Caring for Pediatric Patients: DOACs for Acute VTE Treatment and Secondary Prophylaxis

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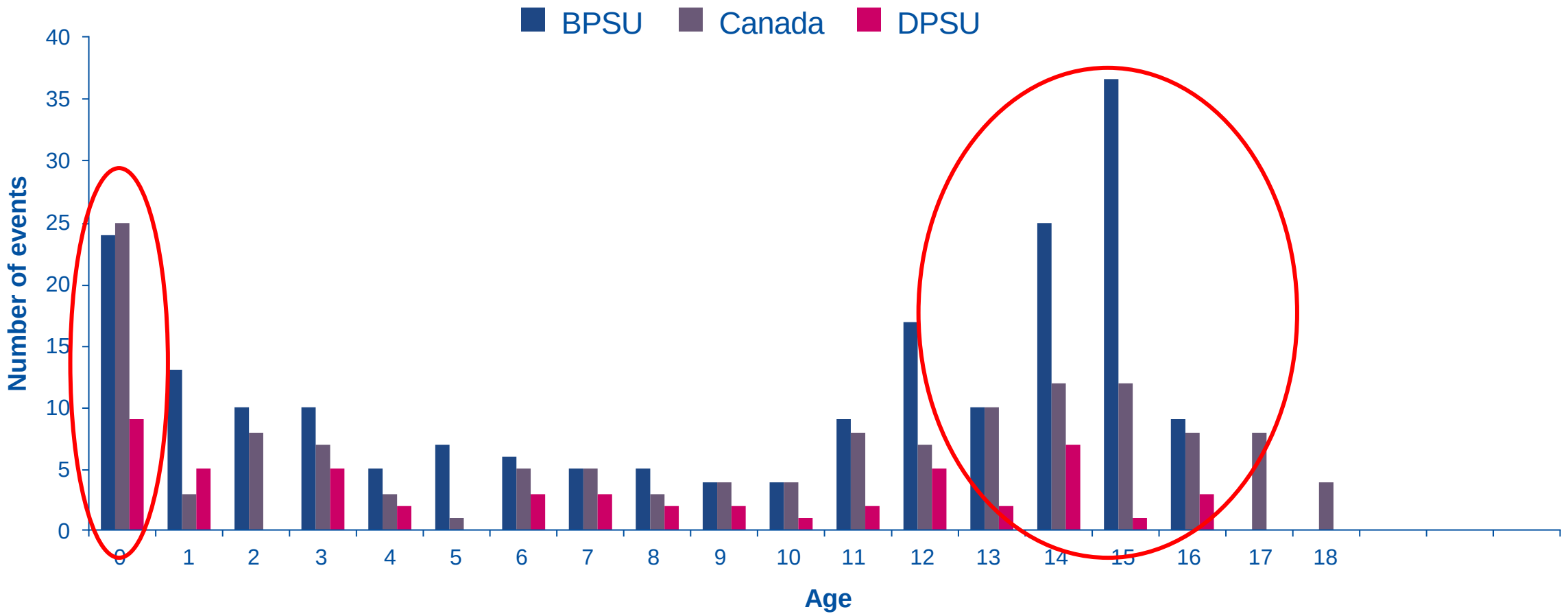
Neonates and adolescents have the greatest risk for VTE in the pediatric population

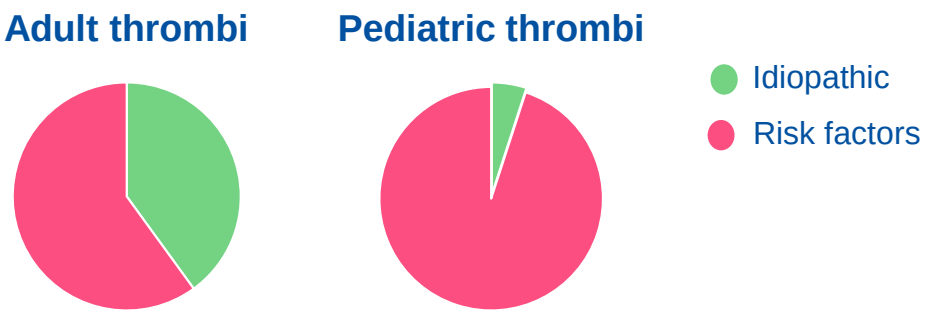


BPSU, British Paediatric Surveillance Unit; DPSU, Dutch Paediatric Surveillance Unit; VTE, venous thromboembolism

