Venous Thromboembolism in Children: The Rivaroxaban Experience

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Abstract

The incidence of venous thromboembolism (VTE) in the pediatric population has increased more than 10-fold in the last 20 years, as a consequence of the advancement of resuscitation and surgical techniques and the global increase in life expectancy of children suffering from chronic pathologies. Monitoring anticoagulant therapy to achieve outcomes within the target range in childhood VTE, parenteral administration of medications, and frequent blood tests in children are often cumbersome. Availability of safe and effective oral agents with pediatric data to support use would be of clear benefit. A physiologically based pharmacokinetic model was developed to estimate the appropriate dosing schedule for rivaroxaban in children. This incorporated growth/maturation and variability in anthropometrics (e.g., body height, weight, and body mass index), anatomy (e.g., organ weight), physiology (e.g., blood flow rates), metabolism and excretion. Rivaroxaban use in pediatric population underwent a complete investigational program, consisting mainly of one phase I pharmacokinetics/pharmacodynamics trial, three phase II trials, one phase III trial. The phase III trial enrolled 500 patients from birth to <18 years and documented the efficacy and safety of rivaroxaban regimens at dose equivalent to the adult 20 mg dose for the prevention of fatal or symptomatic nonfatal recurrent VTE and major bleeding versus heparin or vitamin K antagonists. Results were similar to those in rivaroxaban studies in adults. The efficacy and safety of rivaroxaban in children reported in the EINSTEIN JUNIOR trial provide further support to previous trials in adults (EINSTEIN Program), which demonstrate a favorable profile for the use of rivaroxaban for the management of VTE in challenging patient populations. Other clinical evidence contributing to the use of rivaroxaban among different risk groups in pediatric VTE population confirms the consistency with principal trial. Our review aims to describe the rationale for using rivaroxaban oral suspension in clinical practice and to summarize its multiple indications in each vascular bed (e.g., cerebral venous thrombosis, symptomatic or asymptomatic central venous catheter-associated thrombosis), etiology, and patients setting.

Keywords

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- children
- rivaroxaban

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Venous thromboembolism (VTE) in children is rare, with an estimated 0.01 to 0.05 events occurring per 1,000 children per year.[1,2] If we consider only the population of hospitalized children, however, the incidence is approximately 1/200. The incidence of VTE in adults is approximately 15- to 200-fold higher than in children[3]; however, with advances in treatment for life-threatening or chronic medical conditions and an increased awareness of VTE among pediatricians, reports of VTE in children are increasing.[4–8] An increase in VTE incidence has also been observed in adults; however, these increases are believed to be a result of improvements in imaging techniques rather than improved survival of patients with chronic diseases.[9] Approximately 95% of cases of pediatric VTE are provoked, often as a complication with the use of central venous catheters (CVCs).[10,11] In adults, the proportion of VTE that is provoked is lower than in children, with approximately 60% of cases of VTE in adults being unprovoked.[12,13] CVC-associated complications are a particularly common cause of VTE in children aged < 2 years, accounting for approximately two-thirds of cases of VTE.[11] As observed in adults, active cancer and chemotherapy can also increase the risk of VTE in children.[10,14] The incidence of VTE is also higher in children with comorbidities, e.g., severe infection, sickle cell disease, trauma, antiphospholipid syndrome, nephrotic syndrome, homocystinuria, and with some congenital anomalies that constitute the equivalent of an anatomical thrombophilia, e.g., agenesis of the inferior vena cava, May–Thurner syndrome with compression of one or both iliac veins, and upper thoracic outlet syndrome.[10,14] The diagnosis of VTE in neonatal and pediatric age is often particularly difficult because, beyond the practical problems of performing assessments in children, the vascular diagnostic techniques have been almost exclusively validated in adults and the diagnostic criteria have been extrapolated tout court to the child.

