remaining 4 reported "minor" bleeding events at both time points.

The most commonly reported bleeding was epistaxis and reproductive tract bleeding. None of the reported bleeding events required urgent DOAC reversal. Fifteen (6.7%) participants transiently discontinued DOAC therapy at some point during the follow-up period because of therapy-related bleeding, although 8 (53.3%) were able to restart the DOAC, at the same dose and interval, without further bleeding complications.

The only "major" bleeding event occurred in a participant who was prescribed apixaban. This was spontaneous and affected the gastrointestinal tract. This participant held his anticoagulation but did not require any DOAC-specific reversal agents. The apixaban regimen at the time of the bleeding event was 5 mg per dose twice daily, with no reported concomitant antiplatelet medications. The same DOAC therapy was restarted 48 hours later, upon complete resolution of bleeding. No further complications were reported.

TABLE 4 American Hemostasis and Thrombosis Network 15 study: DOACs safety and effectiveness.

	N (%)
Bleeding events	
Yes	31 (13.8)
No	194 (86.2)
Reported bleeding events by participant (N = 31)	
Minor bleeding	25 (80.6)
Clinically relevant nonmajor bleeding	2 (6.5)
Major bleeding	1 (3.2)
Minor and clinically relevant nonmajor bleeding	3 (9.7)
DOAC-related heavy menstrual bleeding (N = 98)	
Yes	35 (35.7)
No	63 (64.3)
DOAC-specific heavy menstrual bleeding	
Apixaban	
Yes	7 (18.9)
No	30 (81.1)
Rivaroxaban	
Yes	26 (45.6)
No	28 (54.4)
Thrombosis recurrence	
Yes	9 (4)
No	216 (96)

DOAC, direct oral anticoagulant.

When investigating DOAC-related HMB, 98 female participants aged >12 years were evaluated. Age at menarche was not collected. Worsening menstrual bleeding was reported in 35 of the 98 (35.7%) eligible females (Table 4). Most of these females were prescribed rivaroxaban (57 [58.2%]), followed by apixaban (37 [37.8%]). Two (2%) participants were prescribed edoxaban, and 2 (2%) others were prescribed dabigatran.

Seven of 37 (18.9%) females on apixaban reported HMB on at least 1 follow-up form, compared with 26 of 54 (45.6%) females on rivaroxaban (Table 4). There was a significantly lower percentage of females taking apixaban than those taking rivaroxaban (P = .02; CI = −46.99%, −6.40%) who reported HMB.

Thirty (85.7%) reported HMB at only 1-time point, and 5 (14.3%) reported HMB across follow-up forms. Because of HMB, 13 of 35 (37.1%) females had a follow-up action to address this DOAC-related adverse event. Seven females required a modification of their hormonal therapy, and 2 others sought referral to a gynecologist for further HMB management. Four participants reported requiring both interventions. None of the 35 females with DOAC-related HMB reported the need to switch anticoagulation regimens.

3.5 | DOAC effectiveness

Thrombosis recurrence, while taking a DOAC, was reported in 9 of 225 (4%) participants with follow-up forms. All VTE recurrences occurred within 20 days of initiation of the DOAC. Five of these 9 participants experienced a local VTE recurrence; the remaining 4 had a recurrence at a location different from their initial VTE. The most frequent VTE recurrence location was the lower extremity or pelvis (n = 3), followed by upper extremity/thorax and PE (n = 2, each). Five of 9 (55.6%) participants reported the presence of a drug or environmental risk factor at baseline. The use of hormonal therapy was the most common one of them (n = 2, 22.2%). Other reported risk factors included the presence of a CVC, immobility, and steroid therapy, each present in 1 (11.1%) patient. None of these 9 participants reported a congenital thrombophilia diagnosis.

Most participants (7 of 9 [77.8%]) were initially started on a different form of anticoagulation before transition to a DOAC-based regimen. Two (22.3%) participants reported having used a DOAC, rivaroxaban, as their only anticoagulant at the time of recurrence. When analyzing DOAC therapy compliance, 1 of 9 (11.1%) participants reported missing at least one DOAC dose at the time of VTE recurrence. No therapy-related deaths were reported during the study period.

