Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): Results from three multicenter, single-arm, phase 2 studies

- Rivaroxaban has been shown to be efficacious for treatment of venous thromboembolism in adults,
- Rivaroxaban has a reduced risk of bleeding compared with standard anticoagulants
- We aimed to develop pediatric rivaroxaban regimens for the treatment of venous thromboembolism in children and adolescents.

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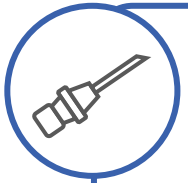
Understanding the Epidemiology of Paediatric VTE

- The incidence of VTE in children is ~15–200 times lower than in the general population[1–4]
  - Estimated to be 0.01–0.05 events per 1000 children per year[2,3]
- However, reported incidence is rising, possibly as a result of therapeutic advances and improved survival for children with conditions that increase risk of VTE, and increased awareness of VTE among paediatricians[5–8]
  - A 70% increase in the incidence of VTE in hospitalized children over a 7-year period has been reported[6]
- Data on VTE recurrence in children are limited; however, registries suggest that 7.5% of children with a history of VTE will experience a recurrent event[9]

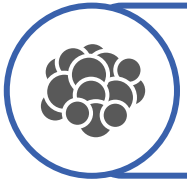
1. Andrew M *et al*, *Blood* 1994;83:1251–1257; 2. van Ommen CH *et al*, *J Pediatr* 2001;139:676–681; 3. Stein PD *et al*, *J Pediatr* 2004;145:563–565;
4. Raskob GE *et al*, *Thromb Res* 2014;134:931–938; 5. Sandoval JA *et al*, *J Vasc Surg* 2008;47:837–843; 6. Raffini L *et al*, *Pediatrics* 2009;124:1001–1008;
7. Tuckuviene R *et al*, *J Pediatr* 2011;159:663–669; 8. Macartney CA *et al*, *Semin Thromb Haemost* 2011;37:763–771; 9. Monagle P *et al*, *Chest* 2012;141:e737S–e801S

Clinical Presentation of VTE in Children

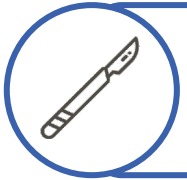
- The majority of cases of VTE are diagnosed in hospitalized children, and 95% of cases of paediatric VTE are provoked:[1–3]



- Presence of a central venous catheter (CVC) is the most common risk factor in neonates and children[2,3]
  - Approximately two-thirds of cases of VTE in children aged <2 years are associated with CVCs[4]
  - It is estimated that 25% to 75% of cases of VTE in children are related to CVCs[5]



- Children with cancer and children undergoing chemotherapy are at higher risk[2,3]

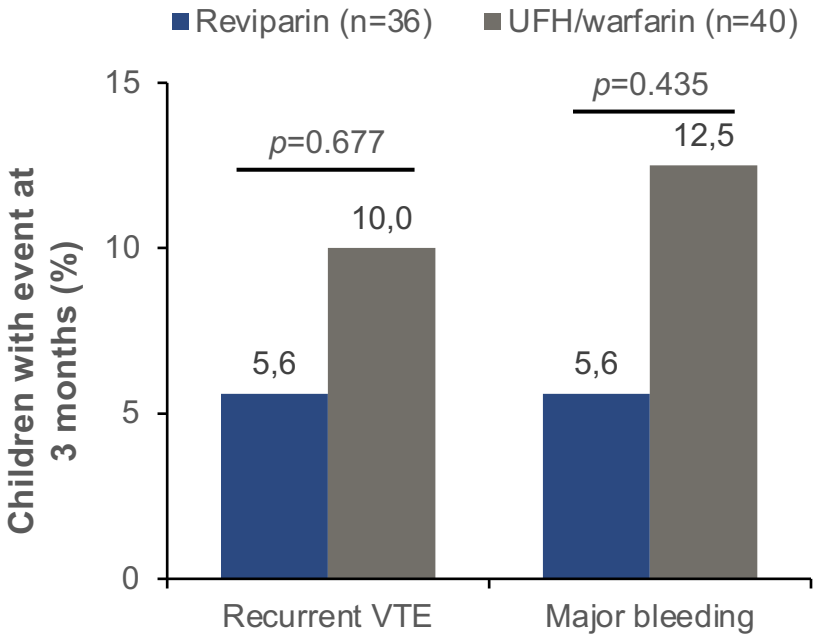


- Pathological conditions (e.g. severe infection, thrombophilia, trauma or surgery) and antiphospholipid syndrome also increase the risk of VTE in children[2,6]

1. Andrew M *et al*, *Blood* 1994;83:1251–1257; 2. Chan AKC & Monagle P, *Hematology Am Soc Hematol Educ Program* 2012;1:439–443;
3. Monagle P *et al*, *Chest* 2012;141:e737S–e801S; 4. Chan A *et al*, *Thromb J* 2018;16:29; 5. Raffini L *et al*, *Pediatrics* 2011;127:e1326–e1332;
6. Sandoval JA *et al*, *J Vasc Surg* 2008;47:837–843

REVIVE: First International RCT Comparing Anticoagulant Therapies in a Paediatric Population

- REVIVE is the only previous RCT to study anticoagulant therapies in children
  - Multicentre, open-label study with blinded central outcome adjudication
  - Randomized paediatric patients with objectively confirmed VTE received either reviparin (anti-Factor Xa level: 0.50–1.0 U/ml) or UFH/warfarin
- Mean age: 9 years
- Safety population: n=78



