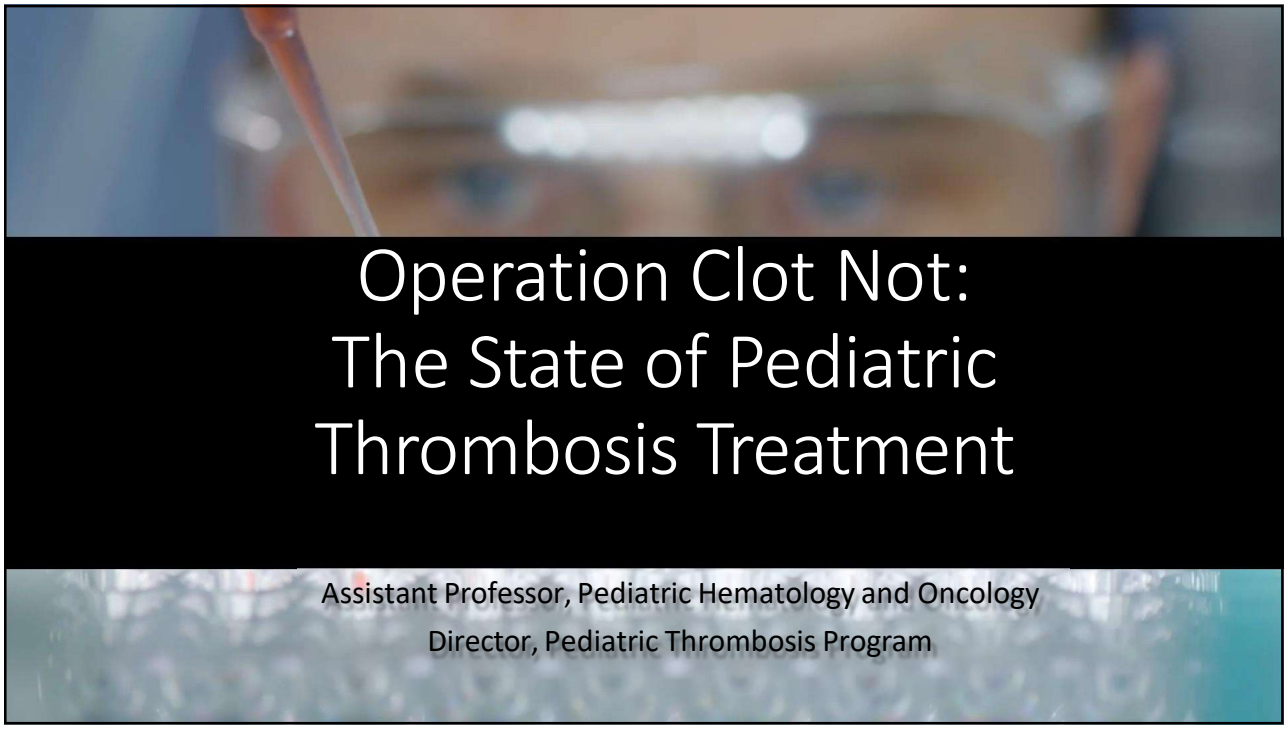


Operation Clot Not: The State of Pediatric Thrombosis Treatment

Assistant Professor, Pediatric Hematology and Oncology
Director, Pediatric Thrombosis Program

1

Objectives

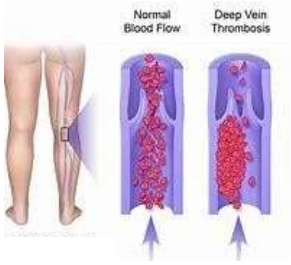
At the completion of this lecture, participants should be able to:

- Recognize risk factors, presentation and diagnosis of venous thromboembolism in children
- Understand the evolution of pediatric thrombosis management
- Recognize contraindications and side effects of anticoagulant therapies in children
- Recognize limitations of direct oral anticoagulant (DOAC) use in children

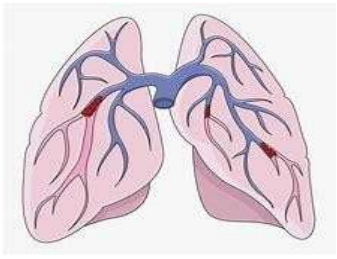
Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

2

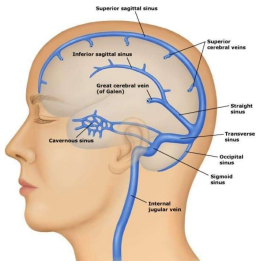
What is venous thromboembolism (VTE)?



Deep Vein Thrombosis (DVT)



Pulmonary Embolism (PE)



Cerebral Sinus Venous Thrombosis (CSVT)

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

3

Pathophysiology

Stasis

Virchow's Triad

Endothelial Injury

Hypercoagulability

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

4

Risk Factors

- Infection
- Cardiac disease
- Malignancy
- Immobility
- Surgery
- Estrogen

Table 2. Prothrombotic Risk Factors in Adolescent VTE.

Risk Factors	References
Anatomic abnormalities	8-11
Inherited thrombophilia	12-14
Antiphospholipid antibody syndrome	15-18
Cancer	19-21
Inflammatory bowel disease	22-25
Trauma	26-29
Hormonal therapy	30-38
Pregnancy	39-40
Iron deficiency anemia	41-42
Obesity	43-47
Sedentary causes	48-51
Sickle cell disease	52-54

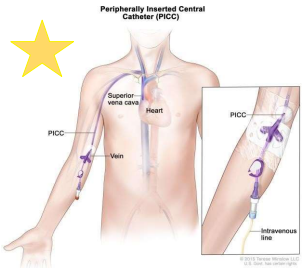
Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

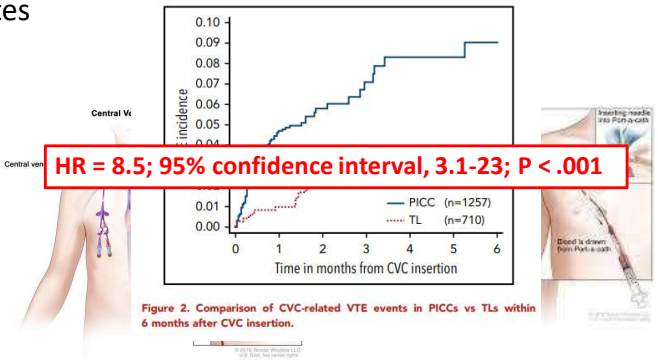
UAB MEDICINE

5

Risk Factors

- The most common provoking factor in pediatrics is the presence of a central venous catheter (CVC)
  - ~90% of VTE in neonates
  - 60% in older children





HR = 8.5; 95% confidence interval, 3.1-23; P < .001

Figure 2. Comparison of CVC-related VTE events in PICCs vs TLs within 6 months after CVC insertion.

