Direct Oral Anticoagulants

in Children and Adolescents

Venous thromboembolism in children and adolescents

- Almost always provoked
- Multiple and simultaneous risk factors at the time of diagnosis
- Usually secondary to the use of a central venous catheter in children.
- In adolescents, one of the most common cause of VTE is the use of oral contraceptive.

Current standard of care for VTE treatment

- Unfractionated heparin (UFH)
- Low-molecular-weight heparin (LMWH)
- Vitamin K antagonists(VKA)
- Disadvantages include:
  - Unpredictable pharmacokinetic response
  - Several drug and food interactions
  - The need for parenteral administration
  - Need for frequent monitoring

Current standard of care for VTE treatment

- Generally recommended:
- administer anticoagulation through the central line until it can be removed
- Removal of the central line should occur within 3 to 5 days of initiating
- Serial radiologic imaging is necessary to assess for potential extension of the clot

Table 2 Standard Anticoagulants Used in Children (4)(25)

ANTICOAGULANT	MECHANISM OF ACTION	ROUTE OF ADMINISTRATION	DOSING FOR ACUTE VTE	TARGET THERAPEUTIC RANGE	REVERSAL AGENT	METABOLISM
UFH	Potentiates inhibitory effects of ATIII over activated factors X and II	Intravenous	Bolus: 75–100 U/kg over 10 min Continuous infusion: <1 y: 28 U/kg per hour >1 y: 20 U/kg per hour	aPTT 1.5–2.5 times upper limit of normal Anti-Xa 0.3–0.7 U/mL	Protamine sulfate	Hepatic and RES
LMWH	Similar to UFH but with more specificity toward activated factor X	Subcutaneous	<2 mo of age: 1.5 mg/kg per dose, every 12 h ≥2 mo of age: 1 mg/kg per dose, every 12 h Prophylactic dosing: <2 mo of age: 1.5 mg/kg per dose daily ≥2 mo of age: 1 mg/kg per dose daily or 0.5 mg/kg per dose twice daily	Anti-Xa 0.5–1 U/mL[a] Not necessary to monitor level	Protamine sulfate (partial reversal only)	Renal
Warfarin (VKA)	Inhibits the carboxylation of vitamin K–dependent factors (II, VII, IX, X)	Oral	2–12 y of age: 0.09 mg/kg per dose daily ≥12 y of age: 0.08 mg/kg per dose daily	INR 2–3[b] INR 2.5–3.5 (for patients with valvular heart disease or APS)	Vitamin K, fresh frozen plasma	Hepatic
Argatroban (DTI)	Direct inhibition of thrombin (independently from ATIII)	Intravenous	Continuous infusion: 0.75 μg/kg per minute (no bolus required)	aPTT 1.5–2.5 times upper limit of normal[c]	None	Hepatic

Direct oral anticoagulants (DOACs)

- Proven at least as efficient and safe as standard care including:
- Treatment and prophylaxis of
  - deep venous thrombosis(DVT)
  - pulmonary embolism
  - atrial fibrillation

Direct oral anticoagulants (DOACs)

- Clearly overcome limitations of standard care
- Several phase I–III trials are currently ongoing

Direct oral anticoagulants (DOACs)

- Two type:
  - Direct Thrombin Inhibitors
    - Dabigatran
  - Direct FXa inhibitors
    - Apixaban
    - Betrixaban
    - Edoxaban
    - Rivaroxaban

Table 3 Direct Oral Anticoagulants in Pediatrics (33)(34)

MECHANISM OF ACTION	MEDICATION	PEDIATRIC INDICATIONS UNDER INVESTIGATION IN CURRENT AND FUTURE CLINICAL TRIALS
Factor Xa inhibitors	Rivaroxaban	Arterial TE prevention after Fontan surgery (versus aspirin) Acute VTE treatment VTE prevention in acute leukemia with CVC (versus placebo)
	Apixaban	Arterial TE prevention in cardiac diseases (versus LMWH/VKA) Acute VTE treatment
	Edoxaban	Arterial TE prevention in various cardiac diseases Acute VTE treatment (versus LMWH/VKA)
	Betrixaban	VTE prevention in medical illness or surgery VTE prevention in neonates with umbilical CVC
Direct thrombin inhibitor	Dabigatran	Acute VTE treatment (versus LMWH/VKA) Extended secondary VTE prophylaxis

CVC=central-access vascular catheter; LMWH=low-molecular-weight heparin; TE=thromboembolism; VKA=vitamin K antagonist; VTE=venous thromboembolism.

