ACUTE & CHRONIC ANTICOAGULATION THERAPY IN THE PEDIATRIC POPULATION

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DISCLOSURES

- The content experts have no relevant financial relationships with commercial interests pertaining to the content presented in this program.

- This presentation will include discussion of the off-label use of medications in pediatrics.

OBJECTIVES

At the conclusion of this presentation, participants should be able to:

- Summarize the coagulation cascade
- Discuss the classes of anticoagulation medications utilized in the pediatric population
- Determine appropriate anticoagulation agents for the prophylactic management of thromboembolic events in the pediatric population
- Determine appropriate anticoagulation agents for the treatment of thromboembolic events in the pediatric population.

EPIDEMIOLOGY

- Lower thrombotic potential:
  - Decreased procoagulant factors
  - Increased alpha2-macroglobin
  - Decreased thrombotic potential of vasculature endothelium

58 per 10,000 pediatric admissions
8% mortality rate of VTE admissions
9-21% recurrence rate after resolution

McCrory MC et al. *Pediatr Crit Care Med*. 2011;12(1):80-89.
Parasuraman S et al. *Circulation*. 2006;113:e12-e16.
Raffini L et al. Pediatrics. 2009;124(4):1001-1008.
Monagle P et al. *Pediatr Res*. 2000;47(6):763-766.
Stein PD et al. *J Pediatr*. 2004;145(4):563-565.

RISK FACTORS

- Post-pubertal age*
  - Adolescent girls > adolescent boys
  - Estrogen therapy (started < 1 month)
  - Pregnancy
- Neonatal population*
- Central venous catheter*
- Malignancy
- Systemic infection
- Congenital heart disease
- Gastrointestinal failure
- Sickle cell disease
- Traumatic injury
- ICU Admission

- Thrombogenic medications
  - L-asparaginase
  - Steroids
- Immobility
- Mechanical ventilation
- Surgery > 90 min within last 14 days
- Antiphospholipid antibody syndrome
- Congenital & acquired prothrombotic conditions

McCrory MC et al. *Pediatr Crit Care Med*. 2011;12(1):80-89.
Parasuraman S et al. *Circulation*. 2006;113:e12-e16.
Stein PD et al. *J Pediatr*. 2004;145(4):563-565.
Mahajerin A et al. *Haematologica*. 2015;100:1045-50.
Branchford BR et al. *J Thromb Haemost*. 2017;15:2274-78.

MATURATION DIFFERENCES

- Antithrombin will reach levels close to adults by 6 months
- Delayed maturation throughout childhood and adolescence
  - Vitamin-K dependent factors (i.e. II, VII, IX, and X)
  - 50% of adult values at infancy
  - 80-90% of adult levels throughout childhood
  - Protein C & S reach 20-60% of adult levels throughout childhood
- Maturation differences effect inhibition of thrombin generation, decreasing sensitivity to anticoagulants, and increasing clearance

