REGULAR ARTICLE

blood advances

Anticoagulation in pediatric cancer–associated venous thromboembolism: a subgroup analysis of EINSTEIN-Jr

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Key Points

- Anticoagulation appeared safe and efficacious in children with cancer and VTE, including those with anticoagulant treatment interruptions.
- Anticoagulation appeared safe and efficacious in children with cancer and VTE, including those who had anticoagulant treatment interruptions.
- Rivaroxaban exposures were within the adult exposure range despite significant polypharmacy use.

Anticoagulant treatment of pediatric cancer–associated venous thromboembolism (VTE) has not been prospectively evaluated. Management of anticoagulation for cancer-associated VTE is often challenged by drug interactions and treatment interruptions. A total of 56 of the 500 children (11.2%) with VTE who participated in the recent EINSTEIN-Jr randomized study had cancer (hematologic malignancy, 64.3%, solid malignant tumor, 35.7%). Children were allocated to either therapeutic-dose bodyweight-adjusted oral rivaroxaban (n=40) or standard anticoagulation with heparins, with or without vitamin K antagonists (n=16) and received a median of 30 concomitant medications. Based on sparse blood sampling at steady-state, pharmacokinetic (PK) parameters of rivaroxaban were derived using population PK modeling. During the 3 months of treatment, no recurrent VTE or major bleeding occurred (95% confidence interval, 0.0%-6.4%), and 3-month repeat imaging showed complete or partial vein recanalization in 20 and 24 of 52 evaluable children (38.5% and 46.2%, respectively). Anticoagulant treatment was interrupted 70 times in 26 (46.4%) children because of thrombocytopenia, invasive procedures, or adverse events, for a mean individual period of 5.8 days. Anticoagulant therapy was resumed in therapeutic doses and was not associated with thrombotic or bleeding complications. Rivaroxaban exposures were within the adult exposure range and similar to those observed in children with VTE who did not have cancer-associated VTE. Rivaroxaban and standard anticoagulants appeared safe and efficacious and were associated with reduced clot burden in most children with cancer-associated VTE, including those who had anticoagulant treatment interruptions. Rivaroxaban exposures were within the adult exposure range despite significant polypharmacy use. This trial was registered at www.clinicaltrials.gov as #NCT02234843.

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Introduction

In adults, venous thromboembolism (VTE) is a frequent complication of cancer, and its treatment and anticoagulation is associated with an increased bleeding risk.[1,2] Management of anticoagulation for cancer-associated VTE is often challenged by the risk of drug interactions due to polypharmacy use and the requirement of treatment interruptions because of chemotherapy-induced thrombocytopenia, adverse events, surgery, and invasive procedures, such as lumbar puncture, bone marrow aspiration, and drain placement.[3] In contrast with adults, little is known about anticoagulant management in children with cancer-associated VTE.

Recently, the EINSTEIN-Jr study compared the oral direct factor Xa inhibitor, rivaroxaban, with standard anticoagulants in 500 children of all ages for treatment of acute VTE of any type.[4] Bodyweight-adjusted pediatric rivaroxaban–dosing regimens using a tablet or oral suspension formulations successfully targeted the adult rivaroxaban exposure range without requiring laboratory monitoring.[5,6] Recurrent VTE occurred infrequently with both rivaroxaban and standard anticoagulants, and no major bleeding event was observed in the 335 children who received rivaroxaban.[4] The absolute incidences of study outcomes and relative treatment effects observed with rivaroxaban were similar to those seen in the larger rivaroxaban VTE studies in adults.[7-10]

In this subgroup analysis of the EINSTEIN-Jr study, we report on the clinical presentation and clinical outcomes of children with cancer-associated VTE and describe the management of anticoagulation in children who had anticoagulant treatment interruptions because of chemotherapy-induced thrombocytopenia, adverse events, or invasive procedures. Furthermore, we explored the pharmacokinetic (PK) parameters of rivaroxaban.