Adapted from Chalmers. Thromb Res 2006;118:3

VTE etiology is different in children compared with adults
The long-term consequences of VTE in children vary by location

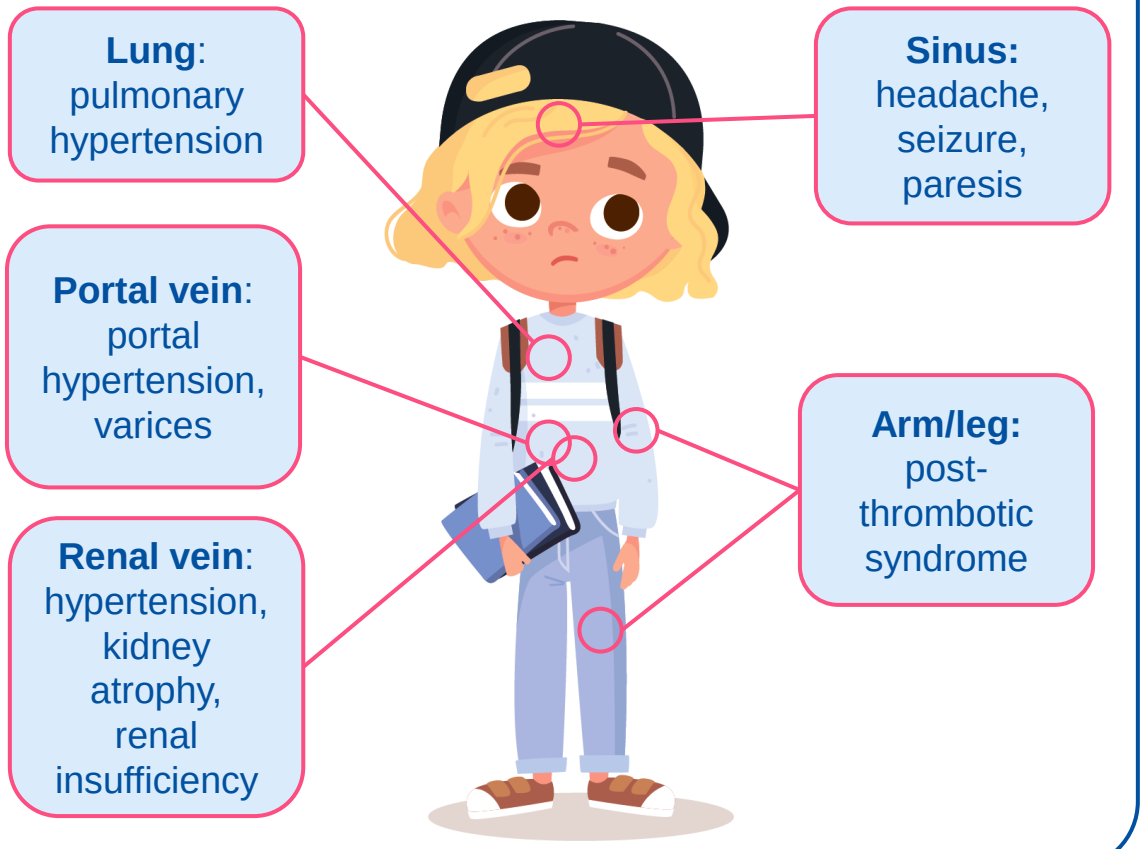
Children have different VTE etiology vs adults[1,2]



Risk factors for VTE in children[1,2]

- **Central venous catheters**
- **Chronic diseases:** kidney, congenital heart disease
- **Medication:** asparaginase, contraceptives
- **Thrombophilia:** protein C, S, antithrombin deficiency

Locations and long-term consequences of pediatric VTE[1,3–5]



VTE, venous thromboembolism

1. Spentzouris et al. J Vasc Surg 2012;55:1785; 2. Chalmers. Thromb Res 2006;118:3; 3. Jensen et al. Liver Transpl 2013;19:315; 4. Brandão et al. Semin Fetal Neonatal Med 2011;16:323; 5. Felling et al. Neurol Clin Pract 2020;10:232