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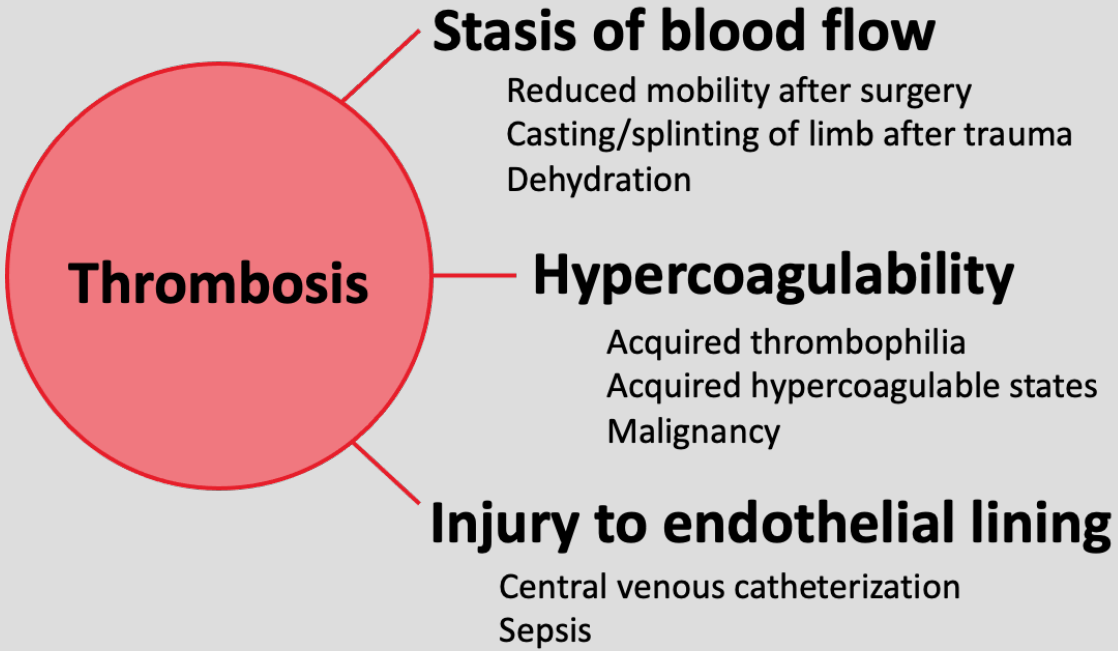
Parasuraman S et al. *Circulation*. 2006;113:e12-e16.
Monagle P et al. *Pediatr Res*. 2000;47(6):763-766.