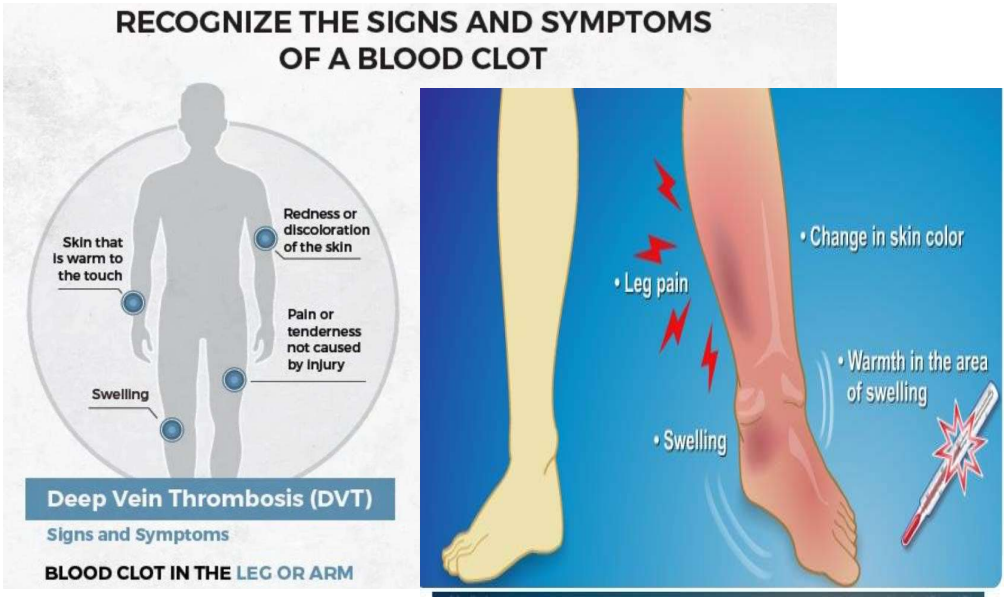
Jaffray J, Witmer C, O'Brien SH, Diaz R, Ji L, Krava E, Young G. Peripherally inserted central catheters lead to a high risk of venous thromboembolism in children. Blood. 2020 Jan 16;135(3):220-226. doi: 10.1182/blood.2019002

Images: Cancer.gov

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

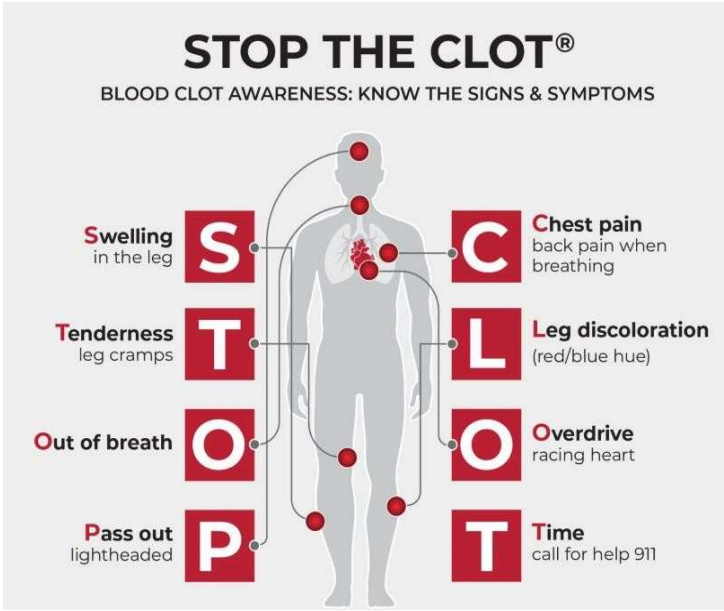
6



National Blood Clot Alliance stoptheclot.org @stoptheclot

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

7



National Blood Clot Alliance stoptheclot.org @stoptheclot

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

8

Diagnosis

*Depends on location of thrombosis

- Doppler ultrasound
  - Of affected extremity/area
    - No compressibility of the vein with or without visible intraluminal thrombus
- Chest CT angiogram with contrast
- CT venogram
- MR venogram

9

Diagnostic Workup

- Labs to measure AT (not FOR) diagnosis
  - HISTORY!
  - CBC
  - Coagulation Studies
    - PT/PTT
    - Fibrinogen
    - D-Dimer
    - Factor VIII
  - Creatinine
    - Prior to starting low molecular weight heparin (LMWH)
  - Pregnancy Test
    - Prior to starting warfarin, direct oral anticoagulants (DOACs)
  - **Thrombophilia Evaluation**

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

10

TREATMENT

11

Pediatric VTE Treatment Guidelines-Duration

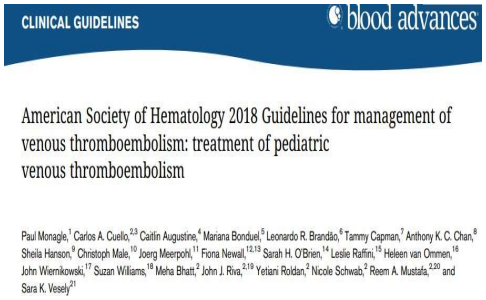
CHEST Supplement

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. Ichord, 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] Caitlin Augustine,[4] Mariana Bonduel,[5] Leonardo R. Brandão,[6] Tammy Capman,[7] Anthony K. C. Chan,[8] Sheila Hanson,[9] Christoph Male,[10] Joerg Meerpohl,[11] Fiona Newall,[12,13] Sarah H. O'Brien,[14] Leslie Raffini,[15] Heleen van Ommen,[16] John Wiernikowski,[17] Suzan Williams,[18] Meha Bhatt,[2] John J. Riva,[2,19] Yetiani Roldan,[2] Nicole Schwab,[2] Reem A. Mustafa,[2,20] and Sara K. Vesely[21]

- suggests using anticoagulation for up to **3 months** rather than anticoagulation for longer than 3 months in pediatric patients with **provoked DVT or PE**
- suggests using anticoagulation for **6-12 months**…in pediatric patients with **unprovoked DVT or PE**

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

12

13

Kids-DOTT-Inclusion/Exclusion Criteria

eTable 1. Inclusion and exclusion criteria

Inclusion Criteria

1. Children (birth to <21 years of age) with radiologically-confirmed acute deep venous thrombosis in the past 30 days
2. In the opinion of the investigator, the venous thrombosis was a provoked (i.e., non-spontaneous) event (e.g.: hospitalization; Central venous catheterization; infection; dehydration; surgery; trauma; immobility; use of estrogen-containing oral contraceptive pills; flare of autoimmune/rheumatologic condition).

Exclusion Criteria

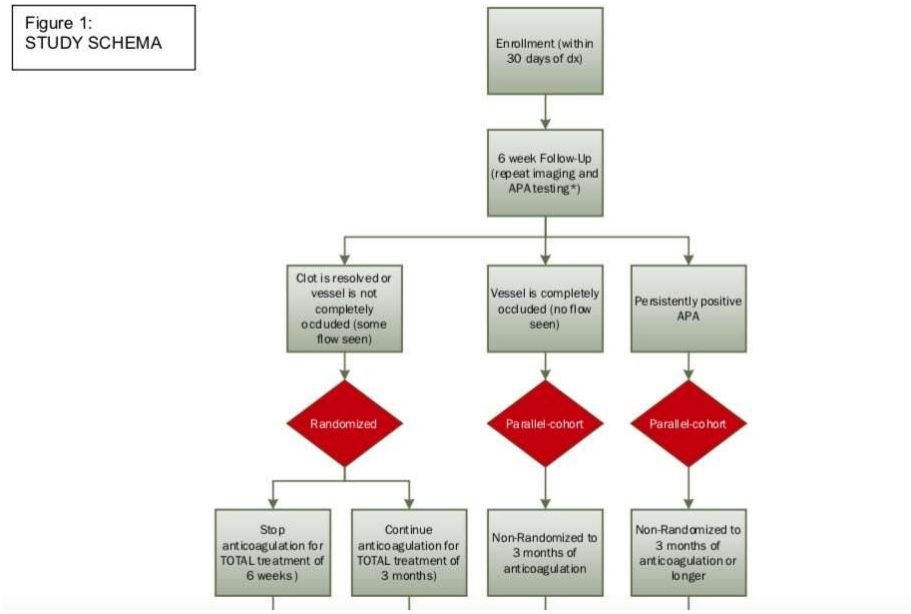
1. Prior episode of VTE
2. Malignancy that, in the opinion of the treating oncologist, is not in remission (note: remission may exist on or off anti-neoplastic therapy)
3. Systemic lupus erythematosus
4. Pulmonary embolism that is not accompanied by DVT or is more proximal than segmental branches of the pulmonary artery
5. Use of, or intent to use, thrombolytic therapy
6. Chronic anticoagulant at prophylactic dosing is being or will be administered beyond 6 months post VTE diagnosis
7. Moderate/severe anticoagulant deficiency (defined by any one of the following):
   a. protein C <20 IU/dL if patient is ≥3 months of age, or protein C below lower limit of detection if patient is <3 months of age;
   b. antithrombin <30 IU/dL if patient is ≥3 months of age, or antithrombin below lower limit of detection if patient is <3 months of age;
   c. protein S (free antigen or activity) <20 IU/dL.