DOAC characteristics and suitability for use in pediatric patients

DOAC dosing:

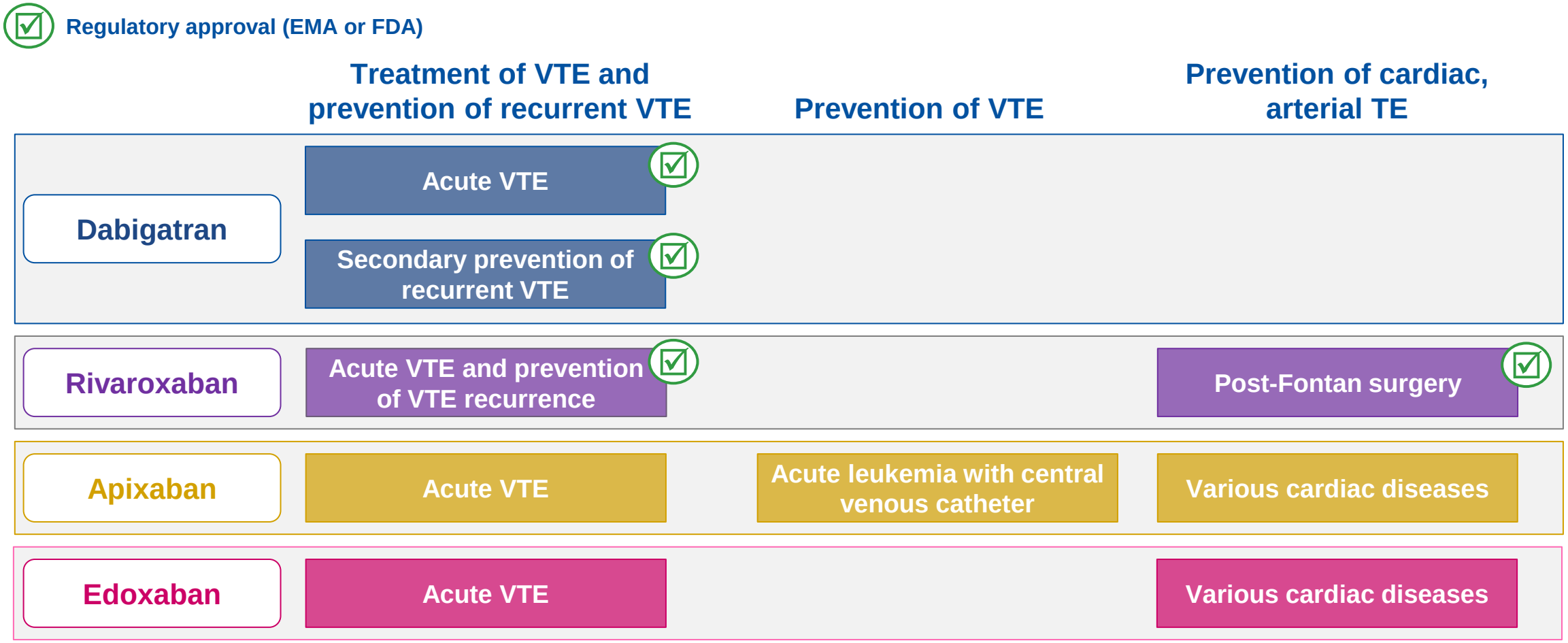
- ✓ Reduced injections vs LMWH and UFH[1]
- ✓ No plasma level monitoring[1]
- ✓ No antithrombin dependence[1]
- ✓ Fewer drug interactions vs VKA[1]
- ✓ Few food interactions[1]
- ✓ Pediatric preparations*[2,3]

*The coated granules and oral solution formulations of Pradaxa® are licensed in Great Britain and the European Union but are not yet available for use

DOAC, direct oral anticoagulant; SPC, Summary of Product Characteristics

1. Male et al. J Pediatr 2022;240:14; 2. Pradaxa SPC; 3. Xarelto SPC

Overview of indications targeted by the ongoing Pediatric Investigation Plans for DOACs