4 | DISCUSSION

The results of the ATHN 15 study demonstrate that despite the lack of pediatric indication for DOACs until 2021, pediatric hematologists in participating specialized hemostasis centers have been using these agents for the treatment and prevention of VTEs since 2015, primarily in adolescents and young adult patients.

Our study also reports that rivaroxaban and apixaban were the preferred DOACs, with 59.1% and 38.8% of participants reporting using these agents, respectively. The use of dabigatran, the first DOAC to receive FDA approval, was reported in 1.3% of the participants. Factors that might have influenced DOAC selection for each participant include the specific DOAC available in the hospital formulary, participation in a DOAC pediatric clinical trial at the time of enrollment, and available DOAC dosage formulation (liquid vs tablet, including the inability of dabigatran to be crushed). It is important to note that, throughout the study, apixaban and edoxaban were still in clinical trials in patients aged <18 years.

Most patients (89.7%) enrolled in the ATHN 15 study were aged >13 years. This finding is similar to the previously published data describing treatment characteristics of patients aged up to 21 years with VTE diagnosed from 2010 to 2019 and reported in the ATHN-dataset [10]. The distribution of age ranges in our study, although predominantly adolescent, is not dissimilar to the data from the EINSTEIN-Jr (NCT02234843) and DIVERSITY 2b/3 (NCT01895777) noninferiority trials, where 55% and 63% of participants, respectively, were aged >12 years [13,14]. We hypothesize that during the ATHN 15 study time, pediatric providers felt more comfortable using DOACs in

older children and young adults because they have weight and pharmacokinetic characteristics more comparable to adults. We expect that DOAC use will continue to expand across the pediatric age range as results from phase 3 clinical trials are available. A potential area for future research certainly includes the integration of DOACs in the care of younger children, infants, and neonates with VTE.

In contrast to the previously published pediatric VTE registries [15,16], the most commonly reported VTE site in the ATHN 15 study participants was the lower extremity or pelvis, as opposed to the upper extremity/thoracic DVTs. This finding might be explained by the clinical characteristics of the study participants. In the ATHN 15 study, the median age at initial VTE diagnosis was 16.5 years, 9.9% of participants were aged <13 years, and the presence of a CVC, at the time of VTE diagnosis, was reported in 13.3% of the participants. We acknowledge that this is not representative of the pediatric population, where one- to two-thirds of VTEs are associated with CVCs, especially in those aged <1 year [15,17–19]. Our cohort consists of predominantly patients aged >13 years who are less likely to require a CVC. Furthermore, patients with CVC-related VTEs may be less likely to be captured into the ATHNdataset as they may not be followed or only followed for a very short time at hemophilia treatment centers, compared with those patients with unprovoked or non–CVC- related VTEs.

In children, UFH, enoxaparin, and warfarin remain widely used for the treatment of acute VTEs or VTE prevention. DOACs offer advantages over the current standard of care, due to lack of laboratory monitoring requirements and available oral formulations offering ease of administration and fewer drug interactions. When investigating the reason for selecting a DOAC-based regimen, the 2 most common patient-related reasons among the ATHN 15 study participants were patient desire to avoid injections and preference for anticoagulant regimen that does not require laboratory monitoring (75 [18.3%] and 54 [13.2%], respectively).

The most serious complication of anticoagulation therapy is the occurrence of a major or life-threatening bleeding event or increased bleeding risk associated with procedures or surgery. The EINSTEIN-Jr study (NCT02234843), which evaluated the efficacy and safety of rivaroxaban as standard of care for the treatment of acute VTE in children aged 0 to 17 years, reported a 3% incidence of CRNMB and no major bleeding events in participants who received at least 1 dose of the study medication [14]. Similarly, in the DIVERSITY trial (NCT01895777), a randomized, open-label, parallel-group, non-inferiority trial comparing standard of care with age-adjusted and weight-adjusted doses of dabigatran in children aged <18 years with newly diagnosed VTE, 22% of children receiving dabigatran reported a bleeding event with major and CRNMB rates of 2% and 1%, respectively [13]. The ATHN 15 study reported that bleeding event rates were similar, if not better, than these 2 studies with 31 (13.8%) participants reporting a bleeding complication at least at 1 of the 2 assessed time points. The majority of these events were categorized as “minor,” with 5 (2.2%) bleeding events reported as CRNMB, and 1 (0.4%) event reported as “major” bleeding. None of the participants experienced a bleeding event that required emergent reversal of their DOAC therapy.

