REGULAR ARTICLE

blood advances

Safety and efficacy of anticoagulant therapy in pediatric catheter-related venous thrombosis (EINSTEIN-Jr CVC-VTE)

Katharina Thom,[1] Anthonie W. A. Lensing,[2] Ildar Nurmeev,[3] Fanny Bajolle,[4] Damien Bonnet,[4] Gili Kenet,[5,6] M. Patricia Massicotte,[7] Zeynep Karakas,[8] Joseph S. Palumbo,[9] Paola Saracco,[10] Pascal Amedro,[11] Juan Chain,[12] Anthony K. Chan,[13] Takanari Ikeyama,[14] Joyce C. M. Lam,[15] Cynthia Gauger,[16] Ákos Ferenc Pap,[2] Madhurima Majumder,[17] Dagmar Kubitza,[2] William T. Smith,[17] Scott D. Berkowitz,[17] Martin H. Prins,[18] Paul Monagle,[19] Guy Young,[20] and Christoph Male,[1] for the EINSTEIN-Jr CVC-VTE investigators

[1]Department of Paediatrics, Medical University of Vienna, Vienna, Austria; [2]Bayer AG, Wuppertal, Germany; [3]Kazan State Medical University, Kazan, Russia; [4]M3C-Necker Enfants Malades, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; [5]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [6]Israeli National Hemophilia Center and Thrombosis Unit and The Amalia Biron Thrombosis Research Institute, Sheba Medical Center, Tel Hashomer, Israel; [7]Department of Pediatrics, University of Alberta, Edmonton, AB, Canada; [8]Pediatric Hematology/Oncology, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey; [9]Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; [10]Pediatric Hematology, University Hospital Città della Salute e della Scienza, Turin, Italy; [11]Paediatric and Congenital Cardiology Department, M3C Regional Reference Centre, Montpellier University Hospital, PhyMedExp, INSERM, Centre National de la Recherche Scientifique, Montpellier, France; [12]Hospital del Niño Jesus, San Miguel de Tucumán, Argentina; [13]McMaster Children's Hospital, Hamilton, ON, Canada; [14]Aichi Children's Health and Medical Center, Aichi, Japan; [15]Paediatric Haematology/Oncology Service, KK Women's and Children's Hospital, Singapore, Singapore; [16]Nemours Children's Specialty Care, Jacksonville, FL; [17]Bayer U.S., LLC, Whippany, NJ; [18]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, The Netherlands; [19]Department of Clinical Haematology, Royal Children's Hospital, Haematology Research Murdoch Children's Research Institute, Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia; and [20]Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA

Key Points

- Anticoagulant therapy of symptomatic or asymptomatic CVC-VTE in children was safe, efficacious, and associated with reduced clot burden.
- Residual VTE in children <2 years and continued CVC use were associated with extended anticoagulation.

Anticoagulant treatment of pediatric central venous catheter–related venous thromboembolism (CVC-VTE) has not been specifically evaluated. In EINSTEIN-Jr, 500 children with any VTE received rivaroxaban or standard anticoagulants. A predefined analysis of the CVC-VTE cohort was performed. Children with CVC-VTE (age, birth to 17 years) were administered rivaroxaban or standard anticoagulants during the 1-month (children <2 years) or 3-month (all other children) study period. Predefined outcomes were recurrent VTE, change in thrombotic burden on repeat imaging, and bleeding. Predictors for continuation of anticoagulant therapy beyond the study period were evaluated. One hundred twenty-six children with symptomatic (n = 76, 60%) or asymptomatic (n = 50, 40%) CVC-VTE received either rivaroxaban (n = 90) or standard anticoagulants (n = 36). There was no recurrent VTE (0%; 95% confidence interval [CI], 0.0%-2.8%). Three children had the principal safety outcome: none had major bleeding and 3 children had clinically relevant nonmajor bleeding (2.4%; 95% CI, 0.7%-6.5%), all in the rivaroxaban arm. Complete or partial vein recanalization occurred in 57 (55%) and 38 (37%) of 103 evaluable children, respectively. Results were similar for symptomatic and asymptomatic CVC-VTE. Continuation of anticoagulant therapy beyond the study period occurred in 61 (48%) of children and was associated with residual VTE but only in children <2 years (odds ratio [OR], 20.9; $P = .003$) and continued CVC use (OR, 6.7; $P = .002$). Anticoagulant therapy appeared safe and efficacious and was associated with reduced clot burden in most children with symptomatic or asymptomatic CVC-VTE. Residual VTE and continued CVC use were associated with extended anticoagulation. This trial was registered at www.clinicaltrials.gov as #NCT02234843.

Submitted 10 June 2020; accepted 7 August 2020; published online 30 September 2020. DOI 10.1182/bloodadvances.2020002637.

A data sharing statement is provided in the supplemental Materials.

The full-text version of this article contains a data supplement.