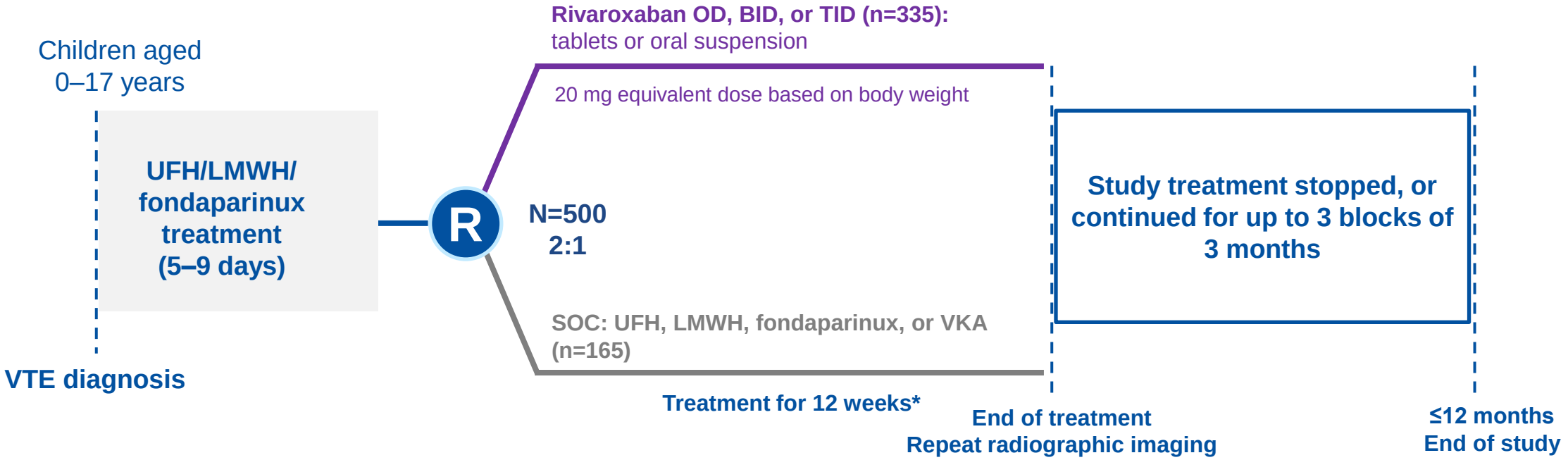


DOAC, direct oral anticoagulant; EMA, European Medicines Agency; FDA, Food and Drug Administration; LMWH, low-molecular-weight heparin; TE, thrombotic events; VKA, Vitamin K antagonist; VTE, venous thromboembolism

Adapted from Male et al. Thromb Res 2019;173:178

EINSTEIN-Jr was a Phase III study of rivaroxaban vs SOC for acute treatment of VTE in children

Parallel-group, open-label, randomized study



Co-primary endpoints
Safety endpoint: major and clinically relevant non-major bleeding
Efficacy endpoint: symptomatic recurrent VTE

*Children with catheter-related thrombosis aged <2 years had a main treatment period of 1 month

BID, twice daily; LMWH, low-molecular-weight heparin; OD, once daily; R, randomization; SOC, standard of care; TID, three times daily; UFH, unfractionated heparin; VKA, Vitamin K antagonist; VTE, venous thromboembolism

Lensing et al. Thromb J 2018;16:34; Male et al. Lancet Haematol 2020;7:e18

EINSTEIN-Jr: VTE recurrence and bleeding rates with rivaroxaban vs SOC for treatment of acute VTE in children

	Rivaroxaban (n=335)	SOC (n=165)	HR (95% CI)	ARR, %
Symptomatic non-fatal recurrent VTE, n (%)	4 (1)	5 (3)	0.40 (0.11−1.41)	1.8
Major or clinically relevant non-major bleeding, n (%)	10 (3)	3 (2)	1.58 (0.51−6.27)	–1.2
Major bleeding	0	2 (1)		
Clinically relevant non-major bleeding	10 (3)	1 (1)		

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; SOC, standard of care; VTE, venous thromboembolism

