



ICT 2023

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Congress on Thrombosis

Anticoagulant treatment of paediatric patients

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Declaration of Conflict Of Interest

- I have no potential conflict of interest to report
- I have the following potential conflict(s) of interest to report

Summary

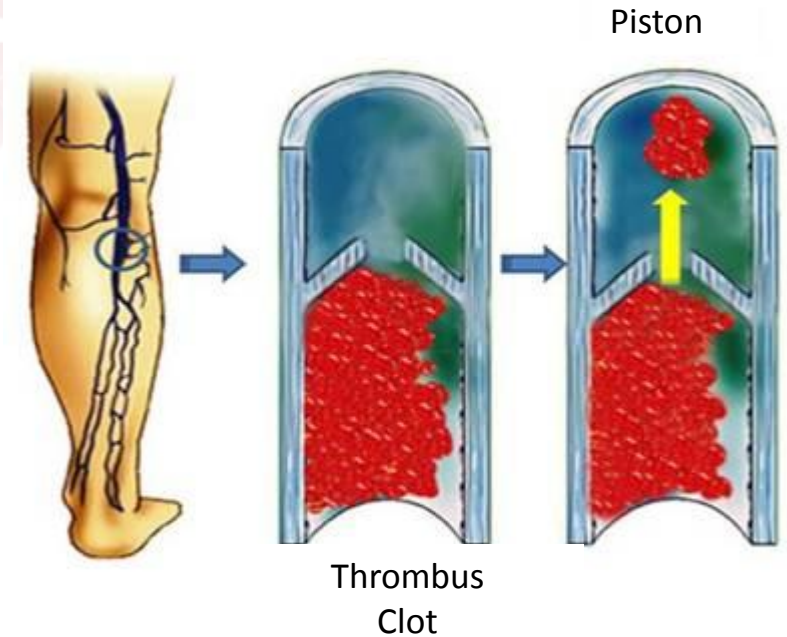
- Introduction
- Pediatric anticoagulant therapy
- Standard anticoagulants: LMWH and oral vitamin K antagonist
- Direct oral anticoagulants: Direct thrombin inhibitors and Factor Xa inhibitors:
 - Mechanism of action
 - Efficacy/Safety
 - Dose and monitoring
 - Pharmacological characteristics
 - Contraindications
- Pediatric anticoagulation recommendations

Pediatric venous thrombosis

- Venous thromboembolism (VTE - non cerebral VTE)
 - Deep vein thrombosis (DVT)
 - Pulmonary thromboembolism (PE)

- Cerebral venous thrombosis (CVT)

- Neonatal thrombosis



“Venous thromboembolic diseases”, NICE guidelines 2012

Venous thromboembolism - Introduction

■ Epidemiology

Rare pathology in children



- Few studies
- Extrapolation from adults

– □ 3 – 10 x frequency in recent years in hospitalized children

0.3-28.8/10,000 admissions (1992-2005)

58/10,000 admissions (2021)

Incidence - Neonate: 0.51/10000

- Child: 0.07 - 0.14/10000

1. □ number of medical interventions
2. > knowledge about the disease
3. Medical/technological advances
4. > number of children in ICU and oncology

Majority associated with precipitating factor

- 6% of VTE/PE associated with medical conditions: CVC (+++), infection, trauma, cancer, heart congenital disease

Witmer C et al. Treatment of Venous thromboembolism in pediatric patients. Blood, 2021
Caldwell A et al. Direct Oral anticoagulants for treatment of venous thromboembolism in children. Journal of Hospital Medicine. 2021
Hong J et al. Updated recommendations for the treatment of venous thromboembolism. Blood Research. 2021

Venous thromboembolism - Introduction

■ Epidemiology

– Bimodal: peak incidence: newborn (90%) and teenagers (60%)

– ♀ = ♂ except teenagers ♀ 2x > ♂

– Mortality:

- 1% - 2,2%
- ☐ 2 -3 times hospital mortality

Risks factors for VTE in children

Acquired

- CVCs^{2,3,16-18,20-26}
- Surgery^{23,26-28}
- Trauma/ICU admission^{17,18,21,23,28,29}
- Length of hospital stay^{18,21,24,30}
- Mechanical ventilation^{17,21,30}
- Immobility¹⁸
- Infection^{3,18,24,30}
- Acquired thrombophilia^{22,31}
- Acquired chronic diseases^{*,23,25,33}
- Medications³¹
- Hormonal therapy^{18,32}
- Obesity¹⁹

Genetic/developmental

- Age (neonates and adolescents)^{2,3,16,17,23,26,28,29}
- Inherited thrombophilia^{22,34}
- Anatomical thrombophilia^{35,36}
- Inherited chronic diseases^{*,23-25,33}