The trial was closed early due to slow patient recruitment

Massicotte P *et al*, *Thromb Res* 2003;109:85–92

Current Therapeutic Management of VTE in Children

- In the absence of suitable randomized clinical trials, clinical practice guidelines for VTE in children are mainly based on an extrapolation of the available data on VTE management in adults[1,2]
  - Treatment with heparins has limitations due to the requirement for daily parenteral injections, frequent blood sampling and adaptations from the adult dose
  - VKAs also pose challenges due to regular coagulation monitoring, dietary limitations, the lack of age-specific liquid preparations and poor compliance
- Pharmaceutical manipulation of the dose may affect the stability and bioavailability of the anticoagulant medication and may lead to dosing errors[3]

1. Monagle P *et al*, *Chest* 2012;141:e737S–e801S; 2. Macartney CA *et al*, *Semin Thromb Haemost* 2011;37:763–771; 3. Richley RH *et al*, *Int J Pharmaceutics* 2017;518:155–166

American College of Chest Physicians (ACCP). 2012 Guidelines

Summary of recommendations[1]	Grade
Paediatric haematologists with experience in thromboembolism should manage paediatric patients with VTE; when this is not possible, it should be a combination of a neonatologist/paediatrician and adult haematologist supported by consultation with an experienced paediatric haematologist	2c
Therapeutic UFH titrated to achieve a target anti-Factor Xa range of 0.35–0.7 U/ml, or an aPTT range that correlates to this anti-Factor Xa range or to a protamine titration range of 0.2–0.4 U/ml	2c
For neonates and children receiving either once- or twice-daily therapeutic LMWH, it is suggested that the drug be monitored to a target range of 0.5–1.0 U/ml in a sample taken 4–6 hours after subcutaneous injection or, alternatively, 0.5–0.8 U/ml in a sample taken 2–6 hours after subcutaneous injection	2c
For central venous access devices with confirmed thrombosis, it is suggested that anticoagulation should be with either (1) LMWH or (2) UFH followed by LMWH; a total duration of anticoagulation of between 6 weeks and 3 months rather than shorter or longer durations is suggested	2c

1. Monagle P *et al*, *Chest* 2012;141:e737S–e801S

ASH 2018 - Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism

The American Society of Hematology (ASH) guideline panel:

- recommends using anticoagulation rather than no anticoagulation in pediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism
- suggests using anticoagulation or no anticoagulation in pediatric patients with asymptomatic DVT or PE
- suggests using either low-molecular-weight heparin or vitamin K antagonists in pediatric patients with symptomatic DVT or PE
- suggest using **anticoagulation for ≤3 months** rather than anticoagulation for >3 months in pediatric patients with **provoked** DVT or PE
  - unless venous thromboembolism risk factors persist after 3 months of treatment, and there is a clinical need to continue with a prophylactic regimen

Monagle P, et al.. *Blood Adv*. 2018;2(22):3292-3316. doi:10.1182/bloodadvances.2018024786

ASH 2018 - Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism

The American Society of Hematology (ASH) guideline panel:

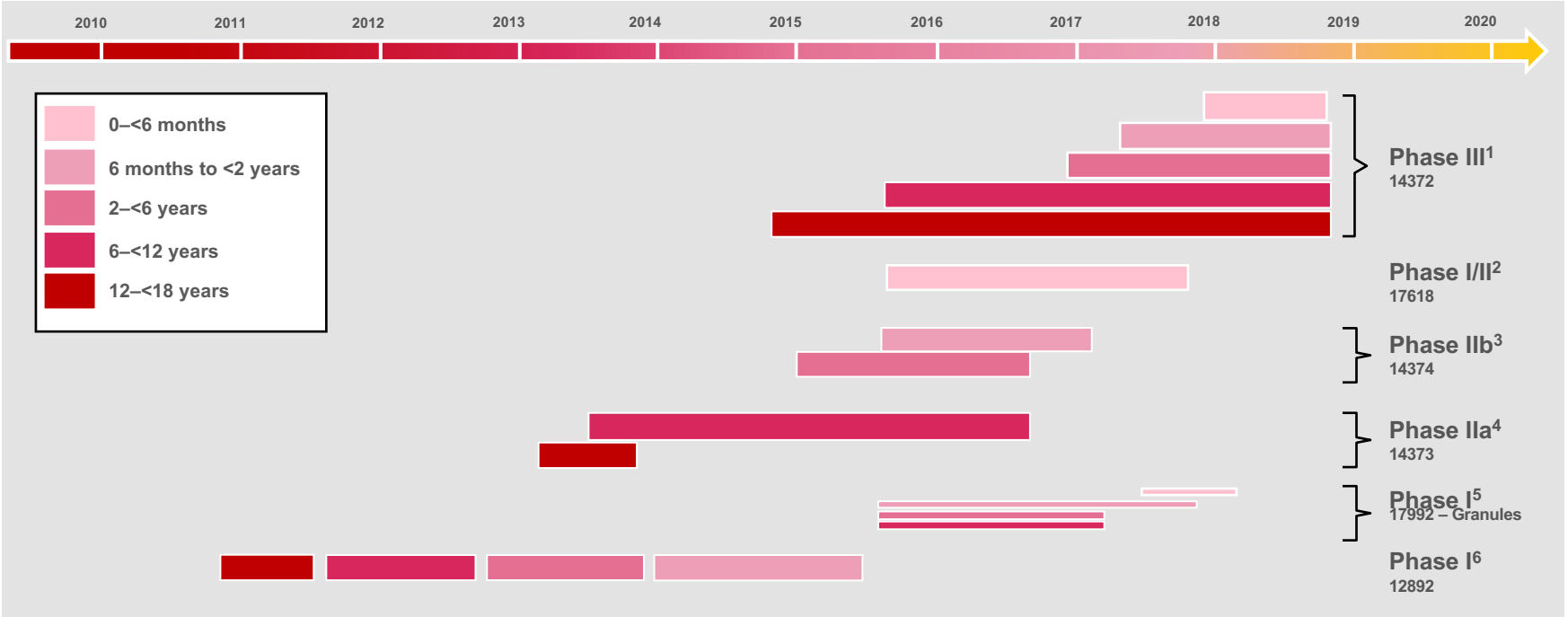
- suggests using anticoagulation for 6 to 12 months rather than anticoagulation for >6 to 12 months in pediatric patients with unprovoked DVT or PE
  - Extrapolation of adult data might favor prolonged treatment periods in terms of VTE recurrence. However, the bleeding risk and impact of prolonged therapy on quality of life were judged to be significantly higher in children compared with adults.