VIRCHOW'S TRIAD

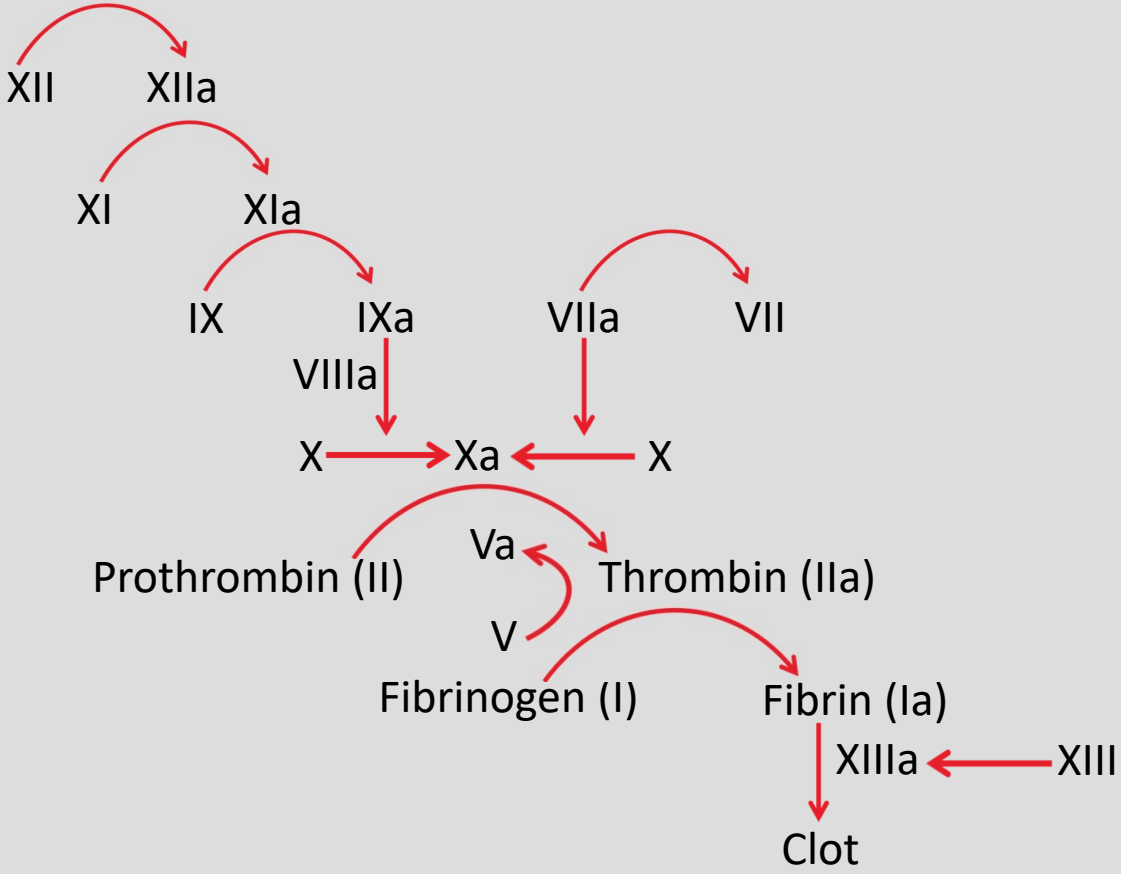


Stein PD et al. *J Pediatr*. 2004;145(4):563-565.
Monagle P et al. *Pediatr Res*. 2000;47(6):763-766.
Goldenberg N. *Clinical Advances in Hematology and Oncology*. 2019;17(6):326-29.

CLINICAL PRESENTATION & DIAGNOSIS

- Pain, discoloration, swelling distal to thrombosis
- Catheter-related thrombosis
  - Malfunctioning intravenous line
  - Infection unexplained by another source
- Thrombocytopenia due to platelet consumption
- Elevated D-dimer
- Doppler ultrasonography, echocardiography, computed tomography

McCrory MC et al. *Pediatr Crit Care Med*. 2011;12(1):80-89.
Parasuraman S et al. *Circulation*. 2006;113:e12-e16.
Monagle P et al. *Pediatr Res*. 2000;47(6):763-766.



ACUTE TREATMENT

Heparin

Enoxaparin

HEPARIN

- Mucopolysaccaride molecule of various lengths (3000 to 30,000 daltons)
- Extracted from porcine intestinal mucosa
- Mechanism of Action
  - Potentiator of anti-thrombin to inhibit protease activation of clotting factors
  - Heparin-anti-thrombin complex is 100-1000 more potent than endogenous anti-thrombin
  - Predominantly inhibits factor IXa, Xa, XIIa and thrombin (IIa)

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HEPARIN – INITIAL DOSING

- Bolus dose (in certain populations)
  - 75 units/kg (max dose: 5000 units) infused over 10 minutes
- Initial Continuous Maintenance Dosing
  - Neonates and Infants (< 1 year): 28 units/kg/hr
  - Children and Adolescents (≥ 1 year): 20 units/kg/hr
  - Adults or obese (BMI ≥ 95th percentile): 18 units/kg/hr (Max dose: 2000 units/hr)

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HEPARIN - MONITORING

- Anti-xa (heparin) level
  - Therapeutic
    - 0.3 – 0.7 units/mL
  - Prophylactic
    - 0.1-0.3 units/mL
- aPTT
  - Therapeutic
    - Between 70-101 seconds
  - Prophylactic
    - Between 40-70 seconds

- CBC
- Hemoglobin
- Hematocrit
- Platelets

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HEPARIN: DOSING TITRATION

Table 1. Heparin Titration Guideline to Target Therapeutic Levels: table modified from Nair et al. *J Thorac Cardiovasc Surg*. 2018.[6] Recommendations are aligned with the TCH Formulary.

Heparin Level \ aPTT	<60	60-69	70-101	102-112	113-130	>130
<0.2	• Bolus 50 units/kg • Increase infusion rate by 10% • Repeat aPTT and heparin level in 4h	• Increase infusion rate by 10% • Repeat aPTT and heparin level in 4h	• Keep rate the same • Repeat aPTT and heparin level in 12h	• Decrease infusion rate by 10% • Repeat aPTT and heparin level in 4h	• Hold infusion for 30 min then restart at 10% decreased rate • Repeat aPTT and heparin level 4h after restarting	• Repeat aPTT and heparin level • Hold infusion for 1h then restart at 15% decreased rate • Repeat aPTT and heparin level 4h after restarting
0.2-0.29	• Increase infusion rate by 10% • Repeat aPTT and heparin level in 4h					
0.3-0.7	• Keep rate the same • Repeat aPTT and heparin level in 12h					
0.71-0.8	• Decrease infusion rate by 10% • Repeat aPTT and heparin level in 4h					
0.81-0.99	• Hold infusion for 30 min then restart at 10% decreased rate • Repeat aPTT and heparin level 4h after restarting					
≥1	• Repeat aPTT and heparin level • Hold infusion for 1h then restart at 15% decreased rate • Repeat aPTT and heparin level 4h after restarting					