MEDICAL PROGRESS www.jpeds.com • THE JOURNAL OF PEDIATRICS
Direct Oral Anticoagulants: Overcoming the Challenges of Managing Venous Thromboembolism in Children
Christoph Male, MD¹, Paul Monagle, MD^{2,3}, Manueta Abbiati, MD¹, Leonardo R. Brandão, MD^{1,4}, and Guy Young, MD⁵

Pediatric cerebral venous thrombosis (CVT) - Introduction

Epidemiology

- Rare type of stroke in childhood
- Incidence 0,7/100000 children/year
- It is estimated to have caused 1 case of perinatal stroke in every 2,200 births.
- Risk factors for pediatric CVT: birth complications, infection of the head or neck, cancer, traumatic head injury, acquired or inherited thrombophilia, use of hormonal contraceptive methods

- Anticoagulant therapy, with the potential for intracranial hemorrhage, is more controversial because of the absence of clinical trials and the infectious nature of CVT in many children

Anticoagulant therapy

Goals

- Prevention local of extension and embolization of thrombus
- Resolution of the existing thrombus
- Prevent VTE recurrence
- Minimize long-term complications (eg, post-thrombotic syndrome)



Anticoagulant agents

- Low molecular weight heparin (LMWH)
- Unfractionated heparin (UFH)
- Vitamin K antagonists (VKA; eg, warfarin)
- Direct oral anticoagulants (DOAC)

Thrombolytic therapy (eg, recombinant tissue plasminogen activator [tPA])

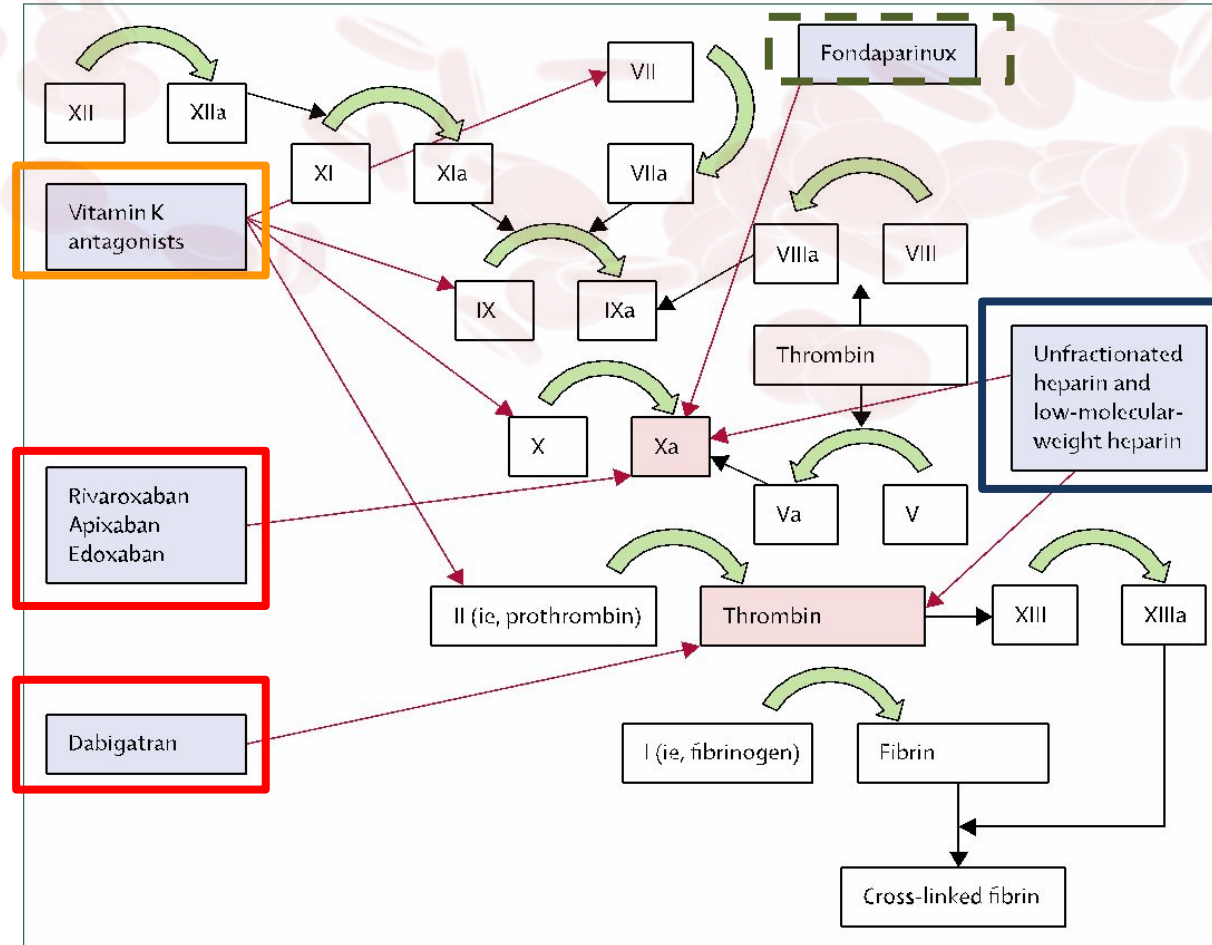
- Rarely used in the management of peadiatric VTE;
- Limited to cases in which thrombosis causes major vessel occlusion with compromise of organs or limbs