Monagle P, et al.. *Blood Adv*. 2018;2(22):3292-3316. doi:10.1182/bloodadvances.2018024786

EINSTEIN JUNIOR Programme

EINSTEIN JUNIOR Paediatric Programme (Phase I–III)

Phase I, II and III conducted in parallel, with staggered age groups



1. Male et al. Lancet Haematol. 2020 Jan;7(1):e18-e27; 2. NCT02564718, Monagle et al. Lancet Haematol. 2019 Oct;6(10):e500-e509;
3. NCT02309411, Monagle Lancet Haematol. 2019 Oct;6(10):e500-e509; 4. NCT01684423;
5. www.clinicaltrials.gov/ct2/show/NCT02497716; 6. www.clinicaltrials.gov/ct2/show/NCT01145859

EINSTEIN JUNIOR

Rivaroxaban: pediatric investigational programme principal results (1)

- EINSTEIN Junior programme is completed and consists mainly of:
  - one phase I pharmacokinetics/pharmacodynamics (PK/PD) trial (1),
  - three phase II trials (2)
  - one phase III trial (3)

Study	Objective	Age of subjects	Findings
Phase I (1) NCT01145859	To confirm pharmacokinetic/ pharmacodynamic (PK/PD) profile of rivaroxaban and to confirm that the exposure is comparable to adults. Single dose study with multiple PK/PD measurements in pediatric subjects at the end of their VTE treatment. 2 different rivaroxaban dose levels tested (10 mg and 20 mg) and 2 different formulation (tablet oral suspension)	0.5 – 18 years (n=59)	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 physiologically based pharmacokinetic model, used to predict the doses for the individual body weight groups, was confirmed. No episodes of bleeding were reported.

1. Kubitza D *et al*, *Thromb J* 2018;16:31

Rivaroxaban: pediatric investigational programme principal results (2)

Study	Objective	Age of subjects	Findings
3 Phase II (1) NCT02564718 NCT02309411 NCT02234843	• Primary aim: to define rivaroxaban treatment regimens that match the target adult exposure range. • Safety outcome: major bleeding and clinically relevant non-major bleeding. • Efficacy outcomes: symptomatic recurrent VTE, asymptomatic deterioration on repeat imaging at the end of the study treatment period.	n=93 < 6 months (n=10); 6 months - 1 year (n=15); 2–5 years (n=25); 6–11 years (n=32); 12–17 years (n=11)	Therapeutic rivaroxaban exposures confirmed with OD in children ≤ 30 kg and BID in children 20 kg < 30 kg. Children with low bodyweights (<20 kg, particularly <12 kg) showed low exposures so rivaroxaban dosages were revised. 0 Major bleeding; 4% CRNM; 0 symptomatic recurrent VTE; 32% patients with thrombotic burden resolved, 57% improved, and 11% unchanged
Phase III (2) NCT02234843	• Main outcome: to document the efficacy of rivaroxaban regimens at a 20 mg-equivalent dose for the prevention of fatal or symptomatic non-fatal recurrent VTE • Safety outcome, major or clinically relevant nonmajor bleeding	n=500 Birth - <18 years	Absolute and relative efficacy and safety estimates of rivaroxaban versus standard anticoagulation estimates were similar to those in rivaroxaban studies in adults.

1. Monagle et al. Lancet Haematol. 2019 Oct;6(10):e500-e509
2. Male et al. Lancet Haematol. 2020 Jan;7(1):e18-e27;

Rationale

- In children, an oral anticoagulant treatment that does not require daily subcutaneous/intravenous injections and regular blood sampling for coagulation monitoring is desirable
- In the absence of dedicated phase III clinical studies, current paediatric dosing recommendations have been developed from adult guidelines based on a Grade 2 level of evidence[1]
- There is a medical need for additional clinical studies that address the efficacy and safety of anticoagulant treatment in children
- In adults, rivaroxaban demonstrated a favourable benefit–risk profile compared with enoxaparin/VKA in the phase III EINSTEIN DVT and EINSTEIN PE studies[2]

1. Monagle P *et al*, *Chest* 2012;141:e737S–e801S; 2. Prins MH *et al*, *Thromb J* 2013;11:21

Selection of the Paediatric Dose of Rivaroxaban in EINSTEIN JUNIOR

- Novel approaches to drug development are required due to the low incidence of VTE in children and other recruitment challenges associated with paediatric trials[1]
- After assessing the PK/PD of rivaroxaban in neonates and children *in vitro*,[2,3] a physiologically based pharmacokinetic (**PBPK) model** was used to estimate the appropriate dosing for rivaroxaban in children[4]
  - The bodyweight-adjusted rivaroxaban dose regimen was designed to match the exposure range in young adults treated with rivaroxaban 20 mg once daily[1]
  - The model incorporated growth/maturation and variability in anthropometrics (e.g. height, weight and BMI), anatomy (e.g. organ weight), physiology (e.g. blood flow rates), metabolism and excretion[5,6]