Treatment of Venous Thromboembolism in Children

At the beginning of 2021, the European Medicines Agency recommended the approval of the new indication of rivaroxaban, an oral factor Xa inhibitor, for the treatment and prevention of VTE in children aged 0 to 17 years, including those with catheter-related thrombosis and cerebral venous thrombosis (CVT). Until then, the treatment of VTE in children was mainly based on observational data or extrapolated from studies in adults. Nevertheless, the use of anticoagulant drugs in pediatric patients is different from that in adults for many reasons including: (1) the epidemiology of VTE; (2) the fact that the hemostatic system in children changes with age; (3) the pharmacokinetics (PK) and pharmacodynamics (PD) of anticoagulants, which also depends on age; (4) the difficulty of the administration routes, which can influence the choice of the drug; (5) the type of diet can strongly influence the absorption of the drug, especially in newborns. Before rivaroxaban approval the recommended treatment options for VTE were unfractionated heparin, low molecular weight heparin (LMWH), fondaparinux, and vitamin K antagonists (VKA). There is therefore no type of treatment for children with VTE that does not require subcutaneous or intravenous injections for long periods of time or laboratory monitoring, which can pose a serious burden to young children, especially newborns, as well as their parents or caregivers. To address this problem, Bayer has developed granules for an oral suspension of rivaroxaban, which does not require injections or regular monitoring, and which allows for precise dosing and more manageable treatment for children with VTE.

Rivaroxaban Pediatric Investigational Program

Due to the low incidence of VTE in children, and the recruitment challenges associated with pediatric trials, a novel approach was required to determine the dosing schedule for rivaroxaban in children. Changes to the hemostatic system that occur during a child's development can have an impact on the PD of a medication, and therefore, it was important to first confirm the PK/PD properties of rivaroxaban in children and neonates using in vitro testing.[15,16] These assessments confirmed that, in vitro, rivaroxaban had a predictable, dose-dependent PK/PD profile across age groups of neonates and children.[15,16] A physiologically based pharmacokinetic (PBPK) model was developed to estimate the appropriate dosing schedule for rivaroxaban in children, which incorporated growth/maturation and variability in anthropometrics (e.g., body height, weight, and body mass index), anatomy (e.g., organ weight), physiology (e.g., blood flow rates), metabolism, and excretion.[17–19] The dosing schedule determined from this model was then confirmed in the EINSTEIN JUNIOR phase I study ($n = 59$), which demonstrated that the PK of rivaroxaban in children with VTE was within the expected range predicted by the PBPK model for the area under the plasma concentration–time curve zero to 24 hours, maximum plasma concentration and minimum plasma concentration measured 20 to 24 hours after rivaroxaban administration across all age groups from 0.5 to <18 years.[19] The phase I trial also demonstrated that the PD parameters of rivaroxaban (e.g., prothrombin time, activated partial thromboplastin time, and anti-factor Xa activity) showed a linear relationship with rivaroxaban plasma concentrations and aligned with previous data from adults.[19] Rivaroxaban use in the pediatric population underwent a complete investigational program, consisting mainly of one phase I PK/PD trial, three phase II trials, and one phase III trial.[19–21] Phase I, II, and III were conducted in parallel, with staggered age groups. In the phase I trial two different rivaroxaban dose levels were tested (10 and 20 mg) and two different formulations (tablet and oral suspension). PD parameters (prothrombin time, activated partial thromboplastin time, and anti-factor Xa activity) showed a linear relationship versus rivaroxaban plasma concentrations and were in line with previously acquired adult data. The rivaroxaban pediatric PDPK model, used to predict the doses for the individual body weight groups, was confirmed. No episodes of bleeding were

Table 1 Efficacy and safety study outcomes[21]

	Rivaroxaban *n* (%)	Heparin or VKA *n* (%)	Hazard ratio (95% CI)
Intention-to-treat population	335	165	–
Symptomatic recurrence of VTE	4 (1)	5 (3)	0.40 (0.11–1.41)
Symptomatic recurrence of VTE or deterioration on repeat imaging	5 (1)	6 (4)	0.41 (0.12–1.36)
Net clinical benefit[a]	4 (1)	7 (4)	0.30 (0.08–0.93)
Mortality[b]	1 (<1)	0 (0)	–
Safety population	329	162	–
Major bleeding	0 (0)	2 (1)	–
Major or CRNM bleeding	10 (3)	3 (2)	1.58 (0.51–6.27)

Abbreviations: CI, confidence interval; CRNM, clinically relevant nonmajor bleeding; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]First occurrence of recurrent VTE or major bleeding.
[b]Only cancer-related occurred.