Anticoagulant therapy -Mechanism of action

Inhibits the synthesis of vitamin K-dependent clotting factors

Direct factor Xa inhibition

Direct thrombin inhibition



Selective activity on Factor Xa and thrombin

Jaffrau J, Young G . The Lancet, 2022

Approach of paediatric anticoagulation Guidelines

CHEST Supplement
ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy in Neonates and Children

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Paul Monagle, MBBS, MD, FCCP; Anthony K. C. Chan, MBBS; Neil A. Goldenberg, MD, PhD; Rebecca N. Iehord, MD; Janna M. Journeycake, MD, MSCS; Ulrike Nowak-Göttl, MD; and Sara K. Vesely, PhD

CLINICAL GUIDELINES **blood advances**

American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism

Paul Monagle,¹ Carlos A. Cuello,^{2,3} Caitie Shea Hanson,⁹ Christoph Male,¹⁰ John Wiernikowski,¹⁷ Suzan Williams,¹⁸ Sara K. Vesely²¹

CLINICAL GUIDELINES **blood advances**

American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism

Thomas L. Ortel,¹ Ignacio Neumann,² Walter Ageno,³ Rebecca Beyth,^{4,5} Nathan P. Clark,⁶ Adam Cuker,⁷ Barbara A. Hutten,⁸ Michael R. Jaff,⁹ Veena Manja,^{10,11} Sam Schulman,^{12,13} Caitlin Thurston,¹⁴ Suresh Vedantham,¹⁵ Peter Verhamme,¹⁶ Daniel M. Witt,¹⁷ Ivan D. Florez,^{18,19} Ariel Izcovich,²⁰ Robby Nieuwlaat,¹⁹ Stephanie Ross,¹⁹ Holger J. Schünemann,^{19,21} Wojtek Wierciach,¹⁹ Yuan Zhang,¹⁹ and Yuqing Zhang¹⁹

Published prior to the availability of paediatric DOAC formulations

Differences between paediatrics/adults □ differences levels of risks for VTE

- Epidemiology of thrombosis
- Developing coagulation pathway in childhood
- Age dependent PK/PD
- Bleeding risk
- Obstacles of anticoagulant therapy



Choice of anticoagulation

- Patient comorbidities
- Drug interactions
- Clinician preference and experience
- Specifics of the therapy: costs, availability, formulation, ease of administration, monitoring

Thrombosis	Prevention	Treatment
Venous	<ul style="list-style-type: none"> • Central venous catheter • Critically ill • Trauma • Perioperative prophylaxis 	<ul style="list-style-type: none"> • Deep vein thrombosis and pulmonary embolism • Cerebral sinovenous thrombosis
Both	<ul style="list-style-type: none"> • Cardiac catheterization • Shunts (e.g., Fontan); stents • Hemodialysis • Extracorporeal membrane oxygenation • Cardiopulmonary bypass surgery • Ventricular assist devices 	<ul style="list-style-type: none"> • Cardiac thrombosis
Arterial	<ul style="list-style-type: none"> • Central arterial catheter • Mechanical heart valves • Dilated cardiomyopathy • Kawasaki's syndrome 	<ul style="list-style-type: none"> • Arterial thrombosis • Arterial ischemic stroke

Male C. Hamostaseologie,2022

- Individualized (preferences of the individual patient/family)
- Risks/benefits

Standard anticoagulants - LMWH or VKA (Warfarin)

- Unpredictable pharmacokinetic response
- Interactions with other drugs and foods
- Parenteral administration
- Need for monitoring

No anticoagulant was initially developed for paediatrics population.
Extrapolated from adults' studies

Caldewell A et al. Direct Oral anticoagulants for treatment of venous thromboembolism in children. Journal of Hospital Medicine. 2021

Standard anticoagulants

■ Low molecular weight heparin (LMWH)

- Selective activity on Factor Xa
- Efficacy similar to classic heparin
- Greater bioavailability – minimal monitoring
- Longer half-life, 2 daily subcutaneous administrations
- More sensitive and consistent anticoagulant effect
- Lower incidence and severity of bleeding