1. Lensing AWA *et al*, *Thromb J* 2018;16:34; 2. Attard C *et al*, *Thromb Res* 2012;130:804–807;
3. Attard C *et al*, *Blood Coagul Fibrinolysis* 2014;25:237–240; 4. Willmann S *et al*, *Thromb J* 2018;16:32;
5. Willmann S *et al*, *Clin Pharmacokinet* 2014;53:89–102; 6. Kubitza D *et al*, *Thromb J* 2018;16:31

EINSTEIN JUNIOR Phase I: Confirmation of Rivaroxaban Dosing in Children

- The EINSTEIN JUNIOR phase I studies confirmed the PK and PD of the predicted dosing schedule of rivaroxaban in children
  - Developmental changes in haemostasis did not affect the anticoagulant effect of rivaroxaban
  - Prothrombin time and activated partial thromboplastin time showed a linear relationship with rivaroxaban plasma concentrations
    - Anti-Factor Xa activity demonstrated a trend for a linear relationship with rivaroxaban plasma concentrations; however, data were limited
  - PK of rivaroxaban in children was as expected; AUC, C_{max} and C_{24h} were completely within the expected ranges from the PBPK model
- In 59 children aged 0.5–18 years, no major bleeding events were reported

Kubitza D *et al*, *Thromb J* 2018;16:31

Rivaroxaban Dose Regimens for Children*

- Body weight-adjusted rivaroxaban regimens in a 20 mg equivalent dose

Body weight (kg)		Formulation	Regimen			Total daily dose
Min.	Max.		od	bid	tid	
2.6	<3	Oral suspension			0.8 mg	2.4 mg
3	<4	Oral suspension			0.9 mg	2.7 mg
4	<5	Oral suspension			1.4 mg	4.2 mg
5	<6	Oral suspension			1.6 mg	4.8 mg
6	<7	Oral suspension			1.6 mg	4.8 mg
7	<8	Oral suspension			1.8 mg	5.4 mg
8	<9	Oral suspension			2.4 mg	7.2 mg
9	<10	Oral suspension			2.8 mg	8.4 mg
10	<12	Oral suspension			3.0 mg	9 mg
12	<30	Oral suspension		5 mg		10 mg
30	<50	Tablet/oral suspension	15 mg			15 mg
≥50		Tablet/oral suspension	20 mg			20 mg

OD denotes once daily, BID twice daily, and TID thrice daily. *Based on clinical data from phase I/II and modelling

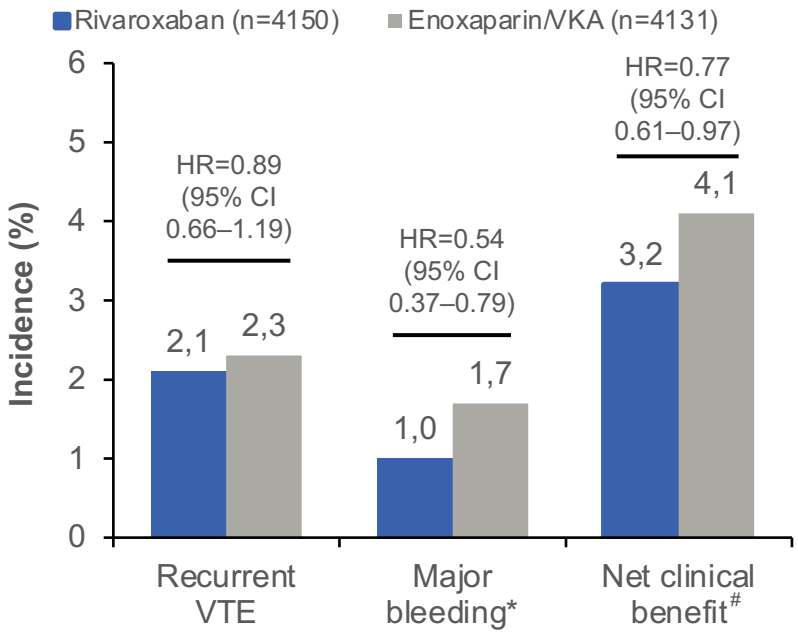
Male C, et al. Lancet Haematol. 2020 Jan;7(1):e18-e27.