reported.[19] The phase II trials (93 patients) investigated the safety and efficacy to define rivaroxaban treatment regimens; therapeutic rivaroxaban exposures were confirmed with once daily dose in children ≥30 kg and twice daily in children 20 < 30 kg. Children with even lower body weights (<20 kg, particularly <12 kg) showed low exposures so rivaroxaban dosages were revised.[20] The phase III trial enrolled 500 patients from birth to <18 years and documented the efficacy and safety of rivaroxaban regimens at a 20 mg equivalent dose for the prevention of fatal or symptomatic nonfatal recurrent VTE and safety regarding major bleeding versus heparin/VKA (►**Table 1**).[21] Results were similar to those in rivaroxaban studies in adults.[22]

EINSTEIN Program Complete Data

The results from EINSTEIN JUNIOR support existing data on management of VTE with rivaroxaban in challenging patient populations; subgroup analyses of the pooled data from the EINSTEIN Deep Vein Thrombosis (DVT) and EINSTEIN Pulmonary Embolism (PE) trials in adults have demonstrated a favorable benefit–risk profile in several challenging patient populations including frail patients (defined as one or more of aged > 75 years, creatinine clearance [CrCl] < 50 mL/min, low body weight [≤50 kg]),[22] patients with renal impairment,[23] and patients with cancer.[24] Further evidence in adult patients with cancer-associated thrombosis has also been obtained from the SELECT-D pilot study.[25] The rates of recurrent VTE reported in frail patients were 2.7% with rivaroxaban and 3.8% with enoxaparin/VKA (hazard ratio [HR] = 0.68; 95% confidence interval [CI] = 0.39–1.18).[22] In patients with moderate renal impairment (CrCl = 30–49 mL/min), 3.4% treated with rivaroxaban and 3.2% treated with enoxaparin/VKA had a recurrent VTE event (HR = 1.05; 95% CI = 0.44–2.47).[23] Rates of major bleeding were also lower in these patient populations; 1.3 and 4.5% for rivaroxaban and enoxaparin/VKA, respectively, in frail patients (HR = 0.27; 95% CI = 0.13–0.54) and 0.9 and 3.9% for rivaroxaban and enoxaparin/VKA, respectively, in patients with moderate renal impairment (HR = 0.23; 95% CI = 0.06–0.81).[22,23] The composite of recurrent VTE and major bleeding in frail patients was 4.6% for rivaroxaban and 8.4% for enoxaparin/VKA, indicating an improvement in net clinical benefit (HR = 0.51; 95% CI = 0.34–0.77).[22] A similar profile of net clinical benefit has also been observed in patients with cancer-associated thrombosis, in both the EINSTEIN DVT and EINSTEIN PE subgroup analysis and the dedicated cancer-associated thrombosis trial, SELECT-D.[24,25] The overall incidence of recurrent VTE is higher in patients with cancer, with rates of 4.5 and 6.6% for rivaroxaban and enoxaparin/VKA, respectively, in the pooled analysis of patients with active cancer in EINSTEIN DVT and EINSTEIN PE (HR = 0.67; 95% CI = 0.35–1.30).[3] In SELECT-D, the 6-month cumulative rate of VTE recurrence was 4% in patients treated with rivaroxaban and 11% in patients receiving dalteparin (HR = 0.43; 95% CI = 0.19–0.99).[4] Major bleeding rates in patients with cancer in EINSTEIN DVT and EINSTEIN PE were 2.3% with rivaroxaban and 5.0% with enoxaparin/VKA (HR = 0.42; 95% CI = 0.18–0.99), corresponding to an overall trend toward an improvement in net clinical benefit (HR = 0.50; 95% CI = 0.24–1.03).[24] Low major bleeding rates were also demonstrated in SELECT-D, with a 6-month cumulative incidence of major bleeding of 6% in patients treated with rivaroxaban and 4% in patients treated with dalteparin (HR = 1.83; 95% CI = 0.68–4.96).[25] In EINSTEIN JUNIOR 56 children with cancer were included, allocated to either therapeutic dose bodyweight-adjusted oral rivaroxaban and received a median of 30 concomitant medications. 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 (thrombocytopenia, invasive procedures or adverse events).[26] During the 3 months of treatment, no recurrent VTE or major bleeding occurred (95% CI = 0.0–6.4%), and 3-month repeat imaging showed complete or partial vein recanalization in 20 and 24 of 52 evaluable children (38 and 46%, respectively).