■ **Limitation**

Subcutaneous administration

- **Antidote**— Protamine sulfate

Only anticoagulant approved for Pediatrics
until June 2021

Standard anticoagulants

■ Low molecular weight heparin (LMWH)

- **Enoxaparin**
- Dalteparin
- Nadroparin
- Reviparin
- Tinzaparin

Drug	Therapeutic anticoagulation (for treatment of thrombosis)	Prophylaxis (for prevention of thrombosis)
Enoxaparin	<p>Preterm neonates: 2 mg/kg/dose subQ every 12 hours</p> <p>Term neonates: 1.5 to 1.7 mg/kg/dose subQ every 12 hours</p> <p>Infants ≥2 months, children, and adolescents: 1 mg/kg/dose subQ every 12 hours[¶]</p>	<p>Infants <2 months: 0.75 mg/kg/dose subQ every 12 hours</p> <p>Infants ≥2 months, children, and adolescents: 0.5 mg/kg/dose subQ every 12 hours</p>

Dose titration (for therapeutic anticoagulation only) [◇]		
Anti-factor Xa level	Dose titration	Time to repeat anti-factor Xa level
<0.35 units/mL	Increase dose by 25%	4 hours after next dose
0.35 to 0.49 units/mL	Increase dose by 10%	4 hours after next dose
0.5 to 1 unit/mL	Keep same dose	Repeat the next day (4 hours after dose) If stable, can go to weekly monitoring
1.1 to 1.5 units/mL	Decrease dose by 20%	Before next dose
1.6 to 2 units/mL	Hold dose for 3 hours, then decrease dose by 30%	Before next dose, then 4 hours after next dose
>2 units/mL	Hold all doses until anti-factor Xa is 0.5 units/mL, then decrease dose by 40%	Before next dose and every 12 hours until anti-factor Xa is <0.5 units/mL

Venous thrombosis and thromboembolism (VTE) in children: Treatment, prevention, and outcome - UpToDate

Standard anticoagulants

■ Unfractionated heparin (UFH)

- Initial therapy in some circumstances (kidney failure or considerable bleeding risks who require finely tuned titration and the ability to quickly turn the infusion on or off (eg, patients requiring multiple surgeries or other invasive procedures))
- Selective activity on Factor Xa
- **Limitation**
Intravenous administration
- **Antidote**— Protamine sulfate

Standard anticoagulants

Vitamin K antagonist (Warfarin)

- Oral Vitamin K Antagonist
- Inhibits the synthesis of vitamin K-dependent clotting factors - Prothrombin, factor VII, IX and X
- Indirect and prolonged action

Limitations

- Late start of action
- Very narrow therapeutic level, difficult to stabilize --> requires frequent monitoring
- Unpredictable and variable pharmacological response
- Multiple drug and food interactions

Reversal – vitamin K

Protocol for warfarin administration and adjustment to maintain INR between 2 and 3 for pediatric patients

1. Day 1 – If the baseline INR is 1.0 to 1.3, initial dose of warfarin is 0.2 mg/kg orally in a single dose*	
2. Days 2 to 4 – Adjust warfarin dose according to INR:	
INR 1.1 to 1.3	Give same dose as on day 1
INR 1.4 to 3.0	Give 50% of day 1 dose
INR 3.1 to 3.5	Give 25% of day 1 dose
INR >3.5	Hold warfarin until INR <3.5, then restart at 50% reduced dose
3. Maintenance dose – Adjust warfarin dose according to INR:	
INR 1.1 to 1.4	Increase dose by 20%
INR 1.5 to 1.9	Increase dose by 10%
INR 2.0 to 3.0	No change
INR 3.1 to 3.5	Decrease dose by 10%
INR >3.5	Hold warfarin until INR <3.5, then restart at 20% reduced dose

Venous thrombosis and thromboembolism (VTE) in children: Treatment, prevention, and outcome - UpToDate

Direct Oral Anticoagulants

- **Direct factor Xa inhibitor**
 - *Rivaroxaban* ☐ **2020 – peadiatric**
 - *Apixaban*
 - *Edoxaban*

- **Direct thrombin inhibitor**
 - *Dabigatran* ☐ **2020 – 2021 – peadiatric**

PEADIATRICS

Rivaroxaban - approved in EU, Canada, UK for acute treatment and prevention of VTE in peadiatric patients

Dabigatran - approved in EU and US FDA for acute treatment and secondary prevention of VTE in peadiatric patients ≥ 3 months old

DOAC : Advantages VS Disadvantages

Benefits

- Quick start of action
- Easy reversal
- Oral administration
- No need to monitor
- Does not depend on antithrombin
- Few drug and food interactions