EINSTEIN Study Programme

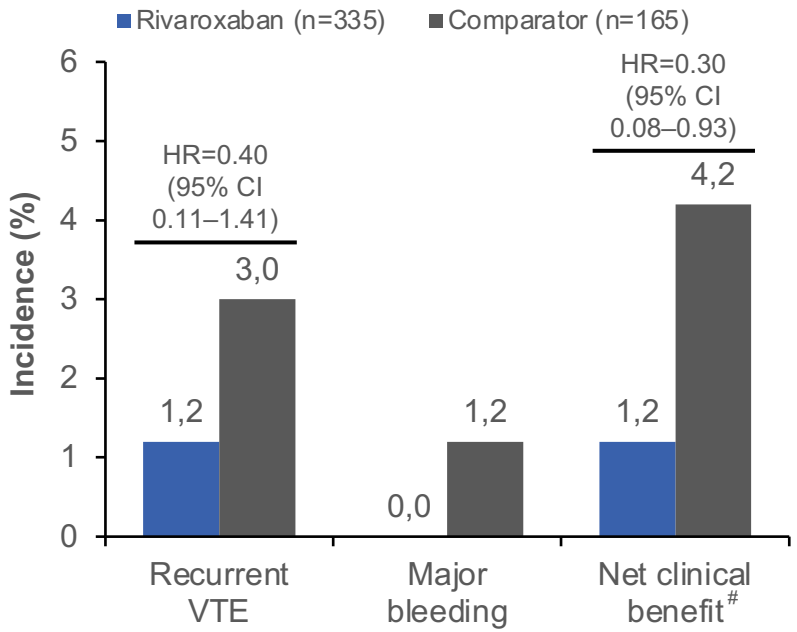
Rivaroxaban Consistent Results in Challenging Patient Scenarios

Rivaroxaban Demonstrated Consistent Efficacy and Safety Results in Children and Adults

EINSTEIN pooled[1]



EINSTEIN JUNIOR[2]



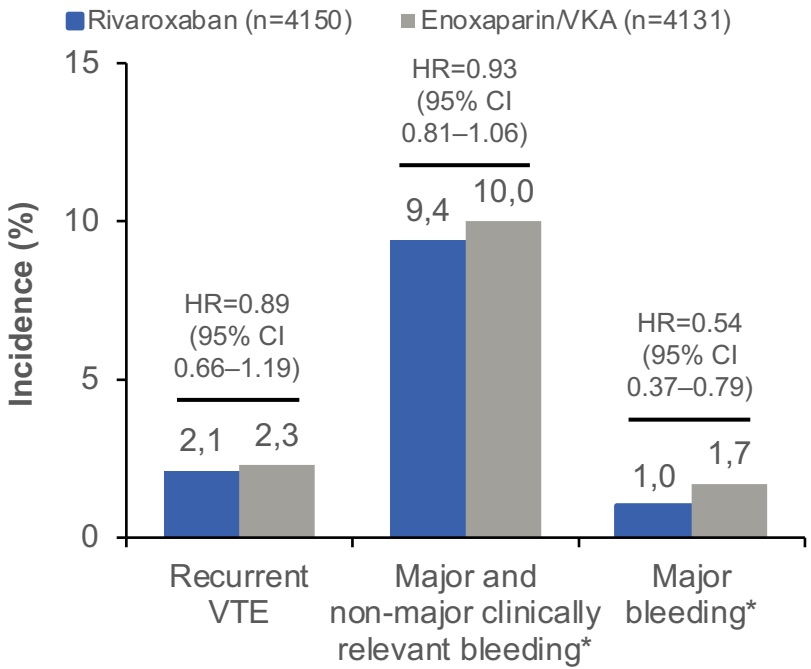
*Safety analysis: rivaroxaban n=4130, enoxaparin/VKA n=4116; #Composite of recurrent VTE or major bleeding

1. Prins MH *et al*, *Thromb J* 2013;11:21; 2. Male C *et al*, Presented at ISTH 2019; Oral presentation LB 01.5

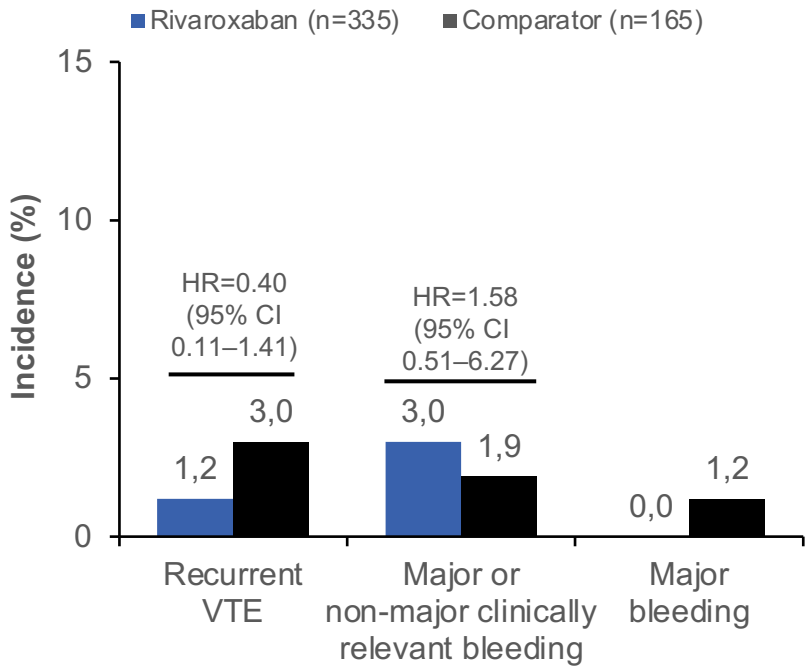
EINSTEIN JUNIOR

Rivaroxaban Demonstrated Consistent Efficacy and Safety Results in Children and Adults

EINSTEIN pooled[1]



EINSTEIN JUNIOR[2]