NOTE regarding pregnancy and eligibility:

A patient who develops a DVT while pregnant who has no other provoking factor beyond the pregnancy will remain ineligible for this study.

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders | UAB MEDICINE

14

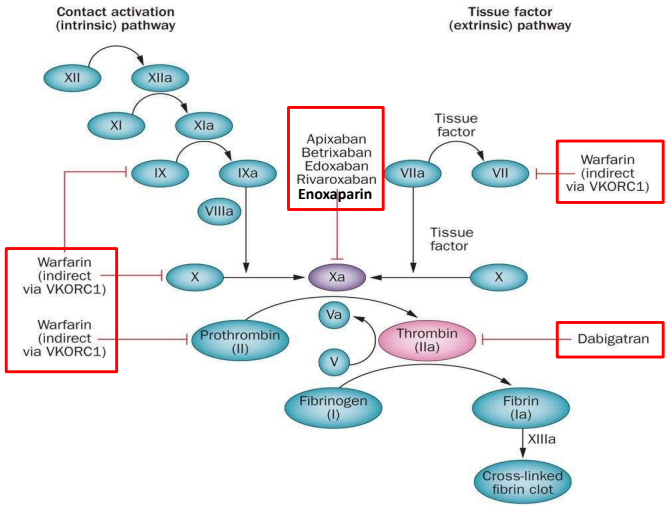


Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

15

Anticoagulant Mechanism of Action



Sabir, I., Khavandi, K., Brownrigg, J. *et al.* Oral anticoagulants for Asian patients with atrial fibrillation. *Nat Rev Cardiol* **11**, 290–303 (2014). https://doi.org/10.1038/nrcardio.2014.22

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

16

Contraindications to Anticoagulation

Absolute

- Active bleeding
- Severe bleeding diathesis
- Recent, planned, or emergency high bleeding-risk surgery/procedure
- Major trauma
- Recent history of intracranial hemorrhage

Relative

- Recurrent bleeding from multiple gastrointestinal telangiectasias
- Intracranial or spinal tumors
- Large abdominal aortic aneurysm with concurrent severe hypertension
- Stable aortic dissection
- Recent, planned, or emergent low bleeding-risk surgery/procedure

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

17

Standard of Care Treatment

Low Molecular Weight Heparin

Enoxaparin →

Dalteparin

8.4 Pediatric Use

Safety and effectiveness of Lovenox in pediatric patients have not been established.

Lovenox is not approved for use in neonates or infants.

Vitamin K Antagonist

Warfarin

8.4 Pediatric Use

Adequate and well-controlled studies with COUMADIN have not been conducted in any pediatric population, and the optimum dosing, safety, and efficacy in pediatric patients is unknown. Pediatric use of COUMADIN is based on adult data and recommendations, and available limited pediatric data from observational studies and patient registries. Pediatric

18

Challenges

INJECTIONS

DRUG MONITORING

DIET AND FOOD INTERACTIONS

FREQUENT LAB DRAWS

19

Enoxaparin-Dosing

Route of Administration: Subcutaneous

Indication(s): VTE treatment and prevention

Dosage Forms:

- Vials: 300 mg/3 mL
- Prefilled Syringes: 30, 40, 60, 80, 100, 120 or150 mg

How to monitor: Anti-Xa, draw 4-6 hours post dose

Renally cleared

Age	Treatment Dosing	Prophylaxis
Premature less than 1 month	2mg/kg/dose subQ every 12 hours	0.75mg/kg/dose subQ every 12 hours
Full term less than 1 month	1.7mg/kg/dose subQ every 12 hours	0.75mg/kg/dose subQ every 12 hours
1 to 2 months	1.5mg/kg/dose subQ every 12 hours	0.75mg/kg/dose subQ every 12 hours
2 months to less than 14 years	1mg/kg/dose subQ every 12 hours (Max: 150mg/dose)	0.5mg/kg/dose subQ every 12 hours
Greater than or equal to 14 years:	1mg/kg/dose (Max: 150mg/dose) subcutaneous every 12 hours - or- 1.5mg/kg/dose (Max: 225mg/dose) subcutaneous every 24 hours	0.5mg/kg/dose (Max: 30mg/dose) subcutaneous every 12 hours - or- 40mg subcutaneous every 24 hours (*40mg twice daily in obese patients with BMI ≥ 40 kg/m²)

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

20

Enoxaparin-Monitoring

***Enoxaparin Dosing Adjustment Recommendations for TWICE Daily Dosing:** Goal: 0.5-1

Anti-Xa Level (units/mL)	Recommended Dosage Adjustment	Time to Repeat Anti-Xa Level
Less than 0.35	Increase dose by 25%	4 hours after next dose
0.35 – 0.49	Increase dose by 10%	4 hours after next dose
0.5 – 1	Continue current dose	Next day, then 1 week, then monthly
1.1 – 1.5	Decrease dose by 20%	4 hours after next dose
1.6 – 2	Hold dose for 3 hours and decrease dose by 30%	Before next dose, then 4 hours after the next dose
Greater than 2	Hold all doses until anti-Xa is 0.5 units/mL, then decrease by 40%	Before next dose, every 12 hours until anti-Xa less than 0.5

***Please consider dosage formulation when adjusting doses to round to easily measurable doses on prefilled syringes if dose is 30mg or greater. Consult pharmacy for any questions regarding available formulations.**

Massicotte MP, Adams M, Leaker M et al. A nomogram to establish therapeutic levels of the low molecular weight heparin (LMWH), clivarine in children requiring treatment for venous thromboembolism (VTE) Thromb Haemostas. 1997;78(suppl):282.