Introduction

Venous thromboembolism (VTE) in children is commonly associated with use of central venous catheters (CVCs).[1,2] CVC-related VTE is most frequently observed in neonates, with most clots discovered through catheter malfunction or routine screening, whereas clinically symptomatic CVC-related VTE occurs in a small proportion.[3-6] There is uncertainty regarding the optimal management of CVC-VTE because of a lack of randomized trials and paucity of prospective studies. There is only a single randomized trial in the literature on anticoagulant treatment of VTE in 76 children, of whom about two thirds (63%) had CVC-VTE.[7] Unfortunately, results were not presented separately for those with or without CVC-VTE. Potential objectives of anticoagulant treatment of CVC-VTE are to reduce or prevent symptoms, to prevent extension or embolization into more central veins, to prevent chronic venous occlusion, and to prevent recurrent venous thromboembolic complications.[8] In addition, CVC-VTEs are associated with an increase of bloodstream infections[8-12] and thus cause additional morbidity and a substantial increase in health care costs.[13] Based on very limited pediatric data and extrapolation from adults,[14] recent pediatric guidelines recommend therapeutic anticoagulation for symptomatic CVC-VTE but give no explicit recommendation for or against anticoagulation for asymptomatic CVC-VTE.[15]

Recently, the EINSTEIN-Jr study compared the oral direct factor Xa inhibitor rivaroxaban to standard anticoagulants (heparin, vitamin K antagonists) in 500 children of all ages for treatment of acute VTE of any type.[16,17] The body weight–adjusted pediatric rivaroxaban dosing regimens successfully targeted the adult rivaroxaban exposure range without requiring laboratory monitoring.[18,19] Recurrent VTE occurred infrequently with both rivaroxaban and standard anticoagulation, and no major bleeding events were observed in the 335 children who received rivaroxaban.[17] The absolute incidences of study outcomes and relative treatment effects observed with rivaroxaban were similar to those in the large rivaroxaban VTE studies in adults.[17,20-22]

Here, we present a predefined exploratory analysis of the subgroup of 126 children of EINSTEIN-Jr who presented with symptomatic or asymptomatic CVC-VTE. We aimed to describe their clinical characteristics and VTE risk factor profiles, report the efficacy and safety of anticoagulation, and evaluate factors potentially associated with pediatricians' decisions on individual patient's duration of anticoagulant treatment. We hypothesized that differences in risk factor profiles of children with CVC-VTE compared with children with other VTE may influence the duration of anticoagulant therapy and potentially result in differences in the safety and efficacy of anticoagulation.

Methods

Study design

This is a substudy of the EINSTEIN-Jr phase 3 study (clinicaltrials.gov: NCT02234843), which was a multicenter, open-label, randomized trial that compared the efficacy and safety of rivaroxaban with those of standard anticoagulants for the treatment of pediatric VTE.[17] The study protocol, clinical efficacy and safety results, and the rivaroxaban dose-exposure-response have previously been published.[16,17,19] The protocol was approved by the institutional review board at each participating center. Written permission from a parent or guardian and, when appropriate, child assent, were obtained. An independent data monitoring committee periodically reviewed trial conduct and safety. The substudy was conducted at 57 sites in 22 countries (supplemental Material). The study treatment period was 1 month (30 $\pm$ 7 days) for children younger than 2 years and 3 months (90 $\pm$ 7 days) for the remaining children, similar for both treatment arms.[23] CVC-VTE was defined as occlusive or nonocclusive venous thrombosis that occurred in the proximity of a (recent) indwelling CVC or associated embolism. VTE was classified locally as symptomatic or asymptomatic based on presence of pain, swelling, and skin discoloration, whereas asymptomatic VTE was identified because of CVC malfunction, incidental finding, or surveillance screening.

Children with CVC-VTE were considered for study inclusion if they had initiated treatment with unfractionated heparin, low-molecular-weight heparin (LMWH) or fondaparinux. Children younger than 0.5 years were required to have a gestational age at birth of at least 37 weeks, a body weight above 2600 g, and had oral feeding for at least 10 days. The main exclusion criteria were active bleeding or high risk of bleeding contraindicating anticoagulant therapy and an estimated glomerular filtration rate $<$30 mL/min per 1.73 m^2, or if younger than 1 year, serum creatinine $>$97.5th percentile. The full list of eligibility criteria is provided in supplemental Table 1. Enrollment started with children aged 12 to 17 years, followed by those aged 6 to 11, 2 to 5, 0.5 to 1 years, and younger than 0.5 years, as described previously.[16,17]

Randomization and study medication

After completion of 5 to 9 days of anticoagulation with unfractionated heparin, LMWH, or fondaparinux, children were randomized in a 2:1 ratio to open-label rivaroxaban or comparator.[17] In the main EINSTEIN-Jr phase 3 study, randomization was stratified per age group and site of VTE (straum 1: extremity venous thrombosis, pulmonary embolism; stratum 2: CVC-VTE, cerebral venous, jugular, caval, renal, or portal vein thrombosis). Children in the comparator group continued with heparin treatment or switched to a vitamin K antagonist, at the discretion of the treating physician, at therapeutic doses, according to international guidelines.[24] Children allocated to rivaroxaban received body weight–adjusted 20-mg equivalent doses, given once daily, twice daily, or thrice daily for body weights $\geq$ 30, 12 to $<$30, and $<$12 kg, respectively (supplemental Table 2). Rivaroxaban was administered as immediate release film-coated tablets available in strengths of 5, 10, 15, or 20 mg or as a newly developed suspension for oral use.[19] Rivaroxaban was administered with an age-appropriate serving of fluid given with or shortly after a meal.