*Safety analysis: rivaroxaban n=4130, enoxaparin/VKA n=4116

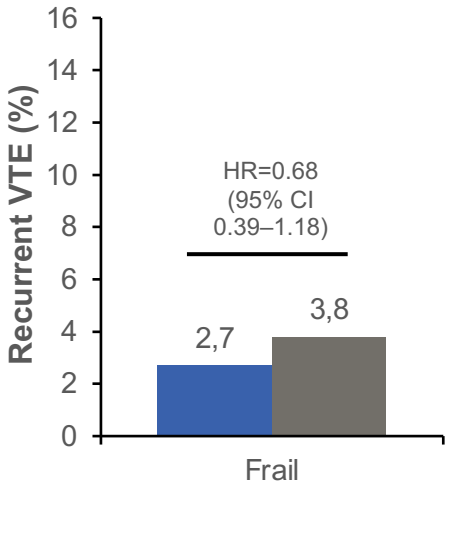
1. Prins MH *et al*, *Thromb J* 2013;11:21; 2. Male C *et al, Lancet Haematol* 2020;7(1):e18-e27

EINSTEIN JUNIOR

Rivaroxaban Demonstrated Consistent Efficacy Results in Challenging Patients

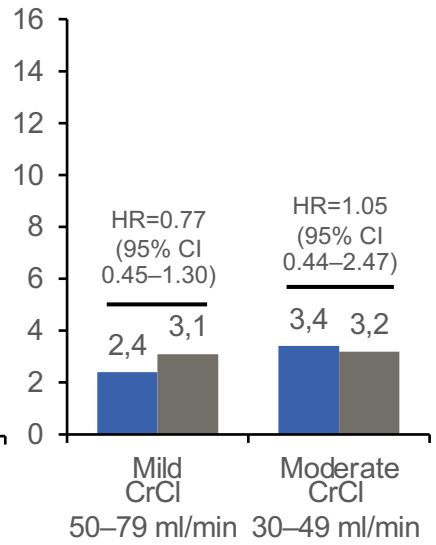
Frail patients*

EINSTEIN DVT and PE pooled[1]



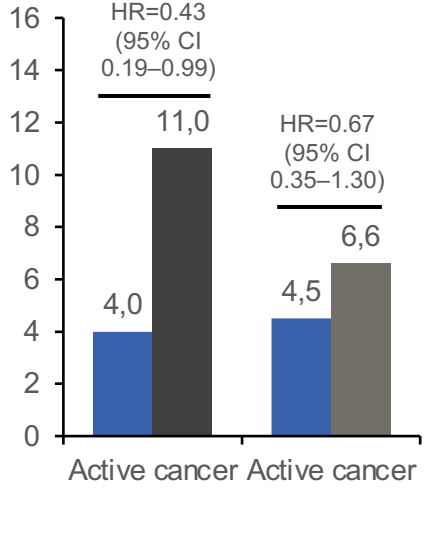
Renal impairment

EINSTEIN DVT and PE pooled[2]



Cancer

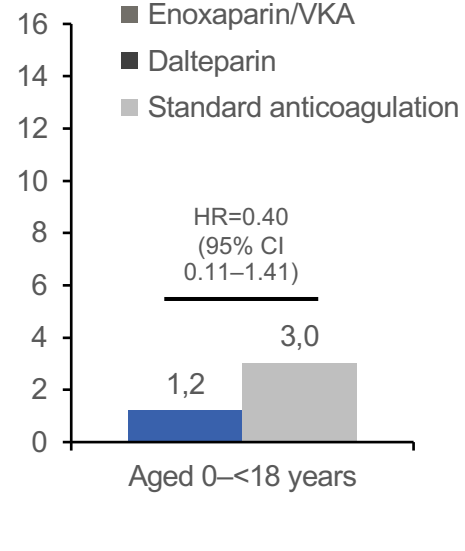
select-d[#3]



EINSTEIN DVT and PE pooled[4]

Children (0–<18 years)

EINSTEIN JUNIOR[5]