Methods

Study design

Using data of the EINSTEIN-Jr phase 3 study (clinicaltrials.gov #NCT02234843),[4,10] which included 500 children with VTE who were treated with either the oral direct factor Xa inhibitor, rivaroxaban, or standard anticoagulants, we describe the clinical presentation, risk of bleeding, and recurrent thromboembolism in the subgroup of children who presented with active cancer–associated VTE. Cancer was defined as active in the presence of metastases or whether it was recently (<6 months) diagnosed or treated. In addition, we describe the anticoagulant management and clinical outcomes in children who developed chemotherapy-induced thrombocytopenia, underwent invasive procedures, or had adverse events.

The protocol was approved by the institutional review board at each participating center. Written permission from a parent or a guardian and when appropriate, child assent, were obtained. This substudy was conducted at 33 sites in 13 countries.

Children with confirmed VTE were considered for study inclusion if they had initiated heparin treatment. The main exclusion criteria were active bleeding or high risk of bleeding contraindicating anticoagulant therapy, a platelet count of $<50 \times 10^9$/L, an estimated glomerular filtration rate <30 mL/min per 1.73 m^2, and the concomitant use of strong inhibitors of the cytochrome P450 isoenzyme 3A4 (CYP3A4), and/or P-glycoprotein (P-gp), as well as the concomitant use of strong inducers of CYP3A4. The full list of eligibility criteria is provided elsewhere.[4] Enrollment started with children aged 12 to 17 years followed by those aged 6 to 11, 2 to 5, and 0.5 to 1 years and younger than 0.5 years.

After the completion of the initial heparin treatment, children were randomized in a 2:1 ratio to an open-label therapeutic dose of oral rivaroxaban (tablets or suspension formulation) or a continuation of therapeutic dose of standard anticoagulants (ie, heparins or vitamin K antagonists). Rivaroxaban was administered in a bodyweight-adjusted 20-mg–equivalent daily dose based on phase 1 and 2 data and comprehensive PK modeling predictions in either a once-daily, twice-daily, or thrice-daily regimen in children with a bodyweight of ≥30 kg, ≥12 to <30 kg, or <12 kg, respectively (Table 1).[5,6,11-13] In children weighing <12 kg, the lower range of the adult rivaroxaban exposure was targeted to avoid excessive concentrations at the end of the dosing interval.

The main treatment duration was 3 months, during which children were followed up for the occurrence of recurrent symptomatic VTE and bleeding. At 3 months, repeat imaging of the VTE was performed depending on feasibility. Detailed information was collected on episodes of thrombocytopenia, invasive interventions, adverse events, and concomitant treatments, including cancer-associated medication. In case of an invasive intervention, the study protocol advised to stop anticoagulation at least 24 hours before the intervention, if possible, and restart after the intervention in therapeutic doses within 24 hours, provided adequate hemostasis had been established. Anticoagulant management in children who developed thrombocytopenia was left to the discretion of the treating physician.

Outcomes

A blinded and independent adjudication committee evaluated all baseline and repeat VTE imaging, bleeding events, and symptomatic recurrent VTEs. Bleeding events were graded as major or clinically relevant non-major (CRNM) bleeding. The committee classified the degree of vein recanalization at 3 months as normalized, improved, no relevant change, or deteriorated.[10]

PK assessments

Blood samples for rivaroxaban PK were taken within specified time windows and analyzed at a central laboratory, as described elsewhere.[6]

A comprehensive pediatric population PK model based on a previous pediatric model version and PK data pooled from all the preceding rivaroxaban pediatric studies[5,11-13] was used to evaluate rivaroxaban PK. The following main rivaroxaban PK parameters were derived at steady state for each individual: area under the plasma concentration–time curve from time 0 to 24 hours ($AUC_{(0\text{-}24)ss}$) as a measure for daily exposure, maximum plasma concentration ($C_{max,ss}$), and concentration at the end of the dosing interval ($C_{trough,ss}$). Individual results of children with cancer-associated VTE were plotted as a function of bodyweight and compared with the adult reference range (obtained from 203 adults with VTE, younger than 45 years of age who had received 20 mg of rivaroxaban once daily),[14] and results obtained from 281 children with VTE but without cancer who were treated with rivaroxaban, as previously published.[6]