To use this table, both aPTT and heparin level must be obtained simultaneously. For the appropriate action to take in titrating the heparin, find where the patient's aPTT (column) intersects with the patient's heparin level (row) and follow instructions .

Texas Children's Hospital. (2021). *Initiation and Maintenance of Unfractionated Heparin (non-ECMO) TXCH Best Current Practice Standard* [Guideline].

HEPARIN – DOSE FORMULATIONS

- IV and SubQ Formulations
  - Many pre-filled syringes and pre-mix bags available
  - Many concentrations available
    - 1 unit/mL –20,000 units/mL
  - Common pre-mix bag:
    - 25,000 units/250 mL = 100 units/mL

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HEPARIN - ADVERSE DRUG REACTIONS

- Bleeding & Bruising
- Hyperkalemia
- Thrombocytopenia
  - Heparin associated thrombocytopenia
  - Heparin induced thrombocytopenia

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Unfractionated Heparin (non-ECMO) TXCH Best Current Practice Standard* [Guideline].

HEPARIN – REVERSAL

- Protamine sulfate - basic, positively charged compound
  - Dosing (Max dose: 50 mg)
    - 1 mg neutralize 100 units of heparin

Time Since UFH Dose	Protamine Dose (mg)
< 30 min	1
30-60 min	0.5 – 0.75
60-120 min	0.375 – 0.5
> 120 min	0.25 – 0.375

  - Administration:
    - Rate not to exceed 5 mg/min

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Unfractionated Heparin (non-ECMO) TXCH Best Current Practice Standard* [Guideline].

ENOXAPARIN

- Fragments of UFH with 1/3 the molecular weight of heparin
- Similar mechanism of action to UFH
  - Potentiate anti-thrombin III

- **Advantages**
  - Quicker action (3-5hrs)
  - Longer half life and better SQ bioavailability
  - Less immunogenic thrombocytopenia
  - Less lab monitoring required
  - More predictable anticoagulation

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ENOXAPARIN – TREATMENT DOSING

- **Premature Neonates & Infants < 2 months**
  - PMA < 32 weeks: 2 mg/kg/dose q12h subcutaneously
  - PMA 33-40 weeks: 1.75 mg/kg/dose q12h subcutaneously
  - PMA > 40 weeks: 1.5 mg/kg/dose q12h subcutaneously
- **Infants > 2 months and Adults**
  - 1 mg/kg/dose q12h subcutaneously

- **Special Populations – Obesity**
  - Patients with BMI > 50 kg/m2: 0.75 to 0.85 mg/kg q12h subcutaneously

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Enoxaparin TXCH Best Current Practice Standard*. [Guideline].

ENOXAPARIN – PROPHYLAXIS DOSING

- **Infants < 2 months old (including premature infants)**
  - 0.75 mg/kg/dose q12h subcutaneously
- **Infants > 2 months old**
  - 0.5 mg/kg/dose q12h subcutaneously
- **Adults and adolescent (≥ 60 kg)**
  - 40 mg/dose q24h subcutaneously

- **Special Populations – Obesity**
  - BMI ≥ 40 kg/m2
    - 40 mg/dose q12h subcutaneously
  - BMI ≥ 50 kg/m2
    - 60 mg/dose q12h subcutaneously

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Enoxaparin TXCH Best Current Practice Standard*. [Guideline].

ENOXAPARIN - MONITORING

- Anti-xa (lovenox) peak level
  - Therapeutic
    - 0.5 – 1 units/mL
  - Prophylactic
    - 0.2-0.4 units/mL

- CBC
- Hemoglobin
- Hematocrit
- Platelets

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Enoxaparin TXCH Best Current Practice Standard*. [Guideline].