Disadvantages

- High cost
- Bi/tridaily administration < therapeutic adherence?
- Antidotes (some DOAC)
- Antidotes not approved in Pediatrics
- Severe bleeding (very rare)

DOAC - Pharmacological Characteristics

- Linear pharmacokinetics and dose - dependent
- Rapidly absorbed GI tract (upper)
- Absorption is not altered by food
- Oral bioavailability 64%
- Maximum plasma concentration (C_{max}) occurs 1-2 hours after administration
- 10-14h half-life
- Plasma protein binding 40-60%
- Double elimination
 - 50% - Kidney
 - 50% - biliary excretion
- Metabolites in small amounts and without anticoagulant activity






DOAC - Clinical Trials (phase 3)

Received: 24 December 2019 | Accepted: 23 March 2020

DOI: 10.1111/jth.14813

ORIGINAL ARTICLE

Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation


Guy Young¹   | Anthonie W. A. Lensing² | Paul Monagle^{3,4} | Christoph Male⁵ | Kirstin Thelen² | Stefan Willmann² | Joseph S. Palumbo^{6,7} | Riten Kumar⁸ | Ildar Nurmeev⁹ | Kerry Hege¹⁰ | Fanny Bajolle¹¹ | Philip Connor¹² | Hélène L. Hooimeijer¹³ | Marcela Torres¹⁴ | Anthony K. C. Chan¹⁵  | Gili Kenet^{16,17} | Susanne Holzhauser¹⁸ | Amparo Santamaría¹⁹ | Pascal Amedro²⁰ | Jan Beyer-Westendorf²¹ | Ida Martinelli²²  | M. Patricia Massicotte²³ | William T. Smith²⁴ | Scott D. Berkowitz²⁴  | Stephan Schmidt²⁵ | Victoria Price²⁶ | Martin H. Prins²⁷ | Dagmar Kubitzka² | for the EINSTEIN-Jr. Phase 3 Investigators

Received: 11 December 2020 | Accepted: 19 February 2021

DOI: 10.1111/jth.15277

ORIGINAL ARTICLE

Pharmacokinetic modeling and simulation support for age- and weight-adjusted dosing of dabigatran etexilate in children with venous thromboembolism

Daniel Röshammar¹ | Fenglei Huang² | Manuela Albisetti³ | Lisa Bomgaars⁴ | Elizabeth Chalmers⁵ | Matteo Luciani⁶ | Jacqueline Halton⁷ | Lesley G. Mitchell⁸ | Martin Bergstrand¹ | Moustafa M. A. Ibrahim^{1,9} | David Joseph² | Igor Tartakovsky¹⁰ | Savion Gropper¹¹ | Martina Brueckmann^{10,12} | Leonardo R. Brandão^{13,14} 

REGULAR ARTICLE

 Check for updates


Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT)

Philip Connor,¹* Mayte Sánchez van Kammen,^{2*} Anthonie W. A. Lensing,³ Elizabeth Chalmers,⁴ Krisztján Kállay,⁵ Kerry Hege,⁶ Paolo Simoni,⁷ Tina Biss,⁸ Fanny Bajolle,⁹ Damien Bonnet,⁹ Sebastian Grunt,¹⁰ Riten Kumar,¹¹ Olga Luova,¹² Rukhmi Bhat,¹³ An Van Damme,¹⁴ Joseph Palumbo,¹⁵ Amparo Santamaría,¹⁶ Paola Saracco,¹⁷ Jeanette Payne,¹⁸ Susan Baird,¹⁹ Kamar Godder,²⁰ Veerle Labarque,²¹ Christoph Male,²² Ida Martinelli,²³ Michelle Morales Soto,²⁴ Jayashree Motwani,²⁵ Sanjay Shah,²⁶ Helene L. Hooimeijer,²⁷ Martin H. Prins,²⁸ Dagmar Kubitzka,² William T. Smith,²⁹ Scott D. Berkowitz,²⁹ Akos F. Pao,³ Madhurima Majumder,²⁸ Paul Monagle,^{30,31} and Jonathan M. Coutinho,² for the EINSTEIN-Jr Cerebral Venous Thrombosis trial investigators



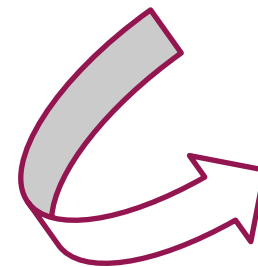
CLINICAL TRIALS AND OBSERVATIONS

Comment on Brandão et al, page 491

The phase 3 pediatric anticoagulant era

Neil A. Goldenberg¹ and Brian R. Branchford² | ¹Johns Hopkins University School of Medicine; ²University of Colorado School of Medicine

In this issue of Blood, Brandão et al report the findings of an open-label, single-arm, phase 3 trial of the direct oral thrombin inhibitor dabigatran for extended secondary thromboprophylaxis in children with a history of venous thromboembolism (VTE) (ClinicalTrials.gov Identifier: NCT02197416).¹



DOAC with potential advantages over traditional therapies several trials of DOAC for VTE management in paediatric patients have been completed.