Dabigatran

- Specifically and reversibly inhibits thrombin
- Orally administered
- Available in three different pharmaceutical formulations:
  - capsule
  - pellets
  - oral liquid formulation
- Half-lives
  - 8 and 10 hours with single dose administration
  - 14 and 17 hours with multiple dose administrations

Dabigatran

- Pediatric Studies:
- From birth to 17 years old
- The responses
  - consistent across all pediatric groups
  - comparable to responses in adults

Dabigatran, Clinical Pediatric Studies

- All studies complete before 2020
- Confirmed effect in children and adolescent VTE and VTE prophylaxis.

Dabigatran, reversal agents

- Idarucizumab
- a humanized monoclonal antibody
- specifically binds to dabigatran and its active metabolite
- only FDA-approved agent for reversing the anticoagulant effect

Apixaban

- Highly selective inhibitory activity against coagulation Fxa
- Inhibits free and clot-bound Fxa
- Available in two different pharmaceutical formulations:
  - tablet
  - oral solution
- Half-life of oral solution 4.3 to 6.8 hours
- Half-life of tablet 11 to 26.8 hours

Apixaban, Preclinical Pediatric Studies

- Explore the potential effect in the pediatric population
- Demonstrated consistent concentration-related FXa inhibition across all age groups
- Trial is currently performing and complete before 2022

Edoxaban

- Highly selective inhibitory activity against coagulation Fxa
- Available in two different pharmaceutical formulations:
  - tablet
  - oral solution
- Half-life ranged from5.79 to 10.7 hours

Edoxaban, Preclinical Pediatric Studies

- Effects were similar at all ages
- The exception of children younger than 2 years
  - the anticoagulant effect was increased
- Phase I-III study is undergoing

Rivaroxaban

- highly potent and selective direct FXa inhibitory activity
- Available in two different pharmaceutical formulations:
  - tablet
  - oral solution
- Half-lives
  - 3.24 to 4.15 hours with single dose administration
  - 7 to 17 hours with multiple dose administrations

Rivaroxaban, Preclinical Pediatric Studies

- Caused a significant increase in the clotting time (PT and aPTT) as well as an increase in lag time in neonates
- No significant differences in effect was observed across the older pediatric age groups
- Recently completed phase 3 trial showed efficacy and safety of rivaroxaban in treatment of pediatric VTE

Rivaroxaban, Pediatric Dosing Regimen

- In infants and preschool children (body weight:<40 kg)
  - increased doses would be required
- once-daily dosing in children with bodyweights of at least 30 kg
- twice-daily dosing in children with bodyweights of at least 20 kg and less than 30 kg
- twice-daily administrations in those with a bodyweight of at least 12 kg but less than 20 kg
- three times daily administrations in those weighing less than 12 kg

Rivaroxaban, Pediatric Dosing Regimen

- 0.8 mg/kg/day to 1.2 mg/kg/day, aged 6 months to less than 12 years
- adjusted to obtain blood levels equivalent to the adult 20-mg dose
- aged 12 to 18 years received 20 mg daily

Reversal agent for rivaroxaban and apixaban

- Andexanet alfa
  - recombinant modified human factor Xa decoy protein
  - binds and sequesters the Xa inhibitors
  - only FDA-approved agent

Summary

- Pediatric VTE occurs in a bimodal distribution, most commonly encountered in neonates and adolescents.
- The most common predisposing VTE risk factor in children is the presence of a central-access vascular catheter, either venous or arterial
- Acute DVT typically presents with unilateral pain, swelling, and/or erythema of the involved extremity.
- The most common imaging technique used for DVT diagnosis is Doppler ultrasonography

Summary

- The prevalence of at least 1 inherited thrombophilia condition in children with a newly diagnosed VTE ranges from 13% to 79%.
- Unfractionated heparin, low-molecular-weight heparin (LMWH), and vitamin K antagonists are first-line therapies for VTE treatment in pediatrics.
- LMWH has become the drug of choice for short- and long-term treatment of an acute DVT as well as for DVT prophylaxis in children.

Summary

- Direct oral anticoagulants are not yet officially approved for use in pediatric patients younger than 18 years.
- Thrombolytic therapy is used only in the setting of a life- or limb threatening thrombosis episode.