The efficacy and safety of rivaroxaban in children reported in the EINSTEIN JUNIOR trial provides further support to previous trials in adults, which demonstrate a favorable profile for the use of rivaroxaban for the management of VTE in challenging patient populations (►**Fig. 1A–C**).[21]

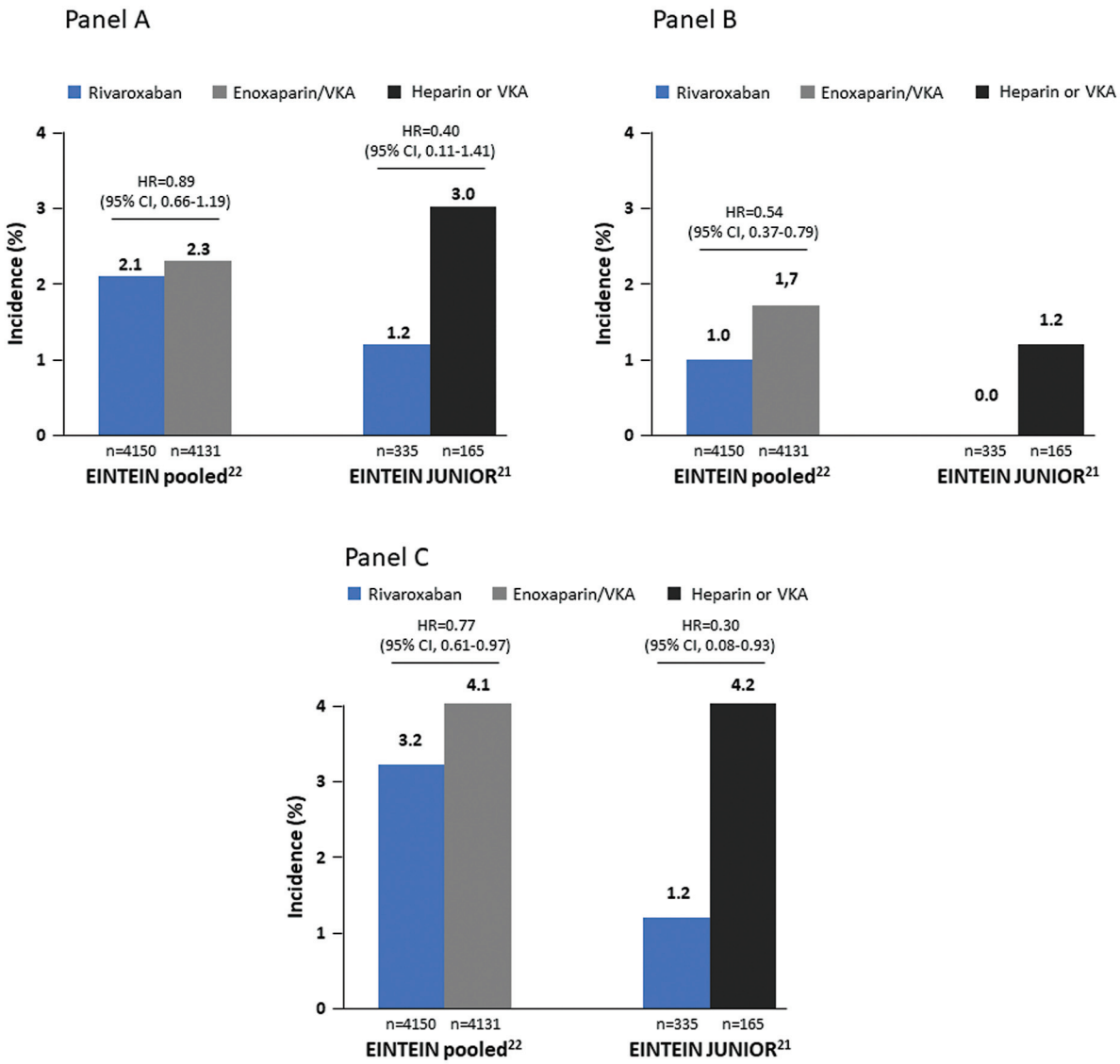

Fig. 1 Recurrent VTE (**A**), major bleeding (**B**), and net clinical benefit (**C**) in the EINSTEIN program in adults and in the EINSTEIN JUNIOR. CI, confidence interval; HR, hazard ratio; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Consistency with Other Clinical Evidence