Follow-up and outcomes

All children who stopped study treatment earlier than scheduled were followed until the end of the study treatment period. Patients and their parents were instructed to report to the study center if they had symptoms suggestive of recurrent thrombosis or bleeding. The primary efficacy outcome was symptomatic CVC-related or non–CVC-related recurrent deep VTE. The principal safety outcome was the composite of overt major and clinically relevant nonmajor bleeding (supplemental Table 3). Clinically relevant other venous thrombosis was an additional outcome.

If no symptomatic recurrent VTE had occurred, repeat imaging of the venous thrombosis was performed at the end of the study treatment period and was compared with baseline images. Degree of vein recanalization was classified as normalized, (ie, no residual thrombus observed), improved (ie, thrombus still present but partly recanalized or involving less venous segments), unchanged (ie, not recanalized and similar in extent), deteriorated (ie, new venous segment involved), or uncertain. For the efficacy analyses, results of repeat imaging were classified as uncertain if repeat imaging was not performed or evaluable, repeat imaging was done >7 days before stop of study medication, or repeat imaging was done >7 days after stop of study medication. However, all available repeat imaging results were considered for their association with the presence of symptoms (symptomatic or asymptomatic), the time course of the index VTE, and the duration of anticoagulant therapy. The time course of the index VTE was classified as acute (0-14 days), subacute (15-28 days), or chronic (>28 days) based on the interval between start of use of the CVC and start of initial heparinization. The duration of anticoagulant therapy was classified as shorter than the intended study period, corresponding to the study period, or continuing beyond the study period. CVC-associated infections were documented through adverse event reporting and defined by moderate to severe fever, bacteremia, or shock, without infection at another site and were related to the presence of residual thrombosis on repeat imaging. An independent adjudication committee, whose members were unaware of study group assignment, evaluated the initial diagnosis, all suspected outcomes and repeat imaging tests. In addition, they classified individual provoking factors for VTE as permanent or transient risk factors and assessed whether the CVC was still present at baseline, during the study period, or at the end of the study treatment period. The members of the adjudication committee were experts in vascular medicine with extensive experience in adjudication of suspected thrombotic events and bleeding (supplemental Material).

Statistical analysis

The EINSTEIN-Jr study, and consequently this substudy, were not powered for confirmatory analyses. Efficacy outcomes were considered during the study treatment period, whereas safety outcomes were considered for the same period but only during the time from administration of the first dose of study medication to 48 hours after the last dose. Because of the low frequency of clinical outcomes, data are primarily presented for the entire cohort. The following prespecified variables were assessed as potential determinants of continuation of any anticoagulation beyond the study treatment period by multiple logistic regression modeling: age group (<2, 2-5, 6-11, and 12-17 years), presentation with a clinically symptomatic index VTE, presence of acute or subacute index VTE, persistent presence of the CVC at end of study treatment, presence of a permanent risk factor for VTE, and any residual VTE on repeat imaging test. Logistic regression also tested for significant level 1 interactions between variables, and 95% confidence intervals (CIs) for incidences were calculated by exact methods. Calculations were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).

Results

From 3 March 2015 through 18 January 2019, 127 children with CVC-VTE were randomized (Figure 1). In 1 child, the presence of VTE was not confirmed after randomization. Demographics, clinical, and radiologic characteristics of the 126 remaining children are shown in Table 1. Ninety children were randomized to rivaroxaban and 36 children to standard anticoagulants. The median follow-up during the study period was 31 day (interquartile range, 29-35 days) for the 36 children younger than 2 years and 91 days (interquartile range, 86-95 days) for the 90 children aged 2 years or older. Three children did not take allocated study medication with rivaroxaban but continued standard of care anticoagulation.

Presentation of CVC-VTE

The percentage of children with CVC-VTE relative to all 500 children in the entire EINSTEIN-Jr study was 25% and was highest for children in the age group birth to 1 year (67%), declining with increasing age to 38%, 24%, and 14% for children aged 2 to 5, 6 to 11, and 12 to 17 years, respectively ($P_{trend} < .0001$; Table 1). Most CVC-VTEs involved the jugular vein (n = 41), the upper extremity (n = 34), and lower extremity (n = 35). CVC-VTE was symptomatic in 76 children (60%) and asymptomatic (ie, detected by CVC malfunction, routine screening, or as incidental finding) in 50 children (40%). CVC-VTE was acute in the majority of children (56%). Table 1 lists VTE risk factor profiles in addition to the use of a CVC. Permanent risk factors for VTE (with or without additional transient risk factors) were observed in 77 (61%) children and transient only risk factors in 49 (39%) children. The main indications for the use of a CVC were major surgery or trauma in 40 children (32%), cardiac disease in 38 children (30%), infectious disease in 34 children (27%), and active cancer in 31 children (25%). The CVC had already been removed before the study in 29 (23%) children, was removed during the study period in 72 (57%) children, and was still in place at the end of the study in 22 (17%) children.

