Appropriate Use of DOACs in the Pediatric Population

BOTTOM LINE

DOAC use in pediatrics is a rapidly evolving area of practice with lack of consensus guidelines at this time due to the newness of clinical data. Current recommendations are based on a critical evaluation of available evidence.

DOACs are an increasingly utilized option for treating and preventing thrombosis in children.

Rivaroxaban and dabigatran are approved for treatment and prevention of VTE in children. Clinical trials using apixaban and edoxaban are underway.

The FDA approved the use of rivaroxaban post-Fontan, but the details of the dose and study population are important to consider (see details below).

While rates of recurrent thrombosis and bleeding in the published DOAC clinical trials were low, the patients enrolled may not reflect the complexity of pediatric patients in clinical practice.

There remains limited data on DOACs in neonates & infants.

Decisions regarding antithrombotic therapy in children are best guided by providers with expertise in pediatric thrombosis.

Considerations for using DOACs in children

Don't use a DOAC in patients who are: critically ill, have prosthetic heart valves, antiphospholipid antibody syndrome, renal failure, and/or significant hepatic dysfunction.

Patient should be tolerating good enteral intake via oral, NG or G-tube.

Need ≥ 5 days of parenteral anticoagulation prior to DOAC for VTE treatment (pediatric regimen).

Check for clinically significant drug interactions.

Have a plan for reversal in case of bleeding or urgent surgery (recognizing the lack of pediatric data for reversal).

Evaluate availability of appropriate drug formulation.

Check for barriers to drug acquisition - insurance coverage.

	RIVAROXABAN	DABIGATRAN
Pediatric FDA approved Indications	**Treatment of VTE (birth-18 yrs)[1]** **Prophylaxis against recurrent VTE (full dose)[1]** **Thromboprophylaxis after Fontan Procedure[2]**	**Treatment of VTE (3m-18 yrs)[6]** **Prophylaxis against recurrent VTE (full dose)[7]**
Pediatric Dose	**Treatment or full-dose prevention of VTE[1,2,3]** • ≥5 days parenteral treatment • With food/enteral nutrition (gastric) • For patients less than 6 months of age: ◦ Must be > 37 weeks gestational age ◦ Weight ≥ to 2.6 kg ◦ Must have ≥ to10 days of feeding • Dosing frequency: ◦ < 12 kg = every 8 hours ◦ 12 – 29.9 kg = every 12 hours ◦ ≥ 30 kg = every day **Thromboprophylaxis after Fontan procedure[2,4,5,10]** **Dosing is weight-based** with many stratifications *(evaluate weight for potential dose change):* • Dosing for ≥ 2 years and adolescents • Dosing frequency: ◦ 7 kg – 29.9 kg = every 12 hours ◦ ≥ 30 kg = every day *(Notes: 1. Clinical trial compared low dose rivaroxaban vs. aspirin in patients age 2-8 years old (without thrombosis) 2. Dosing based on PK/PD modeling for reduced cardiac output and a lower body weight for a given age compared to healthy children – equivalent in Fontan patients 2-8 years to target adult 10 mg per day. 3. Prevention dose for Fontan is lower than expected for a non-Fontan patient and cannot be used in any other population)*	**Treatment or full-dose prevention of VTE[6,7,8,9]** • ≥5 days parenteral treatment **Dosing is BOTH age and weight-based** and specific to the dosage form ***WARNING: dosage forms (pellet vs. capsule) are not interchangeable on a mg:mg basis due to pharmacokinetic differences (eg, bioavailability):*** • Monitor weight for potential dose change • every 12 hours for all ages • Pellets are labeled for **age 3 months (and 3 kg) to < 12 years old** ◦ Patient must be able to swallow soft foods for administration • Capsules for age **≥ 8 years (and ≥ 11 kg) to < 18 years** Doses are higher in pediatric patients with doses of 185-260 mg every 12 hours required for adolescents due to better renal function. • Adult dosing (150 mg BID) is based on trials with mean age of 55-71 years
Pediatric-Specific Dosage Forms	**Suspension 1mg/mL (sweet flavor, gentle mixing to avoid foaming)** **AGITATE BOTTLE SLOWLY for 10 seconds before each use.** **To avoid foaming DO NOT SHAKE.** **Foaming may lead to giving the wrong dose.**  • *Recommend families look at product to ensure suspended prior to leaving the pharmacy* • *Ok for G-tube and NG-tube administration* • *May require Prior Authorization – insurance specific* • *Patient support program may help offset cost* • *Most pharmacies will need to special-order the product – not generally stocked*	**Oral Pellets in a packet** *20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg* **(not currently commercially available)** Store in original package to protect from moisture. • Do not mix with milk or milk containing products • Ok to mix with soft foods or apple juice • Administer with food if GI upset occurs Discard 6 months after opening the aluminum bag containing the packets.)
Dosage Forms	**Tablets:** *2.5 mg (not evaluated in pediatric patients) 10 mg, 15 mg, 20 mg*  10 mg 15 mg 20 mg *https://www.ismp.org/sites/default/files/attachments/2018-11/Xareltofinal.pdf* Note: not scored/not easily quarterable (friable) Ok for G-tube and NG-tube administration (tablets may be crushed and mixed in water; administer the suspension within 4 hours of preparation and follow administration with enteral feeding)	**Capsules age >8 years:** *75 mg, 110 mg, 150 mg*  (Dispense and store in original manufacturer's bottle to protect from moisture; discard 4 months after opening original container.) • Contents of capsules cannot be crushed or chewed (tartaric acid is released causing increased serum concentrations and GI adverse events) • Do not open capsules – increases bioavailability by 75%