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

21

Enoxaparin-Reversal

Time since last dose of LMWH	Reversal Agent	Dose	Example
Less than 8 hours	Protamine (1 mg neutralizes 1 unit of LMWH)	DOSE = 1 mg of protamine IV for every mg of enoxaparin (Max dose = 50mg)	LMWH 40mg last given 4 hours ago = 40 mg protamine IV
8 to 12 hours	Protamine (1 mg neutralizes 1 unit of LMWH)	DOSE = 0.5 mg of protamine IV for every mg of enoxaparin (Max dose = 50mg)	LMWH 40mg last given 9 hours ago = 20 mg protamine IV
Greater than 12 hours	Protamine unlikely to be necessary		

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

22

Unfractionated Heparin (UFH)-Dosing

Age	Initial Bolus Dose	Starting Infusion Rate
Less than 1 year	**75 units/kg/dose (Max: 8,000 units/dose)**	**28 units/kg/hr**
1 to 12 years		**20 units/kg/hr**
Greater than 12 years		**18 units/kg/hr**

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

23

UFH-Monitoring

Goal: 0.3-0.7

Anti-Xa Level (units/mL)	Recommended Dosage Adjustment
Less than 0.2	Bolus 75 units/kg. Increase drip by 4 units/kg/hr
0.2 – 0.29	Bolus 40 units/kg. Increase drip by 2 units/kg/hr
0.3 – 0.7	No change
0.71 – 0.8	Decrease drip by 2 units/kg/hr
0.81 – 0.99	Hold drip for 1 hour. Then decrease drip by 2 units/kg/hr
Greater than or equal to 1	Hold drip for 1 hour. Then decrease drip by 3 units/kg/hr

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

24

UFH-Monitoring Goal: 1.5-2.5x baseline

aPTT (seconds)	Recommended Dosage Adjustment
Less than 50	Bolus 50 units/kg Increase drip by 10%
50 – 59	Increase drip by 10%
60 – 85	No change
86 – 95	Decrease drip by 10%
96 – 120	Hold drip for 30 minutes + Decrease drip by 10%
Greater than 120	Hold drip for 1 hour + Decrease drip by 15%

aPTT=Activated partial thromboplastin time

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

25

UFH-Reversal

Time since last dose of UFH	Reversal Agent	Dose	Example
Less than 1 hour	Protamine (1 mg neutralizes 100 units of UFH)	DOSE in mg of protamine = UFH units infused over last 2 hours divided by 100 (Max dose = 50mg)	UFH infused in last 2 hours = 3000 units / 100 = 30 mg protamine IV
Greater than 1 hour	Protamine (1 mg neutralizes 100 units of UFH)	DOSE in mg of protamine = UFH units infused over last 2 hours divided by 200 (Max dose = 50mg)	UFH infused in last 2 hours = 3000 units / 200 = 15 mg protamine IV

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

26

Heparin Induced Thrombocytopenia (HIT)

- Severe complication
- Can happen in patients after exposed to heparin products
  - Caused by antibodies that recognize complexes of platelet factor 4 and heparin
- Signs
  - Thrombocytopenia (typically day 5-7)
  - Thrombosis (arterial and venous)
- Clinical diagnosis
- Treatment: DISCONTINUE ALL HEPARIN!

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

27

Fondaparinux-Dosing

- Pediatric dosing
  - Treatment
    - 0.1 mg/kg SubQ once daily
- Adult dosing
  - Treatment
    - < 50kg: 5 mg SubQ once daily
    - 50-100 kg: 7.5 mg SubQ once daily
    - >100 kg: 10mg once SubQ daily
- Prophylaxis
  - 2.5 mg SubQ once daily

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders UAB MEDICINE

28

Direct Thrombin Inhibitors

- Bivalirudin
- Argatroban

29

Bivalirudin

- Dosing
  - Continuous infusion of 0.3 mg/kg/hr
- Monitoring
  - aPTT = 1.5 to 3 times initial baseline value per package insert
  - COA recommendations

Patient Risk	Goal aPTT:
High bleeding risk (fresh post op, open chest, ICH)	aPTT 50 - 70 Seconds
Standard Risk	aPTT 60 - 80 Seconds
High Clot Risk (Hisotry of pump/circuit interventions, recurrent fibrin deposits)	aPTT 70 - 90 Seconds
Other	Specify in order

30

Argatroban

- Dosing
  - 0.75 mcg/kg/minute
- Monitoring
  - aPTT = 1.5 to 3 times initial baseline value

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

31

Oral Anticoagulants

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

32

Warfarin-Dosing

Age	Initial Treatment Dosing
All ages	0.1 to 0.2 mg/kg/dose once daily Max: 10 mg/dose

33

Warfarin-Bridging

- The use of parenteral anticoagulant for a period when International Normalized Ratio (INR) is not therapeutic or during interruption of warfarin therapy (i.e., surgery)
- Shouldn't be started alone for VTE treatment
- Warfarin should be continued along with parenteral anticoagulant until INR has remained ≥ 2 for at least 2 days (duration of overlap is typically 4 to 5 days).

34

Warfarin-Monitoring

- INR
- Goal depends on indication for anticoagulation:

Typical Goal: 2-3

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

35

Warfarin-Reversal

INR	Clinical Setting	Intervention	Inpatient	Outpatient
Supratherapeutic, but <5	No bleeding or no significant risk of bleeding	Lower or omit next warfarin dose(s) and reduce subsequent dose(s).	Recheck daily	Recheck within 2 weeks
5 - 9.9	No bleeding or no significant risk of bleeding	Verify MD has been notified. • Hold warfarin until INR therapeutic, then reduce subsequent dose(s) • Consider Vitamin K* PO	Recheck daily	Recheck within 1 week.
5 – 9.9	With bleeding	Verify MD has been notified. • Hold warfarin • Vitamin K* PO	Recheck daily or more often	Recheck 5-7 days with CBC or per MD plan.
≥10	With or without bleeding and/or low-moderate risk of bleeding	Verify MD has been notified. • Hold warfarin until INR therapeutic, then reduce subsequent dose(s). • Vitamin K* PO	Recheck daily or more often	Recheck following business day or per MD plan.
Surgery/procedure requiring emergent warfarin reversal with INR >2 **Rapid Reversal**	Bleeding or high risk for bleeding for surgery/procedure	• Hold warfarin • Consider Vitamin K* +/- FFP • Consider Vitamin K* IV + KCentra** (4-factor PCC) if surgery or procedure within 24 hours. (KCentra** dose dependent on INR and patient weight)	Recheck INR 30 minutes after KCentra** administration. Check INR every 6hrs for 24hrs.	
Severe, life-threatening bleed at ANY INR **Rapid Reversal**	Significant bleeding	• Hold warfarin • Vitamin K* 10mg IV + KCentra** (4-factor PCC) (KCentra** dose dependent on INR and patient weight. Give concurrently with vitamin K*)	Recheck INR 30 minutes after KCentra** administration. Check INR every 6hrs for 24hrs.	

Children's of Alabama | Alabama Center for Childhood Cancer and Blood Disorders

UAB MEDICINE

36

Direct Oral Anticoagulant (DOAC)

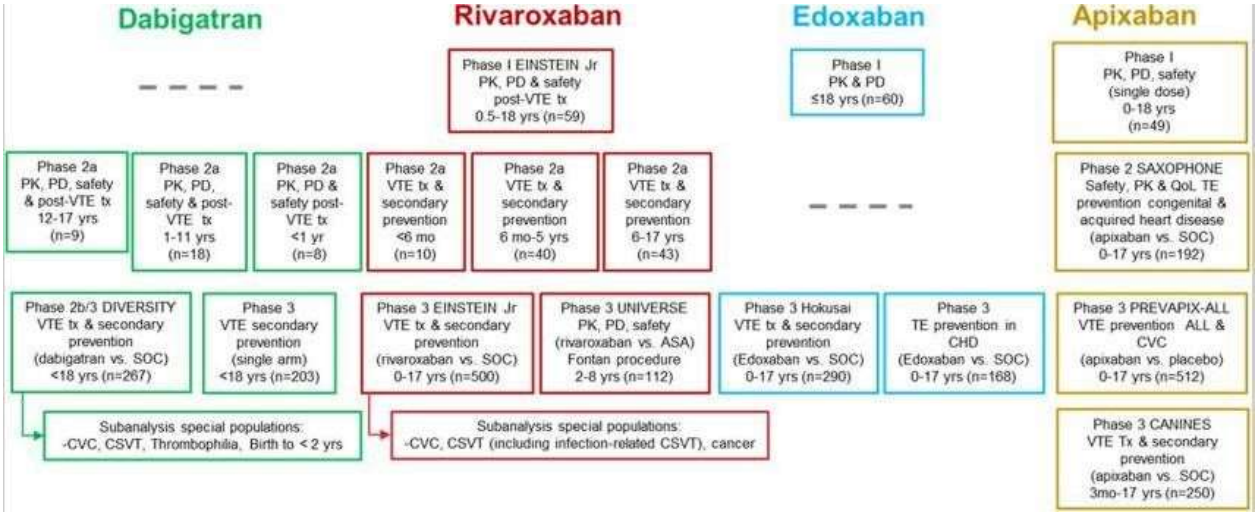
37

DOACs-Benefits

- Wide therapeutic window
  - No laboratory monitoring recommended
- No to minimal dietary restrictions
- Not dependent on antithrombin for therapeutic effect
- Less drug interactions
- No need for bridging due to rapid onset
- Low risk of bleeding