A single center, retrospective, observational cohort study by Hassan and Motwani[27] reported on the effectiveness and safety of rivaroxaban in 52 pediatric VTE patients aged 0 to 16 years in a real-world clinical setting. All patients initially received parenteral anticoagulation with LMWH for at least 5 days prior to rivaroxaban initiation. Patients weighing <30 kg received body weight-adjusted liquid formulation and those weighing ≥30 kg received rivaroxaban tablets of 15 or 20 mg. Overall, no bleeding events were reported, and recurrence of thrombosis occurred in only two (3.6%) patients. About 35% had normalized reimaging, 40.3% improved, 9.6% were unchanged, and 11.5% stopped rivaroxaban without reimaging. Twenty-six (47.2%) patients had CVC-related thrombosis, which was either normalized or improved after 6 weeks, whereas those who required longer duration of anticoagulation had more extensive thrombosis. Of the 11 (20%) patients in the cohort with a CVT, none experienced bleeding or recurrent thrombosis. Rivaroxaban was used for secondary VTE prophylaxis after acute treatment in six (11%) patients in the cohort, with no recurrence of thrombosis or bleeding reports. Twenty-five patients were <2 years old and represented 45% of the cohort including three patients with CVT. Among the 25 patients, 19 (34%) were between 1 month and 2 years of age. Only 3 (16%) out of the 19 patients <2 years of age had their thrombosis unchanged on reimaging, of whom 1 had recurrent thrombosis. Of the 6 (11%) patients who were less than 1 month old at the time of start of rivaroxaban, on reimaging, three patients had normalized results, one improved, one was unchanged, and one stopped rivaroxaban without reimaging based on clinical improvement. The authors concluded that this study demonstrated that the rivaroxaban treatment regimens were well tolerated and as effective as reported in published trials in children. Further real-world data and observational studies are essential to investigate the use of rivaroxaban among different risk groups in pediatric VTE

treatment.[27] Marten et al[28] presented data on the preliminary findings from the prospective Dresden NOAC registry to evaluate the use of rivaroxaban in adolescents for the treatment of VTE. Until September 19, 2018, a total of 23 patients <18 years of age were enrolled (19 female, 4 male; mean age of 15.7 ± 1.1 years; mean body mass index: 22.5 ± 3.3 kg/m^2). During follow-up (median: 1,454 days; interquartile range: 915.5/1737.5 days), three recurrent VTE events were observed (one recurrent DVT 3 years after stopping rivaroxaban, one early recurrent DVT during rivaroxaban therapy with suspected anticoagulation gap due to vomiting, and a late recurrent VTE 590 days after the first VTE in the same patient). A total of 35 bleeding events occurred (International Society on Thrombosis and Haemostasis definition: 26 minor, 8 clinically relevant nonmajor bleeding, 1 major bleeding). The authors concluded that rivaroxaban treatment for VTE seems feasible and effective in adolescent patients, in whom the prevalence of thrombophilia and a positive family history for VTE is high.[28,29]

Venous Thromboembolism Setting Patients

Rivaroxaban is used not only to treat DVT usually in the leg and PE and to prevent DVT and PE from recurring in adults, but also to treat VTE and prevent VTE from recurring in children and adolescents aged less than 18 years; in this case there is a broad possibility to treat our young patients based on the EINSTEIN JUNIOR trial data.[21] The result relies in part on extrapolation of data obtained with rivaroxaban in adults. As a prerequisite for extrapolation according to the U.S. Food and Drug Administration and European Medicines Agency, on the basis of comparison of the results of this pediatric study with those of large randomized studies in adults, we can deduce a similar clinical outcome of VTE.[21] On the other hand, whereas in the trial in adults with VTE there were only symptomatic proximal DVT and symptomatic PE, in the JUNIOR population we can find a variety of thrombosis phenotypes, such as CVT or sinus thrombosis, catheter-related VTE, lower extremities, caval, renal, or portal vein, right heart, upper extremities, jugular vein, noncatheter-related VTE, symptomatic VTE, first episode of VTE, initial heparinization, plus thrombolysis, or thrombectomy.[21] In particular, safety and efficacy of anticoagulant therapy in pediatric CVT was analyzed in a prespecified substudy of EINSTEIN JUNIOR trial. Children (0–18 years) with CVT were randomized to rivaroxaban or heparin/VKA to assess the safety and efficacy of the two treatments (►**Table 2**).[30] Children with CVT treated with rivaroxaban or heparin/VKA had a favorable clinical outcome, with a low risk of recurrent thrombosis or clinically relevant bleeding.[30] In another subgroup, anticoagulant therapy of symptomatic or asymptomatic CVC-VTE in children was safe, efficacious and associated with reduced clot burden.[31] There was no recurrent thrombosis, 90% thrombus resolution, no major bleeding, 2% clinically relevant bleeding.[31] In conclusion, in clinical practice, the use of a pediatric dose has multiple uses in each vascular bed, etiology, and patient setting. The