Male et al. Lancet Haematol 2020;7:e18

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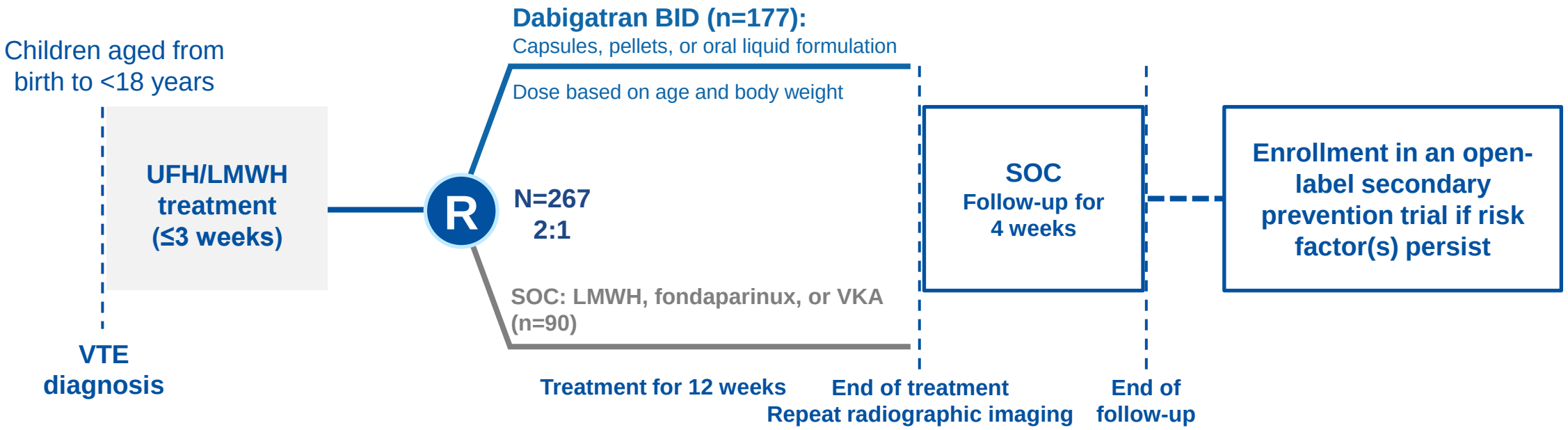
Male et al. Lancet Haematol 2020;7:e18

DIVERSITY was a Phase IIb/III study exploring dabigatran for treatment of acute VTE in children

Non-inferiority, open-label, randomized, parallel-group study



Primary composite efficacy endpoint	Secondary endpoints included:
Proportion of children with complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related death	All components of primary endpoint Freedom from MBEs Incidence of CRNMBEs and minor bleeding events

BID, twice daily; CRNMBE, clinically relevant non-major bleeding event; LMWH, low-molecular-weight heparin; MBE, major bleeding event; R, randomization; SOC, standard of care; UFH, unfractionated heparin; VKA, Vitamin K antagonist; VTE, venous thromboembolism

Albisetti et al. Res Pract Thromb Haemost 2018;2:347; Halton et al. Lancet Haematol 2021;8:e22

DIVERSITY: dabigatran was non-inferior to SOC for the combined efficacy endpoint

	Dabigatran, n (%)	SOC, n (%)	SOC – dabigatran, MH weighted difference	90% CI (P, non-inferiority)
Combined efficacy endpoint	n=177	n=90		
Complete thrombus resolution, freedom from recurrent VTE, freedom from VTE-related death	81 (46)	38 (42)	–0.04	–0.14 to 0.07 **(P<0.0001)**

Safety endpoints	n=176	n=90	**HR**	**95% CI**	**ARR, %**
Major bleeding	4 (2)	2 (2)	0.94	0.17–5.16	–0.2
Clinically relevant non-major bleeding	2 (1)	1 (1)	0.97	0.09–10.64	–0.00036

Randomized set during intention-to-treat period

ARR, absolute risk reduction (post hoc approximation); CI, confidence interval; HR, hazard ratio; MH, Mantel–Haenszel; SOC, standard of care; VTE, venous thromboembolism