The risk for HMB in postmenarcheal women receiving anticoagulation increases by approximately 70% [20]. In the ATHN 15 study, worsening of menstrual bleeding was reported by 35 of 98 (35.7%) female participants eligible for analysis. The adult anti-Xa DOAC trials revealed an overall greater than twofold increased risk of HMB in adult females taking these agents [21], whereas the RECOVER (a randomised, double blind, parallel-group study of the efficacy and safety of oral Dabigatran etexilate compared to warfarin for 6 month treatment of acute symptomatic VTE) and REMEDY (a randomised, multicenter, double-blind, parallel-group, active controlled study to evaluate the efficacy and safety of oral dabigatran Etexilate compared to warfarin for the secondary prevention of VTE) studies (NCT00291330 and NCT00329238, respectively) suggested that dabigatran carries a lower risk for HMB than warfarin [22]. A recent study comparing the risk of HMB in women taking either rivaroxaban or apixaban found that 45% of women prescribed rivaroxaban required treatment for HMB within 6 months of initiating therapy, compared with 23% of women taking apixaban [23]. The ATHN 15 study had similar findings, with 7 of 37 (18.9%) females on apixaban reporting HMB, compared with 26 of 54 (45.6%) females taking rivaroxaban.

Published data from pediatric-specific DOAC trials have reported thrombosis recurrence rates ranging from 1% to 4% [14]. The reported VTE recurrence rate among the ATHN 15 participants was 4%, with only 1 of 9 participants with recurrent VTE reporting missing doses at the time of recurrence. All of these recurrences occurred within 20 days after the initiation of the DOAC therapy.

There are several limitations to this study. First, the participation of selected ATHN-affiliated specialized sites, where we would expect a higher level of expertise in managing pediatric VTE patients with novel anticoagulant therapies, may not fully represent real-world experience. Future studies should include smaller and nonacademic or university-based hemostasis centers. Selection bias is possible because the included data were obtained only from patients who were approached and opted to participate in the ATHNdataset. Much of the data were collected retrospectively; thus, the capture of outcomes such as minor bleeding may have been missed. Finally, the analysis is dependent on the quality and details of entered data by each of the participating sites.

CONCLUSION

In conclusion, pediatric hematologists in participating specialized pediatric hemostasis centers have been prescribing DOACs, primarily to adolescents and young adults, for the treatment and prevention of VTE since 2015. Similar to pediatric-specific DOAC studies, results from the ATHN 15 study demonstrate that these agents are effective and safe. An additional evaluation regarding the impact of DOACs on HMB in adolescents is needed to help guide practice. DOACs have the potential to become the preferred agents for children requiring acute treatment or prevention of VTEs.

AUTHOR CONTRIBUTIONS

F.F.C.-M. and J.D. conceived the study. F.F.C.-M., J.S., and J.D. contributed to data interpretation and writing. M.R., L.R., and C.D.T. contributed to data analysis and interpretation. All authors reviewed the manuscript for intellectual content and approved the final submitted version.

RELATIONSHIP DISCLOSURE

F.F.C.-M. receives research support from Bayer; educational support from Octapharma; and consulting fees from Sanofi, Octapharma, Bayer, and CSL Behring. L.R. receives consulting fees from Boeringer-Ingelheim, CSL Behring, Genentech, and Janssen. M.R. receives grants or contracts to support his employers from Bayer, BioMarin, CSL Behring, Genentech, Grifols, Hema Biologics, LFB, NovoNordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda, and uniQure and receives consulting fees from Catalyst Biosciences, CSL Behring, Genentech, Hema Biologics, Kedrion, NovoNordisk, Pfizer, Sanofi, Takeda, uniQure. C.D.T. receives research support from Bayer. J.D. receives consulting fees from Boeringer-Ingelheim, Genentech, and Octapharma. J.S. declare no competing financial interests.

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SUPPLEMENTARY MATERIAL

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