38

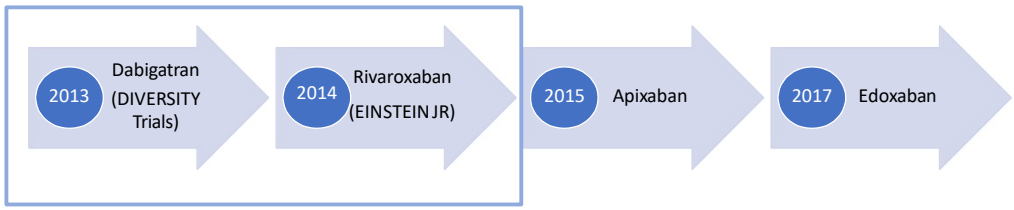
Overview of DOAC Trials



Betensky M, Monagle P, Male C, Goldenberg NA. What did we learn (and did not learn) from the pediatric direct oral anticoagulant trials, and how might we better design pediatric anticoagulant trials in the future? Res Pract Thromb Haemost. 2023 Mar 30;7(3):100140. doi: 10.1016/j.rpth.2023.100140. PMID: 37168398; PMCID: PMC10165148.

39

DOAC Trials



40

Dabigatran- DIVERSITY Trial

Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial

Jacqueline Halton, Leonardo R Brandão, Matteo Luciani, Lisa Bomgaars , Elizabeth Chalmers, Lesley G Mitchell, Ildar Nurmeev, Anjali Sharathkumar, Pavel Svirin, Kirill Gorbatikov, Igor Tartakovsky, Monika Simetzberger, Fenglei Huang, Zhichao Sun, Jörg Kreuzer, Savion Gropper, Paul Reilly, Martina Brueckmann, Manuela Albisetti on behalf of the DIVERSITY Trial Investigators

Savion Gropper,[13] Martina Brueckmann,[13,18] and Matteo Luciani,[19] on behalf of the DIVERSITY Study Investigators

[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Hematology Department, University Children's Hospital, Zürich, Switzerland; [3]Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada; [4]Department of Pediatrics, Texas Children's Cancer and Hematology Centers, Baylor College of Medicine, Houston, TX; [5]Royal Hospital for Children, Glasgow, Scotland, United Kingdom; [6]Department of Pediatrics, University of Alberta, Edmonton, AB, Canada; [7]Pediatric Hospital, Republic of Tatarstan, Kazan Medical University, Kazan, Russian Federation; [8]Pediatric Hematology Department, Municipal Children's Hospital "Morozovskaya," Moscow, Russian Federation; [9]Pediatric Hematology/Oncology Department, University Hospital Ostrava, Ostrava, Czech Republic; [10]Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [11]Pediatric Hematology Department, University Hospital Brno, Brno, Czech Republic; [12]Masaryk University, Brno, Czech Republic; [13]Therapeutic Area Cardiometabolic Medicine, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [14]Department of Clinical Development, Boehringer Ingelheim RCV GmbH & Co KG, Vienna, Austria; [15]Translational Medicine and Clinical Pharmacology and [16]Biostatistics and Data Sciences, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT; [17]Boehringer Ingelheim Singapore Pte Ltd, Singapore; [18]Faculty of Medicine Mannheim of the University of Heidelberg, Mannheim, Germany; and [19]Pediatric Hematology/Oncology Department, Pediatric Hospital Bambino Gesù, Rome, Italy

- Ages 0-17 years
- Compared dabigatran to standard of care (SOC) after 5-21 days of a parenteral anticoagulant
- 267 children enrolled
  - Dabigatran (177), SOC (90)
- **Dabigatran non-inferior to SOC for thrombus resolution, recurrent VTE and VTE related death without increased bleeding risk**

Halton J, Brandão LR, Luciani M, Bomgaars L, Chalmers E, Mitchell LG, Nurmeev I, Sharathkumar A, Svirin P, Gorbatikov K, Tartakovsky I, Simetzberger M, Huang F, Sun Z, Kreuzer J, Gropper S, Reilly P, Brueckmann M, Albisetti M; DIVERSITY Trial Investigators. Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial. Lancet Haematol. 2021 Jan;8(1):e22-e33. doi: 10.1016/S2352-3026(20)30368-9. Epub 2020 Dec 5. PMID: 33290737.

41

Dabigatran- DIVERSITY Trial

blood Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children

Leonardo R. Brandão,[1] Manuela Albisetti,[2] Jacqueline Halton,[3] Lisa Bomgaars,[4] Elizabeth Chalmers,[5] Lesley G. Mitchell,[6] Ildar Nurmeev,[7] Pavel Svirin,[8] Tomas Kuhn,[9,10] Ondrej Zapletal,[11,12] Igor Tartakovsky,[13] Monika Simetzberger,[14] Fenglei Huang,[15] Zhichao Sun,[16] Jörg Kreuzer,[17] Savion Gropper,[13] Martina Brueckmann,[13,18] and Matteo Luciani,[19] on behalf of the DIVERSITY Study Investigators

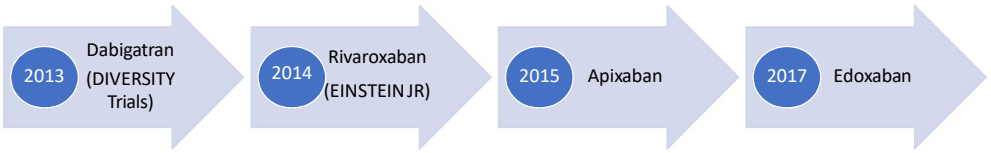
[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Hematology Department, University Children's Hospital, Zürich, Switzerland; [3]Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada; [4]Department of Pediatrics, Texas Children's Cancer and Hematology Centers, Baylor College of Medicine, Houston, TX; [5]Royal Hospital for Children, Glasgow, Scotland, United Kingdom; [6]Department of Pediatrics, University of Alberta, Edmonton, AB, Canada; [7]Pediatric Hospital, Republic of Tatarstan, Kazan Medical University, Kazan, Russian Federation; [8]Pediatric Hematology Department, Municipal Children's Hospital "Morozovskaya," Moscow, Russian Federation; [9]Pediatric Hematology/Oncology Department, University Hospital Ostrava, Ostrava, Czech Republic; [10]Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic; [11]Pediatric Hematology Department, University Hospital Brno, Brno, Czech Republic; [12]Masaryk University, Brno, Czech Republic; [13]Therapeutic Area Cardiometabolic Medicine, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [14]Department of Clinical Development, Boehringer Ingelheim RCV GmbH & Co KG, Vienna, Austria; [15]Translational Medicine and Clinical Pharmacology and [16]Biostatistics and Data Sciences, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT; [17]Boehringer Ingelheim Singapore Pte Ltd, Singapore; [18]Faculty of Medicine Mannheim of the University of Heidelberg, Mannheim, Germany; and [19]Pediatric Hematology/Oncology Department, Pediatric Hospital Bambino Gesù, Rome, Italy