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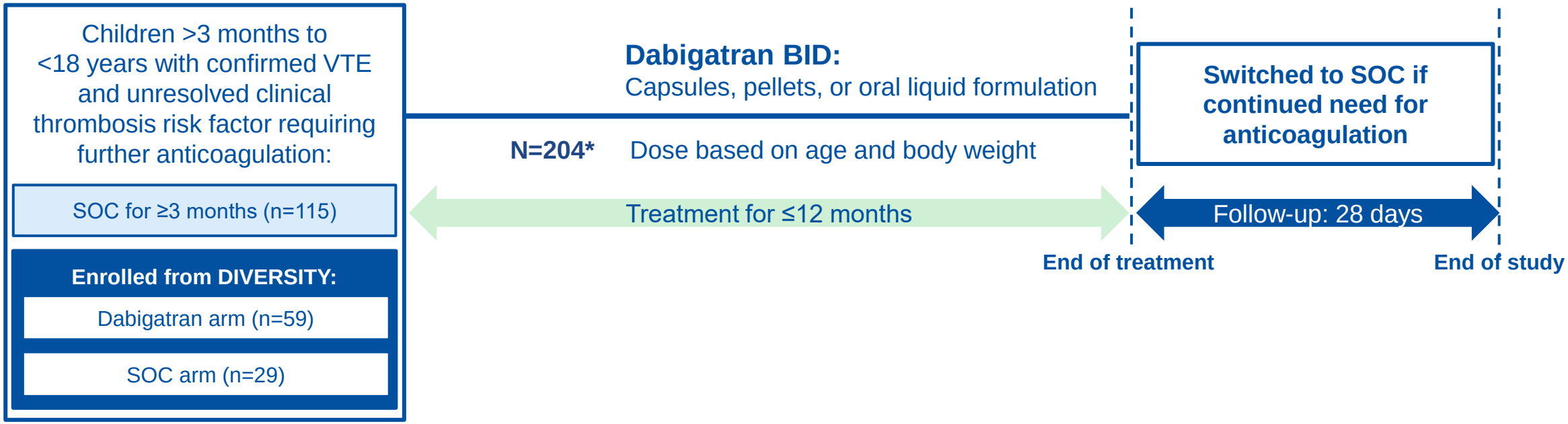
Halton et al. Lancet Haematol 2021;8:e22

Safety of extended dabigatran therapy for secondary VTE prevention in children has been investigated in a Phase III study

Open-label, single-arm, prospective cohort study



Primary endpoints

- **Recurrence of VTE**
- **Mortality** (overall and thrombotic/thromboembolism related)
- **Bleeding events** (major, clinically relevant non-major, and minor)

*One adolescent was not treated (due to inability to take treatment)

BID, twice daily; SOC, standard of care; VTE, venous thromboembolism

Brandão et al. Blood 2020;135:491; Luciani et al. Res Pract Thromb Haemost 2018;2:580

VTE recurrence, bleeding events, and all-cause death with dabigatran treatment

	Dabigatran			Total (N=203)
	12 to <18 yrs (n=153)	2 to <12 yrs (n=42)	3 m to <2 yrs (n=8)	
Recurrent VTE event, n (%)	2 (1.3)	0	0	2 (1.0)
Bleeding events, n (%)	37 (24.2)	2 (4.8)	1 (12.5)	40 (19.7)
Major	3 (2.0)	0	0	3 (1.5)
Clinically relevant non-major	1 (0.7)	1 (2.4)	0	2 (1.0)
Minor	34 (22.2)	2 (4.8)	1 (12.5)	37 (18.2)
All-cause death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Pradaxa® capsules can be used in pediatric patients aged 8 years or older who are able to swallow the capsules whole
The coated granules and oral solution formulations of Pradaxa® are licensed in Great Britain and the European Union but are not yet available for use
m, months; VTE, venous thromboembolism
Brandão et al. Blood 2020;135:491