Study outcomes

Symptomatic recurrent deep VTE occurred in none of the 126 children (0%; 95% CI, 0.0%-2.8%; Table 2). Other clinically significant venous thromboses (ie, thrombotic occlusion of aorto-pulmonary shunt and arteriovenous fistula for dialysis) occurred in 2 children (1.6%; 95% CI, 0.3%-5.4%). Three children had a principal safety outcome: none had major bleeding (0%; 95% CI, 0.0%-2.8%), and 3 children had clinically relevant nonmajor bleeding events (2.4%; 95% CI, 0.7%-6.5%), who were in the rivaroxaban arm. No child died during the study (Table 2).

In 23 (18%) children, a repeat imaging test was not performed or evaluable (n = 4) or was performed outside the required time window (n = 19), and results were classified as uncertain. Of the 103 children with a repeat imaging test performed during the required time window, complete vein recanalization occurred in 57 (55%), incomplete recanalization in 38 (37%), no relevant change in 7 (6.8%), and asymptomatic deterioration in 1 (1.0%). Overall, a normalized or improved result was observed in a similar frequency in children with symptomatic (n = 70; 92%) or asymptomatic CVC-VTE (n = 43; 86%; Table 3). Unchanged or deteriorated repeat imaging outcomes after anticoagulant treatment were found in 3 (4.2%) of 71 children with acute index CVC-VTE compared with 6 (16.2%) of 37 children with chronic CVC-VTE (odds ratio [OR], 0.23; 95% CI, 0.05-0.97; Table 3). CVC-associated infection during the treatment period occurred in 10 (8.2%) of the 122 evaluable children: 4 (5.8%) among 69 children with a normalized repeat imaging result and 6 (11.3%) among 53 children with residual venous thrombosis on repeat imaging (OR, 0.48; 95% CI, 0.13-1.80).

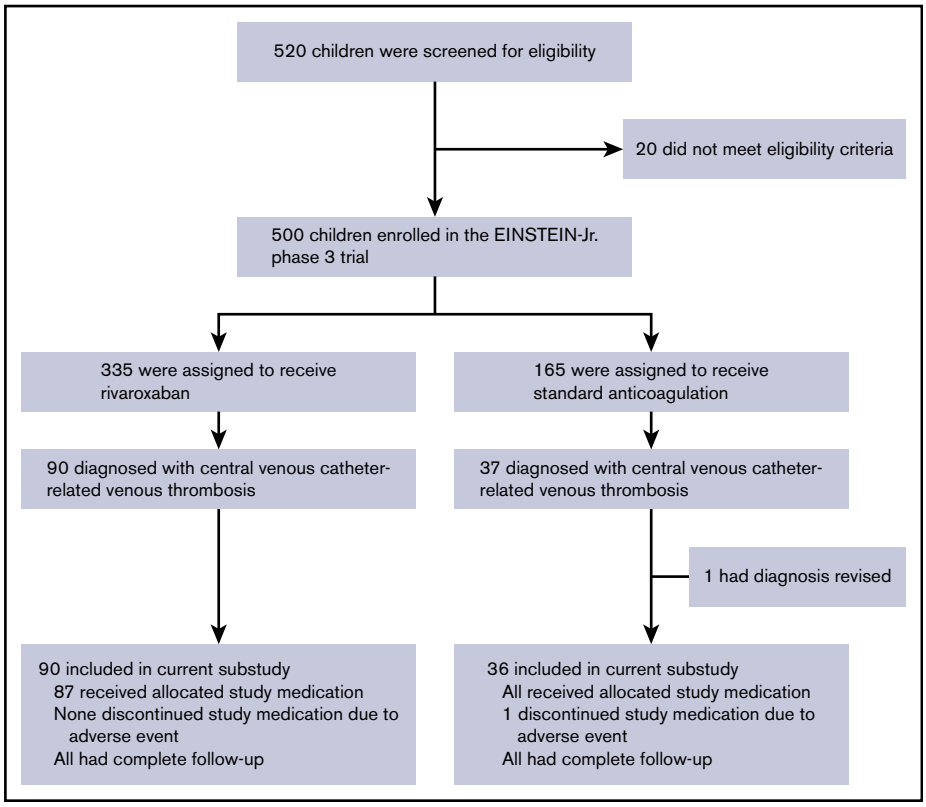

Figure 1. Flowchart of selection of patients for the EINSTEIN-Jr CVC-VTE substudy.

Determinants of extended anticoagulant therapy

Duration of anticoagulant therapy was shorter than the study period in 11 (8.7%) children, corresponding to the study period in 54 (43%) children, and continuing beyond this period in 61 (48%) children. Among the 36 children younger than 2 years, none had anticoagulant therapy duration shorter than 1 month, whereas 22 (61%) of these children continued treatment with any anticoagulant beyond 1 month. Using logistic regression analysis, any residual VTE on repeat imaging, limited to children younger than 2 years (OR, 20.9; 95% CI, 2.8-153.9; $P = .003$), and presence of a CVC at the end of the study period (OR, 6.7; 95% CI, 2.0-22.3; $P = .002$) were independently associated with continued anticoagulant therapy beyond the study period (supplemental Tables 4 and 5).