Table 1. Bodyweight-adjusted rivaroxaban regimens in a 20-mg–equivalent dose

Body weight, kg					
Minimum	Maximum	Once-daily dose, mg	Twice-daily dose, mg	Thrice-daily dose, mg	Total daily dose, mg
2.6	<3	–	–	0.8	2.4
3	<4	–	–	0.9	2.7
4	<5	–	–	1.4	4.2
5	<7	–	–	1.6	4.8
7	<8	–	–	1.8	5.4
8	<9	–	–	2.4	7.2
9	<10	–	–	2.8	8.4
10	<12	–	–	3.0	9
12	<30	–	5	–	10
30	<50	15	–	–	15
≥ 50		20	–	–	20

Statistical analysis

Efficacy outcomes were considered during the 3-month study treatment period, whereas safety outcomes were considered for the same period but only from the 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. 95% confidence intervals (CIs) for incidences were calculated by exact methods. Calculations were performed using SAS 9.2 (SAS Institute Inc, Cary, NC).

Results

A total of 56 children with cancer-associated VTE were randomized (Figure 1). Demographic, clinical, and radiological characteristics are shown in Table 2. The median follow-up during the study period was 91 days (interquartile range, 85-95). Three children did not take the allocated study medication with rivaroxaban. Thirty-six (64.3%) children had a hematologic malignancy of which 23 (63.9%) had acute lymphoblastic leukemias, whereas 20 (35.7%) children had a variety of 13 solid tumors (35.7%; Table 2). The median number of concomitant medications was 30 (interquartile range, 20-49).

Presentation of VTE

The percentage of children with cancer-associated VTE relative to all 500 children in the entire EINSTEIN-Jr study was 11.2% and was highest for children in the age group of 12 to 17 years (51.8%), declining with age to 26.8%, 19.6%, and 1.8% for

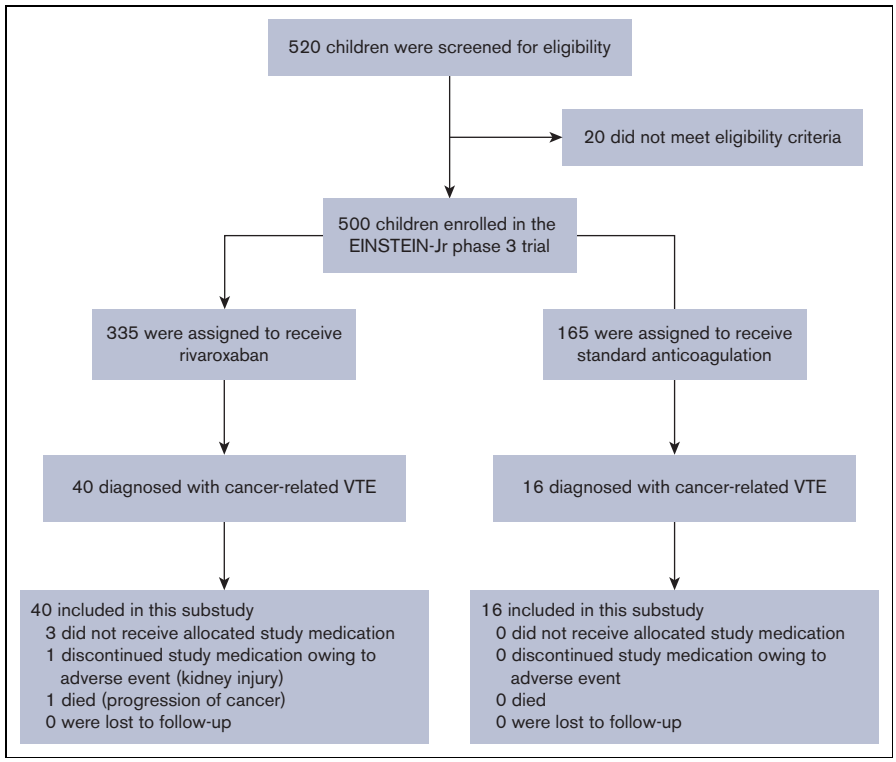

Figure 1. Flowchart of selection of patients for the EINSTEIN-Jr cancer substudy.