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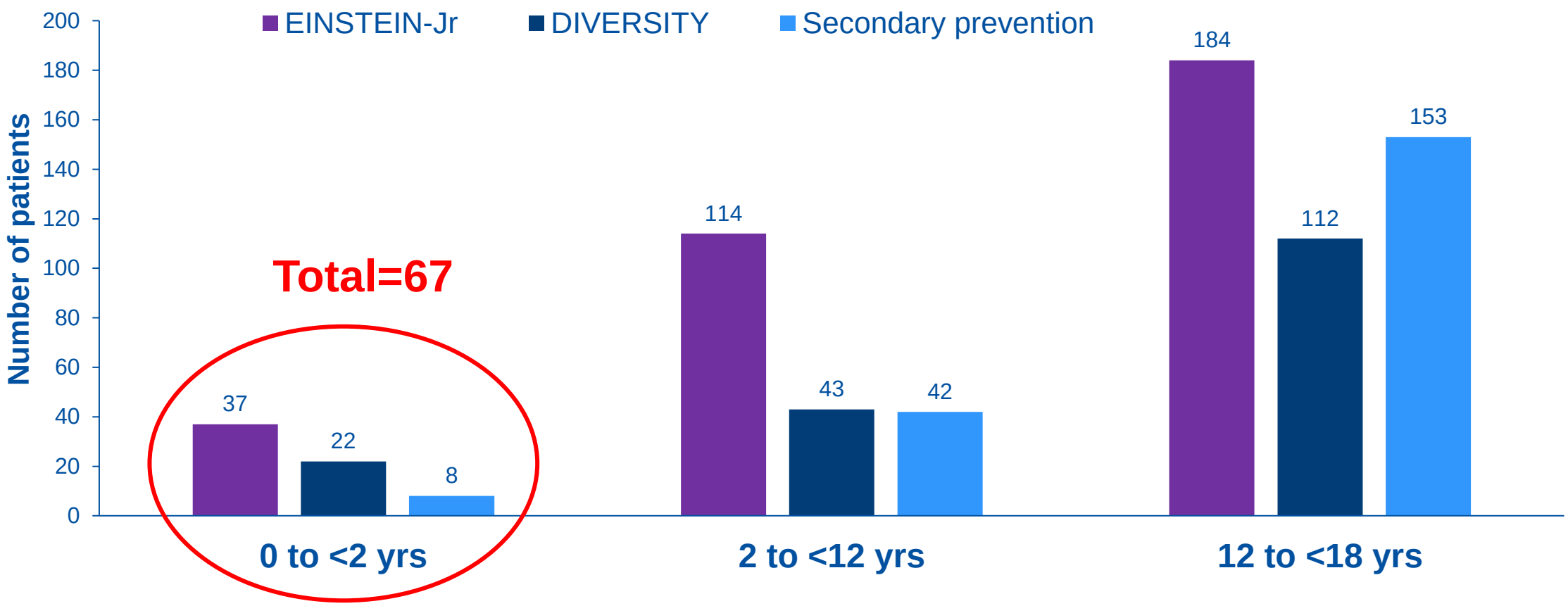
Age distribution of patients enrolled in the DOAC arms of the completed Phase III pediatric trials



DOAC, direct oral anticoagulant

Male et al. Lancet Haematol 2020;7:e18; Halton et al. Lancet Haematol 2021;8:e22; Brandão et al. Blood 2020;135:491

DOACs in the real world: IPTN registry

Validating DOACs for use in children by the Throm-PED DOAC registry of the International Pediatric Thrombosis Network

OC 15.5
Session title: Use of DOACs in Pediatrics
11.45 AM – 12.00 PM Sunday July 10, 2022

DOAC, direct oral anticoagulant; IPTN, International Pediatric Thrombosis Network

Holzhauer et al. ISTH 2022;OC15.5

Summary

- Different formulations and doses of dabigatran and rivaroxaban have been developed and tested for acute VTE treatment and secondary prevention in children[1,2]
- Dabigatran and rivaroxaban have been tested vs SOC in pediatric patients in the acute VTE setting;[3,4] dabigatran was non-inferior to SOC* for the combined efficacy endpoint†[3]
- Dabigatran showed low recurrent VTE and major bleeding rates for secondary VTE prevention in children aged from >3 months to <18 years[5]
- Registry and post-authorization safety studies in children are ongoing[6,7]

*LMWH, fondaparinux, or VKA; †Complete thrombus resolution, freedom from recurrent VTE, freedom from VTE-related death

LMWH, low-molecular-weight heparin; SOC, standard of care; SPC, Summary of Product Characteristics; UFH, unfractionated heparin; VKA, Vitamin K antagonist; VTE, venous thromboembolism

1. Pradaxa SPC; 2. Xarelto SPC; 3. Halton et al. Lancet Haematol 2021;8:e22; 4, Male et al. Lancet Haematol 2020;7:e18; 5. Brandão et al. Blood 2020;135:491; 6. Holzhauer et al. ISTH 2022;OC15.5; 7. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance: EUPAS47909; accessed Jun 2022