DOAC - Clinical Trials (phase 3)

	Prevention of VTEs	Prevention of cardiac/arterial TEs	Treatment of VTEs
Rivaroxaban	-	Post Fontan surgery ^a (rivaroxaban vs. aspirin)	Acute VTEs ^b (rivaroxaban vs. SOC)
Dabigatran	-	-	<ul style="list-style-type: none"> • Acute VTEs^b (dabigatran vs. SOC) • Extended secondary prevention^b (dabigatran single arm)
Apixaban	Acute leukemia/lymphoma, asparaginase treatment, with central venous catheter (apixaban vs. placebo)	Various cardiac diseases (apixaban vs. SOC)	Acute VTEs (apixaban vs. SOC)
Edoxaban	-	Various cardiac diseases (edoxaban vs. SOC)	Acute VTEs (edoxaban vs. SOC)

Results not published

Other DOAC
Various pediatric clinical scenarios

Male C. Hamostaseologie, 2022

DOAC – efficacy - safety (DOAC vs SOC)

Thrombus resolution

	Rivaroxaban, EINSTEIN-Jr trial ¹⁸ n = 500, 6 m – 18 y	Dabigatran, DIVERSITY trial ¹⁹ n = 267, 3 m – 18 y	Dabigatran, secondary prevention ²⁰
Recurrent venous thromboembolism	4* (1%) of 335 1-3%	7 (4%) of 177 4-8%	2 (1%) of 203
Bleeding events	Not reported 3-2%	38 (22%) of 176 2-2%	40 (20%) of 203
Minor	Not reported	33 (19%) of 176	37 (18%) of 203
Clinically relevant non-major	10 (3%) of 329	2 (1%) of 176	2 (1%) of 203
Major	0 (0%) of 329	4 (2%) of 176	3 (1%) of 203
All-cause death	1† (<1%) of 335 ~0-0%	0 (0%) of 176 0-0%	0 (0%) of 203

Data are proportion of treatment population with event (n [%] of N). *Non-catheter-related venous thromboembolism. †The death was due to cancer progression and not considered treatment related.

Safety data from paediatric phase 3 clinical trials of rivaroxaban and dabigatran