ENOXAPARIN DOSE TITRATION

Treatment	Prophylaxis	Dose Titration
< 0.35 units/mL	< 0.15 units/mL	Increase dose by 25%
0.35 - 0.49 units/mL	0.15 - 0.19 units/mL	Increase dose by 10%
0.5 - 1 units/mL	0.2 - 0.4 units/mL	Keep same dosage
1.1 - 1.5 units/mL	0.41 - 1 units/mL	Decrease dose by 20%
1.6 - 2 units/mL	1.1 - 2 units/mL	Decrease dose by 30% and delay by 3 hours
> 2 units/mL	> 2 units/mL	Repeat Lovenox® level; hold all doses until Lovenox®level is 0.5 units/mL, then decrease dose by 40%

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Enoxaparin TXCH Best Current Practice Standard*. [Guideline].

ENOXAPARIN – DOSE FORMULATIONS

- Compounded product (limited availability)
  - 10 mg/mL or 20 mg/mL concentration
- Vial
  - 100 mg/1 mL (3 mL)
- Prefilled syringes, including but not limited to:
  - 100 mg/mL concentration
    - 30 mg; 40 mg; 60 mg*; 80 mg*; 100 mg*
  - 150 mg/mL concentration
    - 120 mg; 150 mg

* Graduations available

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ENOXAPARIN – PEDIATRIC CONSIDERATIONS

- Enoxaparin Dose Rounding
  - **Doses < 10 mg**
    - Round to the nearest whole mg (round down if 0.4 or less; round up if 0.5 or greater.
      - EXAMPLE: 3.4 mg should be rounded to 3 mg; 3.5 mg should be rounded to 4 mg
  - **Doses ≥ 10 mg – < 30 mg:**
    - Round UP to the next whole mg.
      - EXAMPLE: 10.1 mg should be rounded UP to 11 mg
  - **Doses ≥ 30 mg**
    - Round UP by 10% to the nearest prefilled syringe demarcations

ENOXAPARIN – PEDIATRIC CONSIDERATIONS

- Formulation considerations
  - **Doses < 10 mg:**
    - Enoxaparin 100 mg/mL vial (3 mL)
      - REQUIRES: Insulin 30 units/0.3 mL syringes
    - Compounded product (limited availability)
  - **Doses ≥ 10 mg – < 30 mg:**
    - Enoxaparin 100 mg/mL vial (3 mL)
      - REQUIRES: Tuberculin 0.5 mL syringes
    - Compounded product (limited availability)
  - **Doses ≥ 30 mg:**
    - Enoxaparin 100 mg/mL vial (3 mL)
      - REQUIRES: Tuberculin 0.5 mL or 1 mL syringes
    - Pre-filled syringes (various doses)

ENOXAPARIN - ADVERSE DRUG REACTIONS

- Bleeding & Bruising
- Hyperkalemia
- Thrombocytopenia
  - Heparin associated thrombocytopenia
  - Heparin induced thrombocytopenia

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Enoxaparin TXCH Best Current Practice Standard*. [Guideline].

ENOXAPARIN – REVERSAL

- Protamine sulfate - basic, positively charged compound
  - Dosing (Max dose: 50 mg)
    - 1 mg neutralize 1 mg of enoxaparin

Time Since Enoxaparin Dose	Protamine Dose (mg)
< 8 hours	1
8 – 12 hours	0.5
> 12 hours	May not be required

  - Administration:
    - Rate not to exceed 5 mg/min

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Enoxaparin TXCH Best Current Practice Standard*. [Guideline].