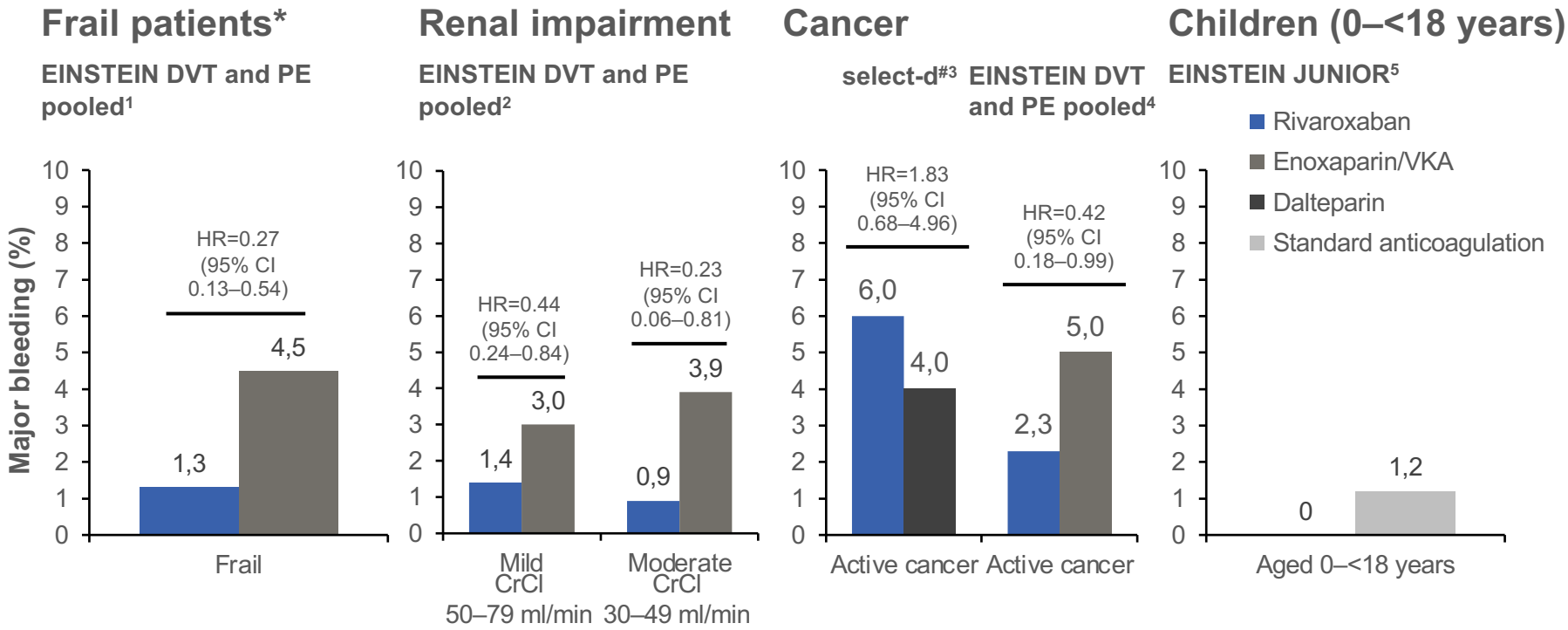


*One or more of: age >75 years, CrCl <50 ml/min, low body weight (≤50 kg); #6-month cumulative incidence

1. Prins MH *et al*, *Thromb J* 2013;11:21; 2. Bauersachs RM *et al*, *Thromb J* 2014;12; 3. Young A *et al*, *J Clin Oncol* 2018;36:2017–2023; 4. Prins MH *et al*, *Lancet Haematol* 2014;1:e37–46; 5. Male C *et al*, Presented at ISTH 2019; Oral presentation LB 01.5

EINSTEIN JUNIOR

Rivaroxaban Demonstrates Low Incidence of Major Bleeding Events in a Variety of Challenging Patients

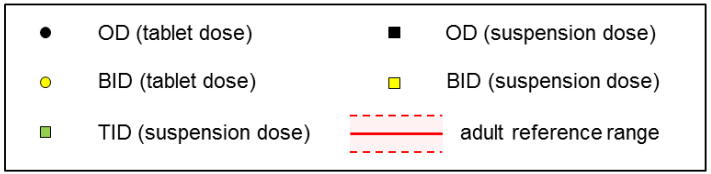


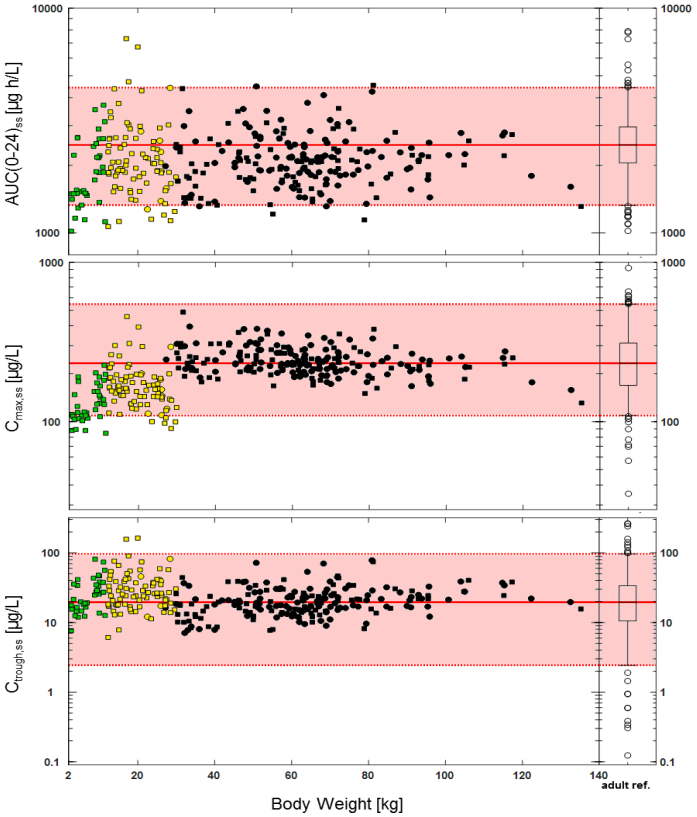
*One or more of: age >75 years, CrCl <50 ml/min, low body weight (≤50 kg); #6-month cumulative incidence

1. Prins MH *et al*, *Thromb J* 2013;11:21; 2. Bauersachs RM *et al*, *Thromb J* 2014;12; 3. Young A *et al*, *J Clin Oncol* 2018;36:2017–2023; 4. Prins MH *et al*, *Lancet Haematol* 2014;1:e37–46; 5. Male C *et al*, Presented at ISTH 2019; Oral presentation LB 01.5

PK Parameters by Bodyweight

- Values of AUC, C_{max}, and C_{trough} within the adult reference range, irrespective of
  - Formulation
  - Age
  - Bodyweight
  - Treatment regimens





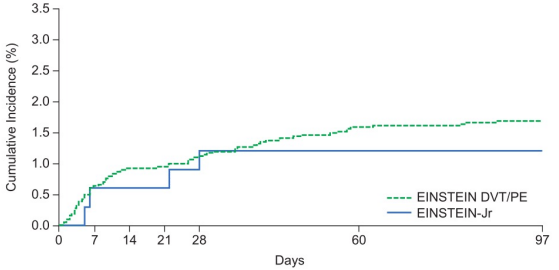
Male C *et al*, Presented at ISTH 2019; Oral presentation LB 01.5