Discussion

The results of our analyses show that anticoagulant therapy with either rivaroxaban or standard anticoagulants in children with symptomatic or asymptomatic CVC-VTE after initial heparin therapy appears safe, efficacious, and associated with complete or partial vein recanalization in more than 90% of children. Continuation of any anticoagulant therapy beyond the study period (1 month in children younger than 2 years and 3 months in all other children) occurred in almost half of the children and was associated with residual VTE on repeat imaging, only in children younger than 2 years, and with continued use of the CVC as independent determinants. Our report is the first prospective study on anticoagulant treatment of pediatric CVC-VTE and further substantiates the efficacy and safety of anticoagulant therapy for this indication.

Children with CVC-VTE differ in several aspects from children with non–CVC-VTE. Relative to presentation with any VTE among the 500 children in the entire EINSTEIN-Jr study,[17] the proportion of children with CVC-VTE was highest (67%) among children younger than 2 years and declined gradually to 14% in older children. Possible reasons for the higher proportion of CVC-VTE among younger children include the frequent need of CVC for treatment of sick neonates and infants[23,25] and vessel obstruction resulting from large CVC to vessel diameter ratios.[26] Moreover, a higher proportion of children with CVC-VTE had underlying diseases, such as cancer or major organ disease. CVC-VTE were more frequently located in the central venous system and were more frequently asymptomatic VTE (40% vs 12% in children with non–CVC-VTE).[17] Children with CVC-VTE more often received shorter duration of anticoagulation, apparently because of a perceived lower VTE risk once the CVC is removed. Finally, children with CVC-VTE had no recurrent VTE at all and a higher proportion of complete thrombus resolution (55% vs 41% in children with non–CVC-VTE), whereas the bleeding risk during anticoagulation was similar.

In general, the prognosis of asymptomatic VTE is uncertain, and there is no consensus whether it requires anticoagulant therapy.[15] A recent systematic review of asymptomatic VTE in children, which included mainly CVC-related VTE, reported that most VTE had a benign clinical course, resolved, and had few immediate or long-term complications.[27] Although the review suggested that anticoagulation therapy may not change the clinical course, it was based on retrospective studies that included children with or without anticoagulant treatment, and outcomes were not uniformly

Table 1. Demographics, clinical presentation, and study treatment at baseline

	Age birth to <2 y* (n = 36)	Age 2 to 5 y (n = 26)	Age 6 to 11 y (n = 24)	Age 12 to 17 y (n = 40)	Total (N = 126)
Demographics					
Male sex, n (%)	22 (61)	10 (38)	15 (63)	23 (58)	70 (56)
Body weight, mean (SD), kg	6.7 (3.1)	14.6 (3.3)	31.3 (7.5)	55.7 (14.3)	28.5 (22.2)
Proportion CVC-VTE of the entire Einstein-Jr population, n/N (%)†	36/54 (67)	26/69 (38)	24/101 (24)	40/276 (14)	126/500 (25)
Clinical presentation of venous thrombosis, n (%)					
Jugular vein	13 (36)	9 (35)	8 (33)	11 (28)	41 (33)
Upper extremity‡	0	4 (15)	7 (29)	24 (60)	35 (28)
Right heart	1 (2.8)	3 (12)	4 (17)	3 (7.5)	11 (8.7)
Caval vein	1 (2.8)	0	0	1 (2.5)	2 (1.6)
Portal vein	0	0	1 (4.2)	0	1 (0.8)
Lower extremity	21 (58)	10 (38)	4 (17)	1 (2.5)	36 (29)
Asymptomatic presentation CVC-VTE	15 (42)	14 (54)	10 (42)	11 (28)	50 (40)
Time course of CVC-VTE, n (%)					
Acute (0-14 d)	25 (69)	14 (54)	13 (54)	19 (48)	71 (56)
Subacute (15-28 d)	6 (17)	3 (11)	3 (13)	6 (15)	18 (14)
Chronic (>28 d)	5 (14)	9 (35)	8 (33)	15 (37)	37 (29)
Etiology of index VTE, n (%)					
Transient risk factor (apart from the CVC)	13 (36)	10 (38)	10 (42)	16 (40)	49 (39)
Persistent ± transient risk factor	23 (64)	16 (62)	14 (58)	24 (60)	77 (61)
Type of risk factor, n (%)					
Major trauma/surgery	15 (42)	9 (35)	7 (29)	9 (23)	40 (32)
Major infectious disease	11 (31)	7 (27)	7 (29)	9 (23)	34 (27)
Use of estrogens or progestins	NA	NA	NA	4 (24)§	NA
Major organ disease	22 (61)	11 (42)	7 (29)	7 (18)	47 (37)
Cardiac	20 (56)	9 (35)	5 (21)	4 (10)	38 (30)
Gastrointestinal	0	0	0	2 (5)	2 (1.6)
Neurological	0	2 (7.7)	0	0	2 (1.6)
Renal	2 (5.6)	0	2 (8.3)	1 (2.5)	5 (40)
Active cancer‖	1 (2.8)	7 (27)	7 (29)	16 (40)	31 (25)
Hematologic cancer	1 (2.8)	5 (19)	3 (13)	11 (28)	20 (16)
Solid tumor	0	2 (7.7)	4 (17)	5 (21)	11 (8.7)
Known inherited thrombophilia¶	1 (2.8)	0	0	0	1 (0.8)
Study treatment, n (%)					
Initial therapy with UFH only	10 (28)	4 (15)	1 (4.2)	3 (7.5)	11 (8.7)
Initial therapy with LMWH	26 (72)	22 (85)	23 (96)	37 (93)	115 (91)
Rivaroxaban group, n (%)**					
Tablet	0	0	5 (31.2)	16 (57.1)	21 (24.1)
Suspension	25 (100.0)	18 (100.0)	11 (68.8)	12 (42.9)	66 (75.9)
Standard anticoagulation group, n (%)					
LMWH	8 (80.0)	5 (71.4)	7 (87.5)	9 (81.8)	29 (80.6)
LMWH followed by vitamin K antagonists	2 (20.0)	2 (28.6)	1 (12.5)	2 (18.2)	7 (19.4)