- Ages 0-17 years
- 203 children enrolled
- Extended secondary prevention up to 1 year
- Primary endpoints: VTE recurrence, bleeding events, mortality at 6 and 12 months
- **2/203 (1%) with on treatment VTE recurrence; 3/203 (1.5%) experienced major bleeding and 2(1%) with CRNMB**

Leonardo R. Brandão, Manuela Albisetti, Jacqueline Halton, Lisa Bomgaars, Elizabeth Chalmers, Lesley G. Mitchell, Ildar Nurmeev, Pavel Svirin, Tomas Kuhn, Ondrej Zapletal, Igor Tartakovsky, Monika Simetzberger, Fenglei Huang, Zhichao Sun, Jörg Kreuzer, Savion Gropper, Martina Brueckmann, Matteo Luciani; on behalf of the DIVERSITY Study Investigators, Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. *Blood* 2020; 135 (7): 491–504. doi: https://doi.org/10.1182/blood.2019000998

42

DOAC Trials



43

Rivaroxaban- EINSTEIN-JR Trials

Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial

Christoph Male, Anthonie W A Lensing, Joseph S Palumbo, Riten Kumar, Ildar Nurmeev, Kerry Hege, Damien Bonnet, Philip Connor, Hélène L Hooimeijer, Marcela Torres, Anthony K C Chan, Gili Kenet, Susanne Holzhauer, Amparo Santamaría, Pascal Amedro, Elizabeth Chalmers, Paolo Simioni, Rukhmi V Bhat, Donald L Yee, Olga Lvova, Jan Beyer-Westendorf, Tina T Biss, Ida Martinelli, Paola Saracco, Marjolein Peters, Krisztián Kállay, Cynthia A Gauger, M Patricia Massicotte, Guy Young, Akos F Pap, Madhurima Majumder, William T Smith, Jürgen F Heubach*, Scott D Berkowitz, Kirstin Thelen, Dagmar Kubitza, Mark Crowther, Martin H Prins, Paul Monagle, for the EINSTEIN-Jr Phase 3 Investigators†

- Ages 0-17
- Compared rivaroxaban vs standard of care after 5-9 days of parental anticoagulation
- 500 children enrolled
- **Similar low recurrence risk and reduced thrombotic burden without increase in bleeding risk in both groups**

Male C, Lensing AWA, Palumbo JS, Kumar R, Nurmeev I, Hege K, Bonnet D, Connor P, Hooimeijer HL, Torres M, Chan AKC, Kenet G, Holzhauer S, Santamaría A, Amedro P, Chalmers E, Simioni P, Bhat RV, Yee DL, Lvova O, Beyer-Westendorf J, Biss TT, Martinelli I, Saracco P, Peters M, Kállay K, Gauger CA, Massicotte MP, Young G, Pap AF, Majumder M, Smith WT, Heubach JF, Berkowitz SD, Thelen K, Kubitza D, Crowther M, Prins MH, Monagle P; 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 Jan;7(1):e18-e27. doi: 10.1016/S2352-3026(19)30219-4. Epub 2019 Nov 5. PMID: 31699660.

44

FDA NEWS RELEASE

FDA Approves First Oral Blood Thinning Medication for Children

2021

Share Tweet LinkedIn Email Print

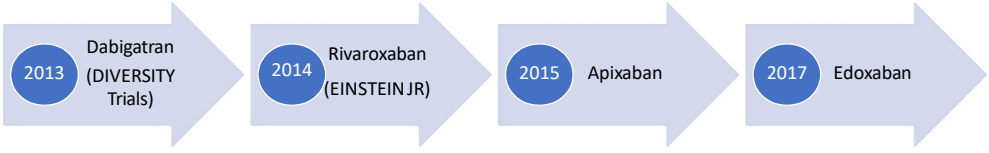
For Immediate Release: June 21, 2021

INNOVATION

FDA Approves Two New Indications for XARELTO® (rivaroxaban) to Help Prevent and Treat Blood Clots in Pediatric Patients

45

DOAC Trials



46

Apixaban Trials

Trial	Results
SAXOPHONE[1] • Phase 2, open label, RCT • Ages 29 days to 17 years • Compared Apixaban vs SOC in children with congenital or acquired heart disease at risk for VTE	Final results have not been published No thrombotic events in the treatment or comparator groups; low bleeding rates
PREVAPIX-ALL[2] • Phase 3, open label, RCT • Ages 0-17 years • 512 children enrolled	31% risk reduction in the primary efficacy end point (composite of VTE and VTE-related death) (12.1% vs 17.6%) with apixaban compared with SOC, but this difference was not statistically significant
*CANINES (NCT02464969) • Apixaban for the Acute Treatment of VTE in Children	Inclusion Criteria: 1. Birth to <18 years of age with a minimum weight of 2.6 kg at the time of randomization. 2. Presence of an index VTE which is confirmed by imaging. 3. Intention to manage the index VTE with anticoagulation treatment for at least 6 to 12 weeks. 4. Subjects able to tolerate oral feeding, nasogastric (NG), gastric (G) feeding and are currently tolerating enteric medications, as per investigator's judgement.

1.Payne R.M., Burns K.M., Glatz A.C., Li D., Li X., Monagle P., et al. A multi-national trial of a direct oral anticoagulant in children with cardiac disease: design and rationale of the safety of ApiXaban on pediatric heart disease on the prevention of embolism (SAXOPHONE) study. Am Heart J. 2019;217:52–63; Payne R, Burns K, Glatz A, Male C, Donti A, Brandao L, et al. The SAXOPHONE study; a multi-center, multi-national randomized trial of apixaban versus standard of care anticoagulation for thromboprophylaxis in children with congenital or acquired heart disease. Res Pract Thromb Haemost. 2022;6:120.
2.O'Brien SH, Li D, Mitchell LG, Hess T, Zee P, Yee DL, Newburger JW, Sung L, Rodriguez V. PREVAPIX-ALL: Apixaban Compared to Standard of Care for Prevention of Venous Thrombosis in Paediatric Acute Lymphoblastic Leukaemia (ALL)-Rationale and Design. Thromb Haemost. 2019 May;119(5):844-853. doi: 10.1055/s-0039-1679938. Epub 2019 Mar 12. PMID: 30861550.

47

Edoxaban Trials

Trial	Results
Hokusai VTE Pediatrics[1] • Phase 3, noninferiority, open-label RCT • **Acute VTE treatment and secondary prevention** • Ages 0-17 years • 290 children enrolled • Compared Edoxaban vs SOC for treatment (3 mo) followed by 9 month extension post treatment	• Final results have not been published
ENNOBLE-ATE[2] • Phase 3, open-label RCT • **VTE prevention in cardiac disease** • Ages 0-17 years • 168 children enrolled • Compared Edoxaban vs SOC for treatment (3 mo) followed by 9 month extension post treatment (147)	• 1 CRNMB in each group • 1 patient with VTE in the SOC group and none in the edoxaban group Extension (147 children) • 1 CRB • 4 VTE

1.van Ommen C.H., Albisetti M., Chan A.K., Estepp J., Jaffray J., Kenet G., et al. The edoxaban Hokusai VTE PEDIATRICS study: an open-label, multicenter, randomized study of edoxaban for pediatric venous thromboembolic disease. Res Pract Thromb Haemost. 2020;4:886–892.