Table 2. Demographics, clinical presentation, and study treatment at baseline

	Rivaroxaban	Standard of care	Total
Demographics	**N = 40**	**N = 16**	**N = 56**
Male, n (%)	20 (50)	11 (68.8)	31 (55.4)
Bodyweight, mean (interquartile range), kg	43.1 (20.3-60.8)	43.5 (26.3-57.8)	43.3 (21.5-58.9)
Creatinine clearance, n (%), mL/min			
80	38 (95)	15 (93.8)	53 (94.6)
50 to <80	0 (0)	1 (6.3)	1 (1.8)
Missing	2 (5)	0 (0)	2 (3.6)
Concomitant medication, median interquartile range	30 (20-50)	28 (19-48)	30 (20-49)
Location of VTE, n (%)			
Upper extremity	12 (30)	4 (25)	16 (28.6)
Jugular vein	7 (17.5)	3 (18.8)	10 (17.9)
Cerebral vein and sinuses	7 (17.5)	2 (12.5)	9 (16.1)
Right heart	4 (10)	4 (25)	8 (14.3)
Lower extremity	5 (12.5)	2 (12.5)	7 (12.5)
Lung	3 (7.5)	1 (6.3)	4 (7.1)
Caval vein	1 (2.5)	0 (0)	1 (1.8)
Portal vein	1 (2.5)	0 (0)	1 (1.8)
Additional risk factors, n (%)			
Major surgery	1 (2.5)	1 (6.3)	2 (3.6)
Prolonged immobilization	1 (2.5)	0 (0)	1 (1.8)
Use of estrogens/progestins	0 (0)	2 (12.5)	2 (3.6)
Central venous catheter	22 (55)	9 (56.3)	31 (55.4)
Hematologic malignancy	25 (62.5)	11 (68.8)	36 (64.3)
Acute lymphoblastic leukemia	15 (37.5)	8 (50)	23 (41.1)
Acute myeloid leukemia	1 (2.5)	0 (0)	1 (1.8)
Hodgkin lymphoma	5 (12.5)	2 (12.5)	7 (12.5)
Non-Hodgkin lymphoma	4 (10)	1 (6.3)	5 (8.9)
Solid tumor*	15 (37.5)	5 (31.3)	20 (35.7)
Chemotherapy	33 (82.5)	15 (93.8)	48 (85.7)
Asparaginase	11 (27.5)	7 (43.8)	18 (32.1)
Corticosteroids	33 (82.5)	12 (75)	45 (80.4)
Rivaroxaban group, n (%)			
Tablet formulation	14 (35)	NA	NA
Suspension formulation	23 (57.5)	NA	NA
Standard anticoagulation group, n (%)			
Low-molecular-weight heparin	NA	13 (81.3)	NA
Unfractioned heparin	NA	1 (6.3)	NA
Low-molecular-weight heparin after vitamin K antagonist	NA	2 (12.5)	NA

NA, not applicable.

*Solid tumors in rivaroxaban arm: astrocytoma (n = 1), Ewing sarcoma (n = 1), fibrosarcoma (n = 1), intracardiac germ cell tumor (n = 1), medulloblastoma (n = 2), myxofibrosarcoma (n = 1), nephroblastoma (n = 1), neuroblastoma (n = 1), opticus glioma (n = 1), osteosarcoma (n = 2), and rhabdomyosarcoma (n = 3). Solid tumors in standard of care arm: craniopharyngioma (n = 1), Ewing sarcoma (n = 2), nasopharynx cancer (n = 1), and oligodendroglioma (n = 1).

children aged 6 to 11 years, 2 to 5 years, and below 2 years, respectively.

Most cases of VTE involved the upper extremity (n = 16), the jugular vein (n = 10), and the cerebral vein and sinuses (n = 9) and were associated with the recent use of a central venous catheter in 31 (55.3%) children.

Study outcomes

Symptomatic recurrent VTE and major bleeding occurred in none of the 56 children (0%; 95% CI, 0.0%-6.0%; Table 3), whereas 1 (1.8%; 95% CI, 0.4%-9.6%) child had a CRNM bleeding related to vomiting-induced Mallory-Weiss esophageal mucosal tear. A single child died during the study period due to the progression of the

Table 3. Clinical outcomes by treatment group during the 3-month main study period