NA, not applicable; SD, standard deviation.
*Children aged birth to <0.5 years, n = 1; children aged 0.5 to 1 year, n = 8.
†The EINSTEIN-Jr study included 500 children with various types of VTE.[17]
‡Including axillary and subclavian vein.
‖Active cancer was defined as presence of metastases, or recently (<6 months) diagnosed or treated.
¶Antithrombin deficiency (heterozygous).
**Three children allocated to rivaroxaban did not receive study medication.
§Calculated for 17 girls aged 12 to 17 years.

Table 2. Clinical outcomes by treatment group

Study outcome, n (%)	Rivaroxaban, n = 90	Standard anticoagulation, n = 36	Absolute risk difference (95% CI), %
Recurrent VTE	0	0	0 (−11 to 4.2)
Other clinically relevant venous thrombosis	1 (1.1)	1 (2.8)	−1.7 (−14 to 3.6)
Major bleeding	0	0	0 (−11 to 4.2)
Clinically relevant nonmajor bleeding	3 (3.3)	0	3.3 (−6.4 to 9.7)
Blood in nasogastric tube	1		
Hematemesis	1		
Hematoma at catheter puncture site*	1		
CVC-related infection	7 (7.8)	3 (8.3)	−0.6 (−10 to 11)
Repeat imaging			
Normalized	42 (47)	15 (42)	
Improved	26 (29)	12 (33)	
Unchanged	2 (2.2)	5 (14)	
Deteriorated	1 (1.1)	0	
Uncertain	19 (21)	4 (11)	

Twenty-three children had a repeat imaging outcome classified as uncertain because the imaging was not performed or it was not evaluable (n = 4), study medication was continued for >7 days after repeat imaging (n = 8), or repeat imaging was done >7 days after stop study medication (n = 11). Of these children, 19 had a repeat imaging that was normalized (n = 12), improved (n = 6), or unchanged (n = 1).

*Bleeding occurred during initial heparinization.

assessed; therefore, it is challenging to draw definite conclusions about the benefit of anticoagulant therapy. In our study, 40% of children had asymptomatic CVC-VTE. Nevertheless, their physicians had decided to administer anticoagulants in therapeutic doses, and consequently, these children were eligible for the study. As preserving a functional CVC, especially in the youngest children, may be of critical importance, and progression of CVC-VTE into more central veins may come with the hazard of (potentially fatal) recurrent VTE, and chronic venous occlusion, pediatricians may elect anticoagulant treatment over a watchful-waiting approach. The absence of recurrent VTE and major bleeding and the high rate of complete and partial resolution of the CVC-VTE on repeat imaging seem to lend credence to the practice of anticoagulant therapy not only for symptomatic CVC-VTE but also for asymptomatic CVC-VTE. Additionally, assuming that anticoagulant treatment leads to a higher rate of complete thrombus resolution, the observation that CVC-related infections tended to occur less frequently in children with complete VTE resolution than in those without might be another argument for this practice. Interestingly, in children with longer intervals from CVC placement to initiation of anticoagulant treatment (ie, chronic VTE), thrombus resolution occurred less frequently, probably because thrombi were already organized.