2. Portman M.A., Jacobs J.P., Newburger J.W., Berger F., Grosso M.A., Duggal A., et al. ENNOBLE-ATE Trial Investigators. Edoxaban for thromboembolism prevention in pediatric patients with cardiac disease. *J Am Coll Cardiol.* 2022;80:2301–2310

48

Dabigatran

- Route of Administration: Oral
- Indications: Approved for pediatric VTE treatment and prevention
- Dosage Forms:
  - Oral pellets: 3 mo-12 years
  - Capsules: >8 years-<18 years
- Avoid in ESRD (eGFR <50); no adjustment in hepatic impairment

49

Dabigatran

Venous thromboembolic event (VTE), treatment and prevention: Note: For treatment, initiate dabigatran after 5 days of treatment with a parenteral anticoagulant; for prevention, initiate dabigatran after treatment is complete. Adjust dose during treatment according to age **and** actual weight:

Oral pellets:

Note: Dosing is based on weight AND age; use caution when selecting dose. Twice-daily dosing should be as close to a 12-hour dosing interval as is possible.

Infants 3 to <4 months:
- Weight 3 to <4 kg: Oral pellets: Oral: 30 mg twice daily.
- Weight 4 to <7 kg: Oral pellets: Oral: 40 mg twice daily.
- Weight 7 to <9 kg: Oral pellets: Oral: 50 mg twice daily.

Infants 4 to <5 months:
- Weight 3 to <4 kg: Oral pellets: Oral: 30 mg twice daily.
- Weight 4 to <7 kg: Oral pellets: Oral: 40 mg twice daily.
- Weight 7 to <9 kg: Oral pellets: Oral: 60 mg twice daily.

Infants 5 to <6 months:
- Weight 3 to <4 kg: Oral pellets: Oral: 30 mg twice daily.
- Weight 4 to <5 kg: Oral pellets: Oral: 40 mg twice daily.
- Weight 5 to <7 kg: Oral pellets: Oral: 50 mg twice daily.
- Weight 7 to <11 kg: Oral pellets: Oral: 60 mg twice daily.

Infants 6 to <7 months:
- Weight 4 to <5 kg: Oral pellets: Oral: 40 mg twice daily.
- Weight 5 to <7 kg: Oral pellets: Oral: 50 mg twice daily.
- Weight 7 to <9 kg: Oral pellets: Oral: 60 mg twice daily.
- Weight 9 to <11 kg: Oral pellets: Oral: 80 mg twice daily.

Capsules:

Children ≥8 years and Adolescents <18 years:
- Weight 11 to <16 kg: Capsules: Oral: 75 mg twice daily.
- Weight 16 to <26 kg: Capsules: Oral: 110 mg twice daily.
- Weight 26 to <41 kg: Capsules: Oral: 150 mg twice daily.
- Weight 41 to <61 kg: Capsules: Oral: 185 mg twice daily.
- Weight 61 to <81 kg: Capsules: Oral: 220 mg twice daily.
- Weight ≥81 kg: Capsules: Oral: 260 mg twice daily.

***The dosage forms are not interchangeable on a mg:mg basis due to pharmacokinetic differences**

50

Rivaroxaban

- Route of Administration: Oral
- Indication(s): Approved for pediatric VTE treatment and prevention (including Fontans)
- Dosage Forms
  - Oral suspension: 1 mg/mL
  - Tablets: 2.5 mg, 10 mg, 15 mg, and 20 mg
- Avoid: CrCl< 30ml/min
- Avoid: moderate to severe impairment

51

Rivaroxaban

Venous thromboembolism (VTE): Note: Dosing based on the EINSTEIN-Jr phase 3 study ([Ref]):

Treatment (after stabilization with ≥5 days of initial parenteral treatment):

Note: Begin treatment after at least 10 days of oral feeding. Recommended duration of treatment is 3 months (up to 12 months when clinically appropriate) unless <2 years of age with catheter-related VTE where recommended duration of treatment is 1 month (up to 3 months when clinically appropriate):

Infants, Children, and Adolescents:

Oral suspension:

2.6 to 2.9 kg: Oral: 0.8 mg/dose every 8 hours.

3 to 3.9 kg: Oral: 0.9 mg/dose every 8 hours.

4 to 4.9 kg: Oral: 1.4 mg/dose every 8 hours.

5 to 6.9 kg: Oral: 1.6 mg/dose every 8 hours.

7 to 7.9 kg: Oral: 1.8 mg/dose every 8 hours.

8 to 8.9 kg: Oral: 2.4 mg/dose every 8 hours.

9 to 9.9 kg: Oral: 2.8 mg/dose every 8 hours.

10 to 11.9 kg: Oral: 3 mg/dose every 8 hours.

12 to 29.9 kg: Oral: 5 mg/dose every 12 hours.

30 to 49.9 kg: Oral: 15 mg/dose every 24 hours.

≥50 kg: Oral: 20 mg/dose every 24 hours.

Oral tablet: **Note:** Rivaroxaban 2.5 mg tablets are not recommended for use in pediatric patients; safety, efficacy, and pharmacokinetic/pharmacodynamic data are lacking for this dosage form.

30 to 49.9 kg: Oral: 15 mg/dose every 24 hours.

≥50 kg: Oral: 20 mg/dose every 24 hours.

52

DOAC Adult Dosing

DOAC	Treatment Dosing
Apixaban	10mg BID x7 days, then 5mg BID (Reduce dose to 2.5mg BID after 6 months of therapy for prophylaxis)
Edoxaban	<60 kg: 30mg ONCE daily after at least 5 days of treatment with UFH/LMWH >60 kg: 60mg ONCE daily after at least 5 days of treatment with UFH/LMWH
***Rivaroxaban**	15mg BID x21 days then 20mg ONCE daily (Reduce dose to 10mg once daily after 6 months of therapy for prophylaxis)
Dabigatran	150mg BID after at least 5 days of treatment with UFH/LMWH

Atrial fibrillation, nonvalvular
Heparin-induced thrombocytopenia
Left ventricular thrombus, treatment or prophylaxis
Venous thromboembolism

Nonvalvular atrial fibrillation
Venous thromboembolism

53

DOAC Comparison				
	Apixaban	**Dabigatran**	**Edoxaban**	**Rivaroxaban**
Adult Dosing	10mg BID x7 days then 5mg BID	150mg BID*	>60 kg: 60 mg daily; ≤60 kg: 30 mg daily*	15mg BID x21 days then 20mg daily
Formulations	Tablets: 2.5mg, 5mg	Capsules: 75mg, 110mg, 150mg	Tablets: 15mg, 30mg, 60mg	Tablets: 75mg, 110mg, 150mg Suspension: 1 mg/mL
Administration	Without regard to food; May crush	Without regard to food; Do not open	Without regard to food; May crush	With food; May crush (swallow whole in pediatrics)
Drug Interactions	CYP	P-Glycoprotein	P-Glycoprotein	P-Glycoprotein
Renal limitations	Avoid: < 15ml/Min (Not studied if CrCl < 25ml/min or SCr > 2.5)	Avoid: CrCl < 30ml/min; Dialyzable	Avoid: CrCl < 15ml/min CrCl > 95 ml/min	Avoid: CrCl< 30ml/min
Hepatic limitations	Avoid: severe impairment	None	Avoid : moderate to severe impairment	Avoid: moderate to severe impairment
Obesity (BMI >40 / 120 kg)	Avoid	Avoid	Avoid	Avoid
Clinical Reversal	Andexanet alfa, activated charcoal, Kcentra	Idarucizumab, activated charcoal, Kcentra	Andexanet alfa, activated charcoal, Kcentra	Andexanet alfa, activated charcoal, Kcentra
Monitoring	Anti-Xa	DTT, ECT	Anti-Xa	Anti-Xa

- After at least 5 days of parenteral anticoagulation
- DTT= direct thrombin time
- ECT= ecarin clotting time

54

DOAC Reversal

- "Reversal agents carry a risk of life-threatening thrombosis and should only be used under the direction of a specialist with expertise in their use and/or in a patient at imminent risk of death from bleeding." Therefore, use should be reserved for life threatening bleeding!