EDOXABAN Hokusai Venous Thromboembolism Pediatrics Study

(n= 274, 38S – 18 A) – finished dez/2021

Pediatric Hematology Unit – HSM - CHULN

Jaffrau J, Young G . The Lancet, 2022

DOAC - Dose

Solution and pills

ORAL

Solution, soluble granules and tablets

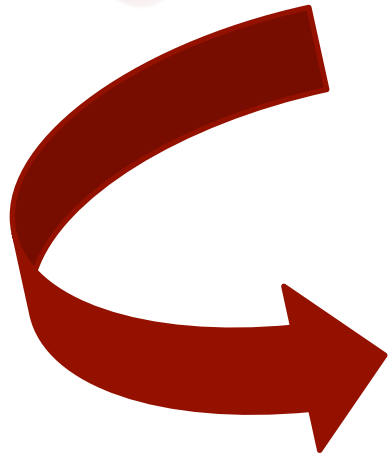
	Dose and frequency for paediatric patients	Dose and frequency for adult patients
Rivaroxaban*		
Venous thromboembolism treatment (primary or extended)	0.8 mg three times a day for patients 2-6 kg to <3 kg bodyweight; 0.9 mg three times a day for patients 3 kg to <4 kg bodyweight; 1.1 mg three times a day for patients 4 kg to <5 kg bodyweight; 1.6 mg three times a day for patients 5 kg to <7 kg bodyweight; 1.8 mg three times a day for patients 7 kg to <8 kg bodyweight; 2.4 mg three times a day for patients 8 kg to <9 kg bodyweight; 2.8 mg three times a day for patients 9 kg to <10 kg bodyweight; 3 mg three times a day for patients 10 kg to <12 kg bodyweight; 5 mg twice a day for patients 12 kg to <30 kg bodyweight; 15 mg once a day for patients 30 kg to <50 kg bodyweight; 20 mg once a day for >50 kg bodyweight	15 mg twice a day for 21 days, then 20 mg once a day
Secondary venous thromboembolism prevention or stroke or embolism prevention	0.8 mg three times a day for patients 2-6 kg to <3 kg bodyweight; 0.9 mg three times a day for patients 3 kg to <4 kg bodyweight; 1.4 mg three times a day for patients 4 kg to <5 kg bodyweight; 1.6 mg three times a day for patients 5 kg to <7 kg bodyweight; 1.8 mg three times a day for patients 7 kg to <8 kg bodyweight; 2.4 mg three times a day for patients 8 kg to <9 kg bodyweight; 2.8 mg three times a day for patients 9 kg to <10 kg bodyweight; 3 mg three times a day for patients 10 kg to <12 kg bodyweight; 5 mg twice a day for patients 12 kg to <30 kg bodyweight; 15 mg once a day for patients 30 kg to <50 kg bodyweight; 20 mg once a day for ≥50 kg bodyweight	20 mg once a day
Primary thromboprophylaxis	Unknown	10 mg once a day
Apixaban		
Venous thromboembolism treatment	Under investigation	10 mg twice a day for 7 days, then 5 mg twice a day
Stroke or embolism prevention	Under investigation	5 mg twice a day
Primary thromboprophylaxis	Under investigation	2.5 mg twice a day
Edoxaban		
Venous thromboembolism treatment	Under investigation	60 mg once a day after 5–10 days of parenteral anticoagulant
Stroke or embolism prevention	Unknown	60 mg once a day
Dabigatran* (oral capsules)		
Venous thromboembolism treatment (capsules):	Age 8 years to <18 years: 75 mg twice a day for patients 11 kg to <16 kg bodyweight; 110 mg twice a day for patients 16 kg to <26 kg bodyweight; 150 mg twice a day for patients 26 kg to <41 kg bodyweight; 185 mg twice a day for patients 41 kg to <61 kg bodyweight; 220 mg twice a day for patients 61 kg to <81 kg bodyweight; 260 mg twice a day for patients ≥81 kg bodyweight	150 mg twice a day
Venous thromboembolism treatment (oral pellets for liquid)	Various dosing for age 3 months to <12 years†	..
Secondary venous thromboembolism prevention or stroke or embolism prevention	Same as venous thromboembolism treatment	150 mg twice a day
Primary thromboprophylaxis	Unknown	220 mg once a day

Recommendations are per full prescribing information for patients with normal creatinine clearance. *After 5 days of initial parenteral anticoagulation in paediatrics and available as granules for oral suspension where approved. †Oral pellets have been approved for use in children who cannot swallow capsules. Full age-based and weight-based dosing are available in the appendix (pp 1-2).

Table 1: Dosing recommendations for direct oral anticoagulants for paediatric and adult patients by indication

DOAC: Bleeding

- Minimal bleeding (2 -3%) □ Stop DOAC
- Moderate bleeding (20%) □ Stop DOAC + DDAVP (desmopressin)
- Severe bleeding (rare) □ Stop DOAC + DDAVP + PCC (prothrombin complex concentrate)



Antidotes (life-threatening bleeding)

- Idarucizumab (US FDA approved – 2015) – Monoclonal antibody against dabigatran
- Andexanet alfa (US FDA approved - 2018) – recombinant form of FXa that sequesters FXa - rivoraxaban, apixaban and edoxaban

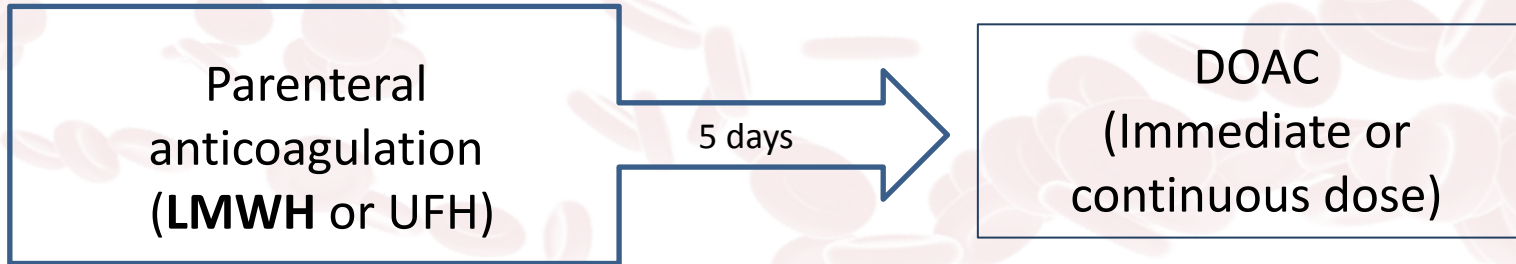
NOT APPROVED FOR PEADIATRICS

DOAC - Contraindications

- Severe bleeding risk
- Pregnancy/breastfeeding
- BMI > 40/m² or P > 120Kg
- Cr Cl < 30ml/min (renal impairment)
- Moderate/severe hepatic impairment
- Neoplasms (bleeding risk)
- Antiphospholipid syndrome