Strengths of our study include the prospective study design, the central blinded outcome evaluation, availability of repeat imaging in almost all children, administration of standard anticoagulation according to current guidelines,[24] and complete follow-up. Several limitations also warrant comment. First, the EINSTEIN-Jr study was designed as a randomized trial comparing rivaroxaban vs standard anticoagulation. However, because of the relatively low sample size of this substudy and infrequency of major clinical outcomes, we decided to present the current data as a single cohort of children with CVC-VTE, as such studies have not been available thus far. Therefore, we focused on describing demography, risk factor profiles for VTE, the effect of anticoagulation on thrombus burden, and clinical course of symptomatic and asymptomatic CVC-VTE and refrained from formal statistical comparisons between rivaroxaban and standard anticoagulation. Second, for ethical reasons, term neonates and infants were included only after demonstration of safety with rivaroxaban in older children.[16] Consequently, the number of neonates and infants included is relatively low. For this

Table 3. Presentation of index CVC-VTE vs degree of thrombus resolution at repeat imaging

	Time course of venous thrombosis					
	Acute (1-14 d)		Subacute (15-28 d)		Chronic (>28 d)	
Repeat imaging result, n (%)	Symptomatic, n = 41	Asymptomatic, n = 30	Symptomatic, n = 12	Asymptomatic, n = 6	Symptomatic, n = 23	Asymptomatic, n = 14
Normalized	23 (56)	19 (63)	8 (67)	3 (50)	11 (48)	5 (36)
Improved	15 (37)	9 (30)	4 (33)	3 (50)	9 (39)	4 (29)
Unchanged	1 (2)	2 (7)	0	0	1 (4)	4 (29)
Deteriorated/recurrent VTE	0	0	0	0	1 (4)	0
Not done or evaluable	2 (5)	0	0	0	1 (4)	1 (7.1)

Classification of venous thrombosis based on interval between start of use of a central venous catheter and start of initial heparinization. For this analysis, repeat imaging results include those that were assessed as uncertain because of performance outside the required time window.

reason, the 25% proportion of CVC-VTE in EINSTEIN-Jr is lower than generally reported for VTE in children.[1,2,28] Importantly, preterm neonates were not eligible for the study because of safety considerations related to the use of rivaroxaban,[16] as maturation of organs involved in rivaroxaban absorption and clearance depend on the gestational and postnatal age. Gastrointestinal function is more stable in children with a gestational age of ≥37 weeks after oral feeding for at least 10 days.[16] Therefore, the results of the present study are not applicable to preterm neonates. Third, participating pediatricians might have included children with asymptomatic CVC-VTE who would not have been treated with anticoagulant therapy outside of an active study. We believe that such a patient selection did not occur to a significant extent because children were required to have had already started therapeutic heparinization before participation in our study. Fourth, our study documented efficacy and safety outcomes limited to a 1- or 3-month study period, but anticoagulation could be given for longer durations. Indeed, almost half of the inception cohort was treated with anticoagulant therapy beyond the study period. The practice of shorter treatment durations for young children has developed based on anecdotal evidence that early thrombosis resolution is not uncommon but anticoagulation is continued in the presence of persisting risk factors.[24] Finally, despite the paucity of pediatric clinical trials, children with VTE are often administered anticoagulants, most likely through extrapolation of the overwhelming evidence in adults with VTE. Therefore, based on the absence of a true state of equipoise among pediatricians regarding the use of anticoagulant therapy in pediatric VTE, we refrained from including a no treatment study arm. However, it should be recognized that, although we evaluated novel and child-friendly anticoagulant treatment regimens that appear to be efficacious and safe, we did not provide ultimate proof of efficacy and safety for the treatment of pediatric VTE. Further studies are required across a multitude of clinical scenarios to determine benefits vs risks of anticoagulant treatment of pediatric VTE.

In conclusion, in children with symptomatic or asymptomatic CVC-VTE, anticoagulant therapy appeared safe and efficacious and was associated with a reduced clot burden in more than 90% of children. Residual VTE on repeat imaging in those younger than 2 years and persistent need of the CVC were associated with continuation of any anticoagulant therapy beyond the study period.

Acknowledgments

The authors thank the children who participated in this study and their supportive families, as well as the investigators, subinvestigators, and coordinators at each of the study sites. The authors thank Laurien E. Lensing for editorial and statistical assistance.

This work was funded by Bayer AG and Janssen Research & Development. LLC.

Authorship

Contribution: K.T., A.W.A.L., G.K., M.P.M., A.K.C., P.M., G.Y., and C.M. designed the study; and all authors contributed to data collection, data analysis, data interpretation, and writing of the manuscript, approved the final version, and agreed to be accountable for all aspects of the report.

Conflict-of-interest disclosure: K.T. reports study patient fees paid to her institution from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. F.B. reports fees paid to her institution from Bayer and Daiichi-Sankyo. D.B. received personal fees from Bayer, Actelion Pharmaceuticals, Janssen, Novartis, Bristol-Myers Squibb, and Abbott and fees paid to his institution from Bayer and Daiichi-Sankyo. G.K. received personal fees from Bayer, Boehringer Ingelheim, and Daiichi-Sankyo and fees paid to her institution from Pfizer. M.P.M. received personal fees from Bayer. A.K.C. received personal fees from Bayer and fees paid to his institution from Bayer, Pfizer, Daiichi Sankyo, and Bristol-Myers Squibb. M.H.P. received personal fees from Bayer AG. G.Y. received personal fees from Bayer AG, Daiichi-Sankyo, and Portola. C.M. received personal fees from Bayer AG, Bristol-Myers Squibb, and Pfizer and fees paid to his institution from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. I.N., Z.K., P.A., and J.C.M.L. received fees paid to their institution from Bayer AG. A.W.A.L., A.F.P., M.M., D.K., W.T.S., and S.D.B. are employees of Bayer. The remaining authors declare no competing financial interests.