Study outcome	Rivaroxaban, N = 40, n (%)	Standard of care, N = 16, n (%)	Total, N = 56, n (%)
Recurrent VTE	0 (0)	0 (0)	0 (0)
Major bleeding	0 (0)	0 (0)	0 (0)
CRNM bleeding, Mallory-Weiss tear	1 (2.5)	0 (0)	1 (1.8)
Mortality	1 (2.5)	0 (0)	1 (1.8)
Repeat imaging	n = 37	n = 15	n = 52
Normalized	13 (35.1)	7 (46.7)	20 (38.5)
Improved	19 (51.4)	5 (33.3)	24 (46.2)
Unchanged	5 (13.5)	3 (20.0)	8 (15.4)
Deteriorated	0 (0)	0 (0)	0 (0)

malignancy (Table 3). Of the 52 children with an evaluable repeat imaging test, complete vein recanalization occurred in 20 (38.5%) children, incomplete recanalization in 24 children (46.2%), and no relevant change in 8 children (15.4%). None had any evidence of thrombus progression.

Treatment interruptions for invasive procedures or adverse events

Sixteen (28.6%) children developed chemotherapy-induced thrombocytopenia, of whom 14 had a platelet count <50 × 10^9/L (mean minimum platelet count, 14 × 10^9/L [range, 2-30]). In 13 of these children, anticoagulant therapy was interrupted 38 times in total (Table 4). Platelet transfusions were given to 3 children, including the child in whom anticoagulation was continued. In an additional 12 children, anticoagulant therapy was interrupted 29 times in total because of lumbar puncture (n = 23) or other invasive interventions (n = 6). Three children had interruptions in the anticoagulant treatment because of CRNM or minor bleeding (n = 3). Overall, the anticoagulant treatment was interrupted in 26 (46.4%) children 70 times, with a mean individual total duration of interruption of 5.8 days, which varied depending on the reason for interruption (Table 4). Anticoagulant therapy was resumed after all treatment interruptions (n = 70) in therapeutic doses and none of the 26 children developed a recurrent VTE, progression of existing thrombus, or a clinically relevant bleeding complication. Normalization on repeat imaging occurred in 10 of the 26 children (38.5%) who had no treatment interruption vs 10 of the 26 children (38.5%) who had their treatment interrupted (risk ratio, 1.0; 95% CI, 0.5-2.0).

Rivaroxaban dose-exposure relationship

Of the 40 children with cancer-associated VTE in the rivaroxaban arm, 35 children were evaluable for PK analyses. Generally, results were comparable for children with or without cancer-associated VTE (Figure 2). Most of the individual values for $AUC_{(0\text{-}24)ss}$, $C_{max,ss}$, and $C_{trough,ss}$ were within the 5th to 95th percentile of the adult exposure range (Figure 2). As intended, in children with bodyweight <12 kg, values for $AUC_{(0\text{-}24)ss}$ scattered below the median of the adult exposure range with decreasing bodyweights. In children with bodyweight <7 kg, some $AUC_{(0\text{-}24)ss}$ values even fell below the fifth percentile of the adult exposure range but were still in the range of individual adult values below the fifth percentile. Trough values in children were above the lower threshold of the adult exposure range. None of the children were administered strong inhibitors of CYP3A4 and/or P-gp or strong inducers of CYP3A4. No influence of weak and moderate CYP3A4 inhibitors and/or P-gp inhibitors and CYP3A4 inducers on rivaroxaban clearance was identified.[6]

Discussion

The results of our analyses suggest that anticoagulant therapy with either rivaroxaban or standard anticoagulants in children with cancer-associated VTE is safe, efficacious, and associated with complete or partial vein recanalization in almost 85% of the children. Almost two-thirds of children had a hematologic malignancy with acute lymphoblastic leukemias occurring most frequently. Anticoagulant treatment was interrupted because of thrombocy-

Table 4. Anticoagulant treatment interruptions

Reason for interruption	Children, n	Interruptions, n	Duration of all interruptions by patient, mean (range), d
Platelet count <50 × 10^9/L	13	38	8.2 (1-18)
Lumbar puncture*	7	23	3.3 (1-4)
Invasive procedure†	5	6	1.6 (1-2)
Minor/CRNM bleed	3	3	4.3 (1-8)
Total	26‡	70	5.8 (1-18)

*Lumbar puncture performed for diagnostic reason (n = 1) or intrathecal drug administration (n = 6).
†Amputation, removal caval filter, bone marrow aspiration, external ventricular drain, or central venous catheter placement.
‡Two children had 2 reasons for interruption.