- Countries without approval

DOAC - Dose



DOAC – previous laboratory evaluation

Blood count
PT, aPTT
kidney function
Liver function (RVB)

Missing

Paediatric Anticoagulation Recommendations

Initial

- Initial parenteral anticoagulation for 5 – 10 days (LMWH (+++) or UFH - parenteral) (G2C)

Subsequent

- Adolescents (> 12 years old) – DOAC (eg dabigatran or rivoraxaban) (G2B)
- Children 2 years and < 12 years – LMWH or DOAC (eg dabigatran or rivoraxaban)
- Children < 2 years – LMWH (G2C)
- **Risk groups:** active-cancer (LMWH or DOAC - teenagers)
nephrotic syndrome (LMWH or VKA)
impaired kidney function (VKA)
heavy menstrual bleeding (VKA)
pregnancy (LMWH)
SLE (LMWH or VKA)
heparin-induced thrombocytopenia (VKA)
Countries: DOAC off label only in adolescents > 50kg with normal renal function

Duration of anticoagulation (recommendations)

JAMA | **Original Investigation**

Effect of Anticoagulant Therapy for 6 Weeks vs 3 Months on Recurrence and Bleeding Events in Patients Younger Than 21 Years of Age With Provoked Venous Thromboembolism
The Kids-DOTT Randomized Clinical Trial

VTE with reversible risk factor (more frequent in paediatrics) eg CVC (+++), surgery, trauma, infection, immobilization, neoplasia and oral contraceptive (estrogen)

- Anticoagulation: 6 weeks - 3 months (G2C): LMWH or UFH LMWH, VKA or DOAC

VTE with no identified risk factor (rare in paediatrics)

- Anticoagulation: 6 – 12 months (G2C): LMWH or UFH LMWH, VKA or DOAC
- Recurrent unprovoked VTE Definitive anticoagulation

EP (Pulmonary embolism)

- Nonsevere PE and reversible risk factor: anticoagulation 6 weeks -3 months and
- No risk factor - G2C anticoagulation 6 – 12 months. Individualized thrombolytic therapy.

Recurrent VTE, SLE, combined thrombophilia, life-threatening VTE

- Definitive anticoagulation (VKA or DOAC). SLE - DOAC not indicated

Duration of anticoagulation (recommendations)

Cerebral venous thrombosis

- Acute phase treatment of CVT is similar to that for adults, but the evidence is weaker since there are no large randomized trials in this age group
- Provoked CVT associated with a transient risk factor – 3 to 6 months.
- Unprovoked CVT - 6 to 12 months.
- For patients with recurrent CVT, VTE after CVT, or a first CVT with a severe thrombophilia (homozygous prothrombin gene *G20210A* variant, homozygous factor V Leiden genetic variant, deficiencies of protein C, protein S, or antithrombin, combined thrombophilia defects, or antiphospholipid syndrome) Definitive anticoagulation.

Neonatal Thrombosis – only LMWH

- Non-asymptomatic thrombosis – conservative management or LMWH (6w to 3m)
- Symptomatic thrombosis - Provoked VTE (LMWH 6w to 3m) and unprovoked VTE (LMWH 3m-6m)

Anticoagulation – Prophylaxis

Primary thromboprophylaxis – it is not consensual if there is no prior VTE

- Acute prophylaxis (hospitalized + risk factors) – LMWH (**non-approved DOAC**)
- Long-term prophylaxis - VKA or DOAC (except SLE and mechanical heart valves)
- Duration – Depends on persistence and number of risk factors

Secondary prevention - Prior episode of VTE or recurrent VTE risk factor long-term thromboprophylaxis

- Chronic conditions: long –term parenteral nutrition, hemodialysis, certain forms of heart disease, nephrotic syndrome, inflammatory bowel disease, SLE

Key messages

- Anticoagulant choice is scarce in children for the treatment or prevention of thrombosis.
- DOAC - change the field of paediatric anticoagulation with their oral formulations and absence of drug monitoring.
- Rivoraxaban and dabigatran - approved for paediatric ages
- Results from ongoing and completed clinical trials evaluating the efficacy and safety of apixaban and edoxaban in children, including trials specifically for children with heart disease or acute lymphoblastic leukaemia, could lead to additional anticoagulant choices.

- Challenges in the next clinical trials - Term neonate and preterm neonate
 - Prevention of VTE by CVC
 - Cancer
 - Adolescent + associated menstrual bleeding with anticoagulant therapy
 - Adolescent with recurrent DVT

- Antidotes not yet approved in pediatrics

New DOAC are under investigation ... FXI/XII inhibitor



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Anticoagulant treatment of paediatric patients

Thank You

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