Rivaroxaban Demonstrated Consistent Efficacy and Safety Results in Children and Adults

Rivaroxaban

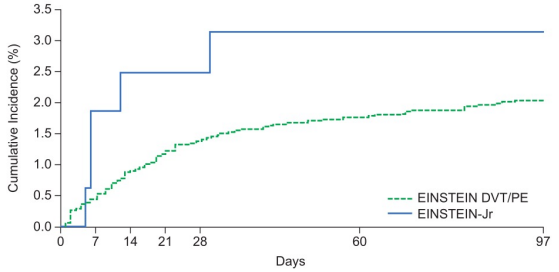
Comparator

Recurrent VTE



No. at Risk

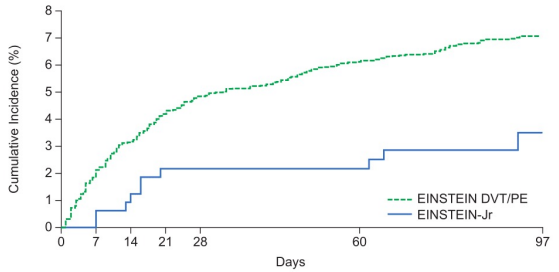
EINSTEIN DVT/PE	4150	4087	4054	4038	4021	3969	3924
EINSTEIN-Jr	335	330	330	330	324	296	0



No. at Risk

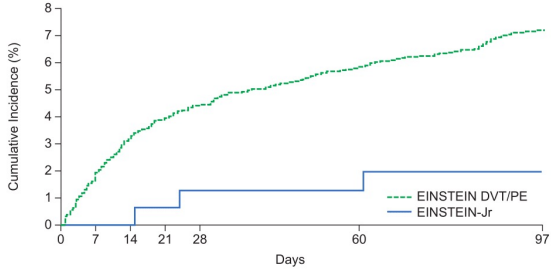
EINSTEIN DVT/PE	4131	4062	4001	3961	3934	3874	3826
EINSTEIN-Jr	165	158	157	157	154	143	0

Major or clinically relevant non-major bleeding



No. at Risk

EINSTEIN DVT/PE	4130	3974	3892	3823	3772	3669	3406
EINSTEIN-Jr	329	326	318	313	309	285	0



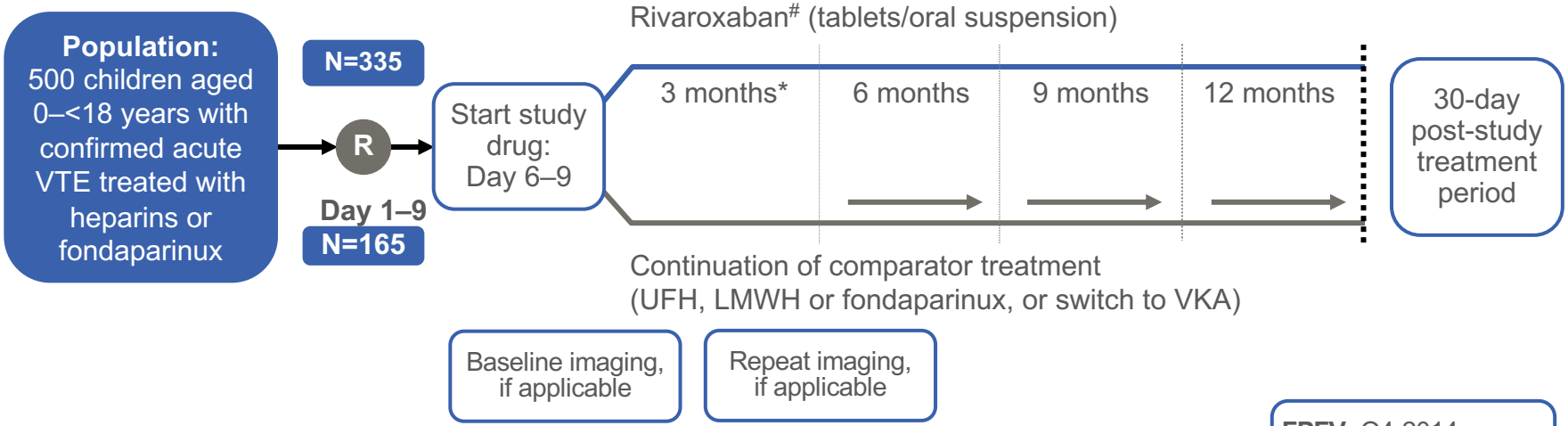
No. at Risk

EINSTEIN DVT/PE	4116	3986	3858	3790	3743	3614	3330
EINSTEIN-Jr	162	159	159	156	152	142	0

Male C, et al. Lancet Haematol. 2020 Jan;7(1):e18-e27.

EINSTEIN JUNIOR Phase III: study design

Objective: Open-label, randomized (2:1) trial to assess the efficacy and safety of bodyweight-adjusted rivaroxaban in a 20 mg-equivalent dose compared with the standard of care in children with acute VTE



FPFV: Q4-2014
LPLV: Q1-2019

*Children aged <2 years with catheter-related VTE: extension with maximum two blocks of 1 month, decision to stop or continue treatment made after each 3- or 1-month period; #bodyweight-adjusted rivaroxaban dose equivalent to 20 mg od adult dose

Lensing AWA *et al*, *Thromb J* 2018;16:34; www.clinicaltrials.gov/ct2/show/NCT02234843

EINSTEIN JUNIOR