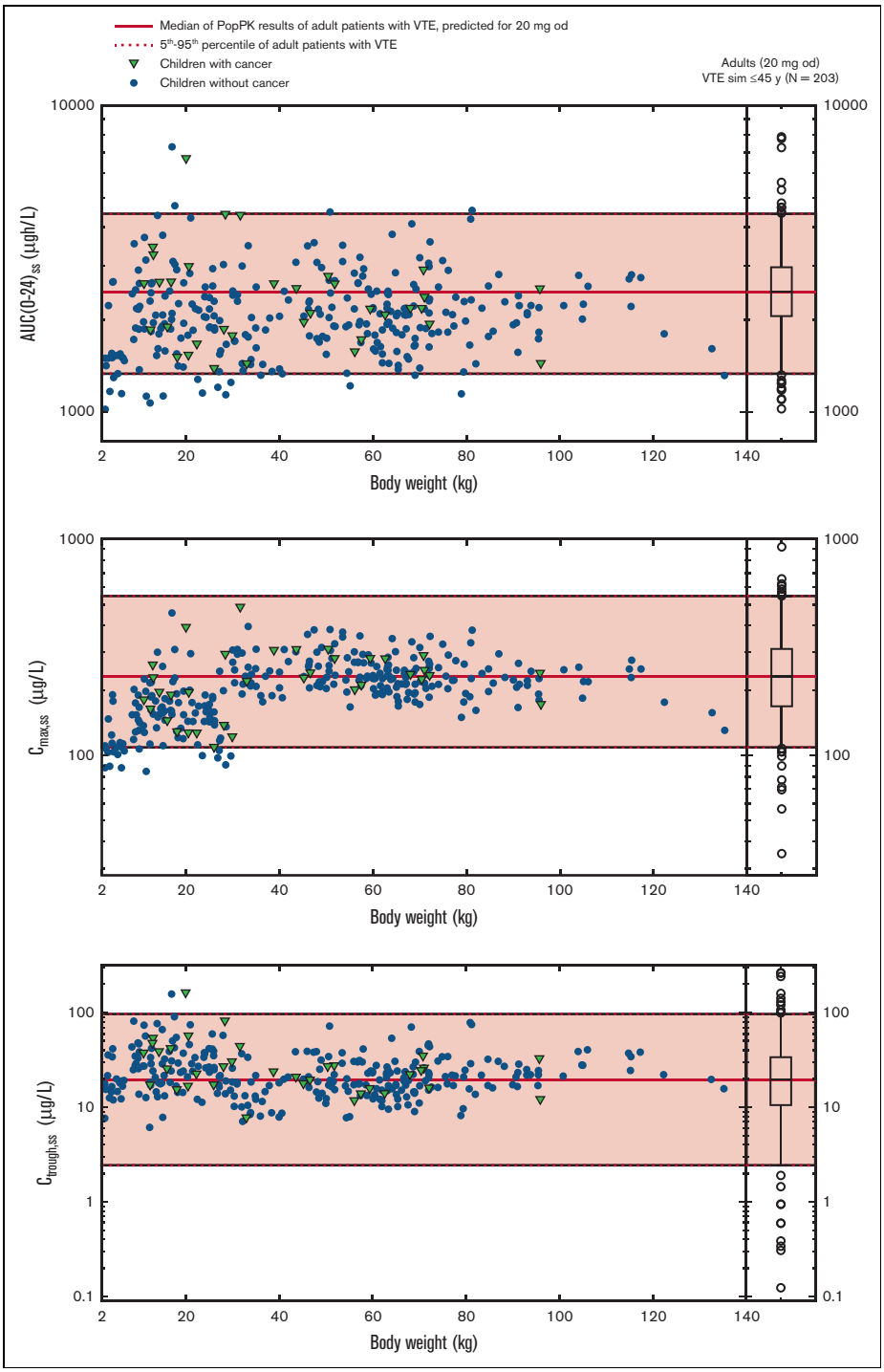

Figure 2. Rivaroxaban population PK modeling results for children with cancer-associated VTE in comparison with adult patients with VTE and children with VTE without cancer.[6] od, once daily; PopPK, population PK.

topenia, invasive procedures, or adverse events in almost half of the children. It was resumed in therapeutic doses and was not associated with bleeding, recurrent VTE events, or asymptomatic thrombus deterioration. Despite a significant polypharmacy use, rivaroxaban exposures were within the adult exposure range and comparable with children with VTE who did not have cancer.