55

DOAC Reversal

- Idarucizumab (Praxabind)
  - A humanized monoclonal antibody fragment that binds dabigatran to neutralize its anticoagulant effects as measured by plasma-dilute thrombin time.
- Andexanet alfa (Andexxa)
  - Recombinant modified human coagulation factor Xa that binds to an sequesters factor Xa inhibitors to neutralize their anticoagulant effects as measured by anti-Xa activity.

56

DOAC Reversal

DOAC	Preferred	*Alternatives	Comments
Apixaban	KCentra (4F-PCC)	Andexanet alfa*	• Can be used for life threatening bleeding or critical site bleeding (i.e. ICH) • Andexanet alfa should not be used if apixaban was last given over 18 hours ago or major embolic event occurred in past two weeks.
Dabigatran	KCentra (4F-PCC)	Idarucizumab*	• Can be used for life threatening bleeding or critical site bleeding (i.e. ICH), or emergent procedure that cannot be delayed at least 8 hours
Edoxaban	KCentra (4F-PCC)	KCentra (4F-PCC)	• Can be used for life saving surgery, life threatening bleeding or critical site bleeding (i.e. ICH)
Rivaroxaban	KCentra (4F-PCC)	Andexanet alfa*	• Can be used for life threatening bleeding or critical site bleeding (i.e. ICH) • Andexanet alfa should not be used if apixaban was last given over 18 hours ago or major embolic event occurred in past two weeks.

***NOTE: Andexanet alfa and Idarucizumab are NOT approved in pediatrics and dosing is unknown; therefore, these agents are NOT currently on formulary at COA at the time of this update, so consider 2nd line intervention. Refer to Lexi-Comp or consult pharmacy for dosing recommendations based on the dose of DOAC that was given and when the last dose was administered.**

57

Who SHOULDN'T be treated with a DOAC…

Known antiphospholipid syndrome (APS) or concern for

Mechanical heart valves

Undergone GI/bariatric surgery or any underlying condition where there is concern for altered absorption

Moderate to severe hepatic or renal impairment

Morbid obesity (BMI >40 kg/m^2)

Patients with current medications that interact with DOAC function

58

Rivaroxaban and APS

blood Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Vittorio Pengo,[1] Gentian Denas,[1] Giacomo Zoppellaro,[1] Seena Padayattil Jose,[1] Ariela Hoxha,[2] Amelia Ruffatti,[2] Laura Andreoli,[2] Angela Tincani,[2] Caterina Cenci,[3] Domenico Prisco,[4] Tiziana Fierro,[5] Paolo Gresele,[5] Arturo Cafolla,[6] Valeria De Micheli,[7] Angelo Ghirarduzzi,[8] Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Doris Barcellona,[13] Maria Gerosa,[14] and Alessandra Banzato[1]

[1]Cardiology Clinic, Thrombosis Centre, Department of Cardiac Thoracic and Vascular Sciences, and [2]Rheumatology Unit, Department of Medicine, University of Padua, Padua, Italy; [3]Rheumatology and Clinical Immunology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; [4]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [5]Section of Internal and Cardiovascular Medicine, Department of Medicine, University of Perugia, Perugia, Italy; [6]Department of Cellular Biotechnologies and Hematology Thrombosis Centre, Sapienza University of Rome, Rome, Italy; [7]Transfusion Medicine, District Hospital, Merate, Italy; [8]Angiology Unit, Department of Internal Medicine, Santa Maria Nuova Hospital, Reggio Emilia, Italy; [9]Hematology Department, San Bortolo Hospital, Vicenza, Italy; [10]Department of Immunohematology and Transfusion Medicine and Hemostasis and Thrombosis Center, Hospital Papa Giovanni XXIII, Bergamo, Italy; [11]A. Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy; [12]Hemostasis and Thrombosis Center, Laboratory Medicine Department, Azienda Socio-Sanitaria Territoriale, Cremona, Italy; [13]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; and [14]Division of Rheumatology, Department of Clinical Sciences and Community Health, Ospedale Gaetano Pini, University of Milan, Milan, Italy

Table 4. Adjudicated efficacy and safety outcomes

Outcome, n	"As treated" analysis				ITT analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01	13 (22)	2 (3)	7.4 (1.7-32.9)	.008
Arterial thrombosis	7 (12)	0	—	—	7 (12)	0	—	—
Ischemic stroke	4 (7)	0			4 (7)	0		
Myocardial infarction	3 (5)	0			3 (5)	0		
Venous thromboembolism	0	0			1 (2)	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3	4 (7)	2 (3)	2.3 (0.4-12.5)	.3
Death	0	0	—	—	1 (2)	0	—	—

Numbers in parentheses denote percentage with respect to total.
—, statistical analysis not applicable.

Vittorio Pengo, Gentian Denas, Giacomo Zoppellaro, Seena Padayattil Jose, Ariela Hoxha, Amelia Ruffatti, Laura Andreoli, Angela Tincani, Caterina Cenci, Domenico Prisco, Tiziana Fierro, Paolo Gresele, Arturo Cafolla, Valeria De Micheli, Angelo Ghirarduzzi, Alberto Tosetto, Anna Falanga, Ida Martinelli, Sophie Testa, Doris Barcellona, Maria Gerosa, Alessandra Banzato; Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood 2018; 132 (13): 1365–1371. doi: https://doi.org/10.1182/blood-2018-04-848333

59

Drug Interactions

	P-gp Inhibitor	Non-P-gp Inhibitor	P-gp Inducer
Strong CYP3A inhibitor	itraconazole, ketoconazole, clarithromycin, lopinavir, indinavir, ritonavir, telaprevir	voriconazole	
Moderate CYP3A inhibitor	erythromycin, verapamil, diltiazem, dronedarone	not identified	doxorubicin
Weak CYP3A inhibitor	lapatinib, quinidine, cyclosporine, felodipine, azithromycin, ranazoline, ticagrelor, chloroquine, hydroxychloroquine	cimetidine	vinblastine
CYP3A Inducers			carbamazepine, phenytoin, phenobarbital, rifampin, dexamethasone, tocilizumab, St. John's Wort

CYP = Cytochrome P 450; P-gp = P-glycoprotein.

Ferri N, Colombo E, Tenconi M, Baldessin L, Corsini A. Drug-Drug Interactions of Direct Oral Anticoagulants (DOACs): From Pharmacological to Clinical Practice. Pharmaceutics. 2022 May 24;14(6):1120. doi: 10.3390/pharmaceutics14061120. PMID: 35745692; PMCID: PMC9229376.

60

Key Points

- Majority of pediatric VTE are provoked, with CVC being the most common provoking factor.
- Individualized approach to treatment needed-DOACs are not appropriate for all children.
- Additional studies of DOACs are needed to further evaluate safety and efficacy in real world practice.

61

Thrombosis Clinic

Patient and family-centered care	Diagnosis and management of DVT/PE
Anticoagulation monitoring	Thrombophilia evaluation and interpretation
Support and education for patient and family	Clinical research and clinical trials

62

✉ hopewilson@uabmc.edu
thrombosis@childrensal.org

63