Table 2 Efficacy and safety study outcomes[30]

Outcomes at 3 mo	Rivaroxaban $n = 73$	Heparin or VKA $n = 41$
Recurrent thrombosis	0	2%
Major bleeding	0	2%
Clinically relevant nonmajor bleeding	7%	0
More help with activities of daily living than before CVT	5%	7%

Abbreviations: CVT, cerebral venous thrombosis; VKA, vitamin K antagonist.

Committee for Medicinal Products for Human Use—European Medicines Agency's Committee, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorization to rivaroxaban (Bayer AG, Leverkusen, Germany) on November 12, 2020. It was authorized for the treatment of VTE and prevention of VTE recurrence in children and adolescents aged less than 18 years weighing from 30 to 50 kg and more than 50 kg, after at least 5 days of initial parenteral anticoagulation treatment. The dose and frequency of administration are determined based on body weight (►**Table 3**). It is necessary to monitor the child's weight, and the dose of rivaroxaban should be reviewed regularly, especially for children weighing less than 12 kg to ensure maintenance of a therapeutic dose. Oral suspension is available in two presentations each consisting of a folding box containing:

- For children weighing less than 4 kg: one brown 100 mL glass bottle containing 2.625 g granules, corresponding to 51.7 mg rivaroxaban, closed with a child-resistant screw cap, two oral dosing syringes 1 mL (blue syringe, marked as liquid dosing device [LDD]) with 0.1 mL marked graduations, one adapter for bottles and oral syringes, one water syringe 50 mL with 1 mL marked graduations.
- For children weighing 4 kg and more: one brown glass bottle 250 mL containing 5.25 g granules, corresponding to 103.4 mg rivaroxaban, closed with a child-resistant screw cap, two oral dosing syringes 5 mL (blue syringe, marked as LDD) with 0.2 mL marked graduations, two oral dosing syringes 10 mL (blue syringe, marked as LDD) with 0.5 mL marked graduations, one adapter for bottles and oral syringes, one water syringe 100 mL with 2 mL marked graduations.

Conclusion

Progress in anticoagulant therapy of the pediatric population with VTE has been slow. A strong medical need is for improving knowledge about different subtypes of thrombosis by age, location, and benefits of treatment more specific to these patients. As for rivaroxaban, the EINSTEIN JUNIOR randomized trial provides a strong support to the evidence in this setting of patient. The results from clinical practice

Table 3 Recommended dose of rivaroxaban in pediatric patients from term newborns

Body weight (kg)	Formulation	Regimen			Total daily dose (mg)
		Once daily	Twice daily	Thrice daily	
2.6– < 3	Oral suspension	–	–	0.8	2.4
3– < 4	Oral suspension	–	–	0.9	2.7
4– < 5	Oral suspension	–	–	1.4	4.2
5– < 7	Oral suspension	–	–	1.6	4.8
7– < 8	Oral suspension	–	–	1.8	5.4
8– < 9	Oral suspension	–	–	2.4	7.2
9– < 10	Oral suspension	–	–	2.8	8.4
10– < 12	Oral suspension	–	–	3.0	9
12– < 30	Oral suspension	–	5	–	10
30– < 50	Tablet/oral suspension	15	–	–	15
≥50	Tablet/oral suspension	20	–	–	20

studies are comparable with this trial; these confirm the benefit–risk profile of rivaroxaban for the treatment of VTE in challenging patient populations either in retrospective cohort study, including CVC-related thrombosis, or in the Dresden Registry observational study.[27,28] Availability of a safe and effective oral agent with pediatric data to support use is of clear benefit. Further advances in VTE management of neonates and children might be obtained from international registries. It would be of interest to investigate the setting of pediatric patients, where clinical evidence is too poor in terms of genetic thrombophilia or in a larger cohort of cancer patients. Another challenge could be to demonstrate improved compliance with oral therapy for the pediatric patients and that this is associated with greater efficacy. Many knowledge gaps remain and require further investigations, which will help advance the treatment of VTE in pediatrics.