Given the coagulopathy associated with active malignant disease in general and hematologic malignancies in particular,[15,16] the absence of thrombotic complications and the low incidence of clinically relevant bleeding in the entire study cohort and in the relatively large group of children who had interruptions in their anticoagulant treatment is notable. In a systematic review and meta-analysis of more than 5000 adult patients with cancer-associated VTE, 6-month incidences of recurrent VTE, major bleeding, and CRNM bleeding with direct oral anticoagulants were 5.8%, 5.5%, and 12.3%, respectively, compared with low-molecular-weight heparin, which were 8.8%, 3.2%, and 6.7%, respectively.[17] In

addition, studies with adults with cancer-associated VTE requiring periprocedural interruption of anticoagulation demonstrated high rates of postprocedure thrombotic and bleeding complications.[3] The reasons for the observed differences in incidences of thrombotic and bleeding complications between children and adults with cancer-associated VTE are likely multifactorial, including differences in types of cancer, cancer response rates to treatment, comorbid conditions, developmental hemostasis, and vascular aging. Regardless of the underlying reasons for the differences in complication rates between children and adults with cancer-associated VTE, the data presented here suggest that therapeutic anticoagulation is generally safe and effective in children with cancer-associated VTE.

Strengths of our study include the prospective study design, the central blinded outcome evaluation, availability of repeat imaging in almost all children, indication for anticoagulation according to current guidelines,[18,19] and complete follow-up. Several limitations also warrant comment. First, the EINSTEIN-Jr study was designed as a randomized trial comparing rivaroxaban with standard anticoagulation. However, because of the absence of major clinical outcomes in this substudy with 56 children, we decided to present the current data as a single cohort of children with cancer-associated VTE, as to our knowledge, such reports are not available so far. Therefore, we focused on describing demography, clinical presentation, the effect of anticoagulation on thrombus burden, and management of anticoagulation at the time of thrombocytopenia, invasive procedures, and adverse events, and refrained from formal statistical comparisons between rivaroxaban and standard anticoagulation. Hence, our subgroup analysis cannot infer the efficacy or safety of rivaroxaban compared with standard anticoagulation but rather anticoagulation as a whole. Second, our study documented efficacy and safety outcomes limited to a 3-month study period, but anticoagulation could be given for longer durations. Indeed, more than half of the inception cohort was treated with anticoagulant therapy beyond the study period. However, in patients with cancer-associated VTE, thrombotic and bleeding outcomes occur most frequently during the first 3 months.[17] Third, our data do not support a definitive rule as to when to stop anticoagulation in the setting of thrombocytopenia, a reasonable approach would be to follow the same principles used for low-molecular-weight heparin in adults,[20] which is to cease or reduce dose administration when the platelet count is $<50 \times 10^9$/L and restart once platelet recovery has occurred. Unfortunately, based on individual circumstances, clinicians will have to decide whether platelet transfusion and ongoing anticoagulation or cessation or dose reduction of anticoagulation is appropriate.

In conclusion, anticoagulation with either rivaroxaban or heparins with or without vitamin K antagonists appeared safe and efficacious and were associated with reduced clot burden in most children with cancer-associated VTE, including the high number of children who had interruptions in their anticoagulant treatment because of chemotherapy-induced thrombocytopenia, invasive procedures, or adverse events. Rivaroxaban exposures were within the adult exposure range despite substantial polypharmacy use.

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Authorship

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

Conflict-of-interest disclosure: A.W.A.L., A.F.P., M.M., D.K., S.W., and K.T. are the employees of Bayer. C.M. reports personal fees and fees paid to his institution from Anthos, Bayer, Bristol-Myers Squibb, Janssen, Norgine, Pfizer, and Boehringer Ingelheim. H.v.O. reports fees paid to her institution from Bayer, Boehringer Ingelheim, and Octopharma. G.K. reports personal fees and fees paid to her institution from Bayer and Pfizer. The remaining authors declare no competing financial interests.

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