	Rivaroxaban	Dabigatran
Pediatric Pharmacokinetic Considerations	**Renal excretion (~ 36%)**[16] Avoid use (no clinical data available): • Infants ≥2.6 kg if serum creatinine is above the 97.5th percentile (no clinical data available) • eGFR < 50 mL/minute/1.73 m^2 **Substrate of P-glycoprotein/CYP3A4/5 (major substrate)** – interaction potential **Half-life:** Shorter in pediatrics compared to adults[3] • For management of a bleeding event, consider elimination half-lives based on age (with normal renal & liver function) supports short time to hemostasis	**Renal excretion (~ 80%)**[16] Avoid use (no clinical data available): • eGFR <50 mL/minute/1.73 m^2 **Substrate of P-glycoprotein/ABCB1 (major substrate) –** interaction potential (e.g. cyclosporine, rifampin) **Half-life:** *Pediatrics:* Capsules: 12 to 14 hours Oral pellets: 9 to 11 hours *Adults:* Capsules: 12 to 17 hours Elderly patients: 14 to 17 hours Mild to moderate renal impairment: 15 to 18 hours Severe renal impairment: 28 hours
Safety Concerns	• TID dosing intervals may be challenging with potential for missed doses • In adults, potential for more GI bleed risk than warfarin, but less intracranial hemorrhage[12] • More heavy menstrual bleeding than warfarin or dabigatran[11]	• Capsules and pellets are not 1:1 for dose. • Many dosage forms are available– potential for error • GI upset/dyspepsia common in pediatrics and adults[6] • Potential for more GI bleed risk than warfarin, but less intracranial hemorrhage[12] • Less heavy menstrual bleeding than rivaroxaban and warfarin[11]
Lab Considerations[15,17]	• Pre-therapy baseline labs should include PT/PTT, CBC, Cr and liver function tests • DOACs interfere with most clot-based assays and can cause a false positive lupus anticoagulant and false increase in clot-based protein C, S and AT assays	
	• *Will prolong anti-Xa* • *May increase PT/INR, PTT*	• *Increases thrombin time, PTT* • *May increase PT/INR (assay dependent)*
Duration of therapy	Provoked VTE: • ASH 2018 guidelines suggest using anticoagulation for ≤ 3 months[14] • KIDS DOTT (Duration of Therapy for Thrombosis)-RCT for 1st, provoked[14], acute VTE in patients <21 years[13] ◦ Treat for 6 wks then reimage (Doppler) – if VTE is resolved or non-occlusive, OK to stop – if VTE is still occlusive, or if antiphospholipid testing is persistently positive, continue anticoagulation for full 3 months Unprovoked VTE: Suggests using anticoagulation for 6 to 12 months[14]	
Anticipated Randomized Control Trial data	**Apixaban:** 1) ALL/lymphoblastic lymphoma and CVC - NCT02369653 completed 3/2022 2) Prevention of thromboses with cardiac defects/diseases - NCT02981472 completed 5/2022 3) Treatment of VTE - NCT02464969 ongoing **Edoxaban:** 1) Treatment of VTE and secondary prevention - NCT02798471 completed 6/2022 2) Prevention of thromboses with cardiac defects/diseases - NCT03395639 completed 7/2022[18]	

BLEEDING / REVERSAL / PROCEDURES[19]

- Rates of major bleeding in the pediatric DOAC trials have been low (0-2%), but it is important to have a plan to address major bleeding in children on DOACs
- In patients with non-life threatening bleeding, supportive care (holding anticoagulants and transfusion) is often sufficient
- Non-specific reversal agents such as 4-Factor PCCs are available
- Targeted reversal agents for DOACs are available for use in adults but have not been studied in children
- An example of a guideline from Seattle Children's Hospital for management of children on DOACs with major bleeding
- Peri-procedural management of DOACs has not yet been studied in children, but it is reasonable to extrapolate adult findings from the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study, until pediatric data is available.[20] The protocol included:
  - Holding the DOAC for 1 day for "low-risk" procedures, and for 2 days for "high-risk" procedures for adults and adolescents
  - May also consider extrapolating the hold from pediatric-specific half-life information
    - For children, consider 2-3 half lives for "low-risk" and 3-5 half lives for "high-risk" procedures

Reversal agents for DOACs have not been studied in children and are off-label.

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