A list of the EINSTEIN-Jr CVC-VTE investigators and collaborators is provided in the supplemental appendix.

ORCID profiles: K.T., 0000-0002-4328-9962; I.N., 0000-0002-1023-1158; F.B., 0000-0002-1106-0987; D.B., 0000-0002-8722-5805; P.A., 0000-0003-3649-0294; A.K.C., 0000-0003-1551-3995; J.C.M.L., 0000-0001-9368-4752Á.F.P., 0000-0002-2161-3151; G.Y., 0000-0001-6013-1254; C.M., 0000-0002-4989-6421.

Correspondence: Christoph Male, Department of Paediatrics, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria; e-mail: christoph.male@meduniwien.ac.at.

References

1. 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(5):1251-1257.
2. van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. *J Pediatr*. 2001;139(5):676-681.
3. 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(6):770-776.
4. Male C, Chait P, Andrew M, Hanna K, Julian J, Mitchell L; PARKAA Investigators. Central venous line-related thrombosis in children: association with central venous line location and insertion technique. *Blood*. 2003;101(11):4273-4278.
5. Hanslik A, Thom K, Haumer M, et al. Incidence and diagnosis of thrombosis in children with short-term central venous lines of the upper venous system. *Pediatrics*. 2008;122(6):1284-1291.

6. Vidal E, Sharathkumar A, Glover J, Faustino EV. Central venous catheter-related thrombosis and thromboprophylaxis in children: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12(7):1096-1109.
7. Massicotte P, Julian JA, Gent M, et al; REVIVE Study Group. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thromb Res*. 2003;109(2-3):85-92.
8. Geerts W. Central venous catheter-related thrombosis. *Hematology Am Soc Hematol Educ Program*. 2014;2014:306-311.
9. Raad II, Luna M, Khalil SA, Costerton JW, Lam C, Bodey GP. The relationship between the thrombotic and infectious complications of central venous catheters. *JAMA*. 1994;271(13):1014-1016.
10. Baskin JL, Pui C-H, Reiss U, et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. *Lancet*. 2009;374(9684):159-169.
11. Timsit JF, Farkas JC, Boyer JM, et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. *Chest*. 1998;114(1):207-213.
12. Jaffray J, Witmer C, O'Brien SH, et al. Peripherally inserted central catheters lead to a high risk of venous thromboembolism in children. *Blood*. 2020; 135(3):220-226.
13. Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. *Int J Crit Illn Inj Sci*. 2014;4(2):162-167.
14. Debourdeau P, Farge D, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. *J Thromb Haemost*. 2013;11(1):71-80.
15. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv*. 2018;2(22):3292-3316.
16. Lensing AWA, Male C, Young G, et al. Rivaroxaban versus standard anticoagulation for acute venous thromboembolism in childhood. Design of the EINSTEIN-Jr phase III study. *Thromb J*. 2018;16(1):34.
17. Male C, Lensing AWA, Palumbo J, et al. Randomised controlled trial of rivaroxaban compared to standard anticoagulants for the treatment of acute venous thromboembolism in children. *Lancet Haematol*. 2020;7:e18-e27.
18. Monagle P, Lensing AWA, Thelen K, et al. Bodyweight-adjusted rivaroxaban in children with venous thromboembolism. An Einstein-Jr. phase II evaluation. *Lancet Haematol*. 2019;6:e500-e509.
19. Young G, Lensing AWA, Monagle P, et al; EINSTEIN-Jr. Phase 3 Investigators. Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation. *J Thromb Haemost*. 2020;18(7):1672-1685.
20. Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010; 363(26):2499-2510.
21. Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297.
22. Prins MH, Lensing AW, Bauersachs R, et al; EINSTEIN Investigators. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;11(1):21.
23. Chan A, Lensing AWA, Kubitza D, et al. Clinical presentation and therapeutic management of venous thrombosis in young children: a retrospective analysis. *Thromb J*. 2018;16(1):29.
24. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e737S-e801S.
25. Veldman A, Nold MF, Michel-Behnke I. Thrombosis in the critically ill neonate: incidence, diagnosis, and management. *Vasc Health Risk Manag*. 2008; 4(6):1337-1348.
26. Park CK, Paes BA, Nagel K, Chan AK, Murthy P; Thrombosis and Hemostasis in Newborns (THiN) Group. Neonatal central venous catheter thrombosis: diagnosis, management and outcome. *Blood Coagul Fibrinolysis*. 2014;25(2):97-106.
27. Sharathkumar AA, Biss T, Kulkarni K, et al; SSC Subcommittee on Pediatrics and Neonatal T&H of the ISTH. Epidemiology and outcomes of clinically unsuspected venous thromboembolism in children: A systematic review. *J Thromb Haemost*. 2020;18(5):1100-1112.
28. Mahajerin A, Branchford BR, Amankwah 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(8):1045-1050.