Conflict of Interest
None declared.

References

1 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(05):676–681
2 Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. J Pediatr 2004;145(04):563–565
3 Raskob GE, Angchaisuksiri P, Blanco AN, et al; ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol 2014;34(11):2363–2371
4 Sandoval JA, Sheehan MP, Stonerock CE, Shafique S, Rescorla FJ, Dalsing MC. Incidence, risk factors, and treatment patterns for deep venous thrombosis in hospitalized children: an increasing population at risk. J Vasc Surg 2008;47(04):837–843
5 Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics 2009;124(04):1001–1008
6 Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen SR. Pediatric venous and arterial noncerebral thromboembolism in Denmark: a nationwide population-based study. J Pediatr 2011;159(04):663–669
7 Macartney CA, Chan AK. Thrombosis in children. Semin Thromb Hemost 2011;37(07):763–771
8 Setty BA, O'Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases. Pediatr Blood Cancer 2012;59(02):258–264
9 Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015;12(08):464–474
10 Chan AKC, Monagle P. Updates in thrombosis in pediatrics: where are we after 20 years? Hematology (Am Soc Hematol Educ Program) 2012;2012:439–443
11 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;16:29
12 Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003;362 (9383):523–526
13 Ageno W, Samperiz A, Caballero R, et al; RIETE investigators. Duration of anticoagulation after venous thromboembolism in real world clinical practice. Thromb Res 2015;135(04):666–672
14 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:e737S–e801S
15 Attard C, Monagle P, Kubitza D, Ignjatovic V. The in vitro anticoagulant effect of rivaroxaban in children. Thromb Res 2012;130 (05):804–807
16 Attard C, Monagle P, Kubitza D, Ignjatovic V. The in-vitro anticoagulant effect of rivaroxaban in neonates. Blood Coagul Fibrinolysis 2014;25(03):237–240
17 Willmann S, Thelen K, Kubitza D, et al. Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. Thromb J 2018;16:32
18 Willmann S, Becker C, Burghaus R, et al. Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. Clin Pharmacokinet 2014;53(01):89–102
19 Kubitza D, Willmann S, Becka M, et al. Exploratory evaluation of pharmacodynamics, pharmacokinetics and safety of rivaroxaban

in children and adolescents: an EINSTEIN-Jr phase I study. Thromb J 2018;16:31
20 Monagle P, Lensing AWA, Thelen K, et al; EINSTEIN-Jr Phase 2 Investigators. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm, phase 2 studies. Lancet Haematol 2019;6 (10):e500–e509
21 Male C, Lensing AWA, Palumbo JS, et al; EINSTEIN-Jr Phase 3 Investigators. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. Lancet Haematol 2020;7(01):e18–e27
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 (01):21
23 Bauersachs RM, Lensing AWA, Prins MH, et al. Rivaroxaban versus enoxaparin/vitamin K antagonist therapy in patients with venous thromboembolism and renal impairment. Thromb J 2014; 12:25–32
24 Prins MH, Lensing AWA, Brighton TA, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. Lancet Haematol 2014;1 (01):e37–e46
25 Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral Factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36(20):2017–2023
26 Palumbo JS, Lensing AWA, Brandão LR, et al. Anticoagulation in pediatric cancer-associated venous thromboembolism: a subgroup analysis of EINSTEIN-Jr. Blood Adv 2022;6(22):5821–5828
27 Hassan E, Motwani J. Real world experience of efficacy and safety of rivaroxaban in paediatric venous thromboembolism. Thromb Res 2023;221:92–96
28 Marten S, Tittl L, Naue C, Beyer-Westendorf J. Treatment of VTE with rivaroxaban in adolescents – preliminary findings from the prospective Dresden NOAC Registry (NCT01588119). Hamostaseologie 2019;39(Suppl_1):S1–S92
29 Marcotte P, Tole S, Bouhelier E, et al. Rivaroxaban in children with nephrotic syndrome. Pediatr Hematol Oncol 2023;40:688–695
30 Connor P, Sánchez van Kammen M, Lensing AWA, et al. Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). Blood Adv 2020;4(24):6250–6258
31 Thom K, Lensing AWA, Nurmeev I, et al. Safety and efficacy of anticoagulant therapy in pediatric catheter-related venous thrombosis (EINSTEIN-Jr CVC-VTE). Blood Adv 2020;4(19): 4632–4639