CHRONIC TREATMENT

Warfarin

Rivaroxaban

Apixaban

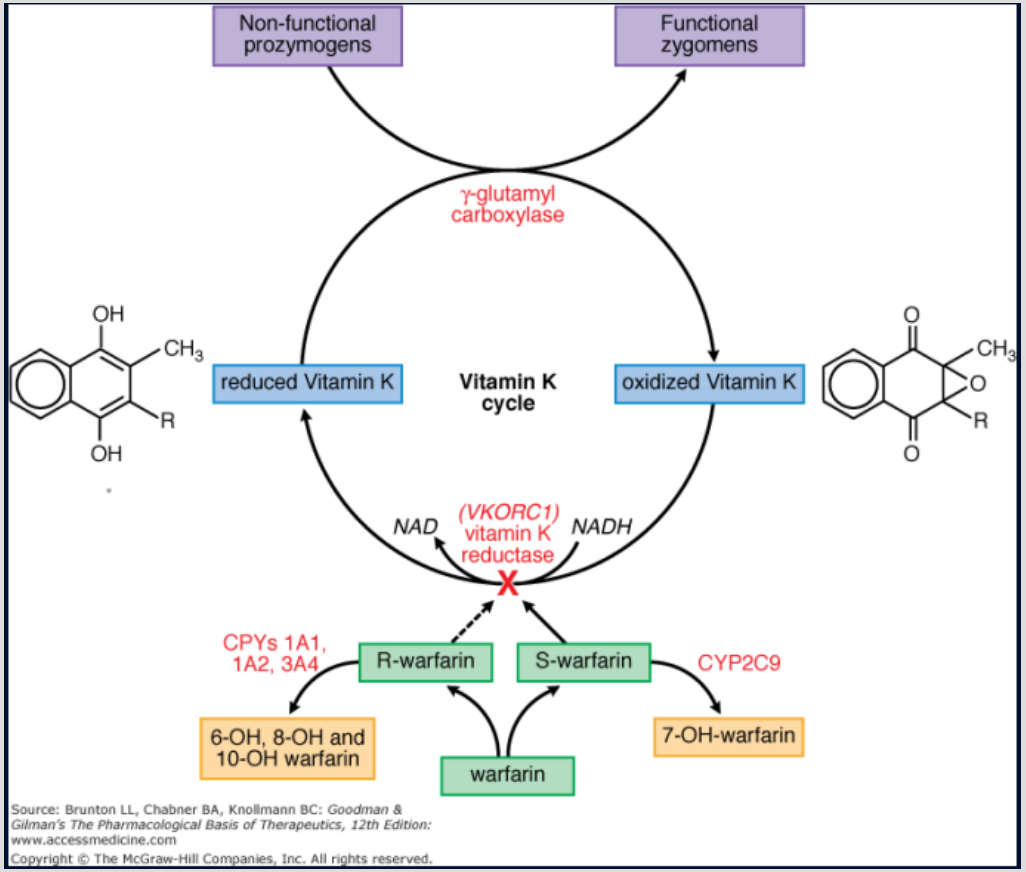
Dabigatran

WARFARIN

- Coumarin derivative - rat poisoning
  - Approved in 1954 for the treatment of thromboembolism
- Mechanism of Action – Vitamin K Antagonist
  - Inhibits vitamin K dependent clotting factors
- Not all factors affected at the same time
  - Bridging with IV anticoagulant recommended

Vitamin K Dependent Proteins	Half-life (hours)
Factor II	42-72
Factor VII	4-6
Factor IX	21-30
Factor X	27-48
Protein C	8
Protein S	60

WARFARIN – MECHANISM OF ACTION



WARFARIN – LOADING DOSE

- For patients transitioning from UFH or LMWH to warfarin
  - Warfarin 0.2 mg/kg/DOSE
    - Max loading dose: 10 mg
- For patients with liver disease, s/p Fontan procedure and/or at high risk for bleeding
  - Warfarin 0.1 mg/kg/DOSE
    - Max loading dose: 5 mg

WARFARIN – DOSE FORMULATIONS

- Tablet strengths
  - 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg

Warfarin tablets may come in different shapes. But each strength comes in just one color. Make sure the color of your tablets matches the strength your doctor prescribed.

WARFARIN – DOSE TITRATION (DAYS 1 – 4)

Table 1. Warfarin Loading Dosing Nomogram (Days 1 to 4)

Day 1	Dose 0.2 mg/kg x 1 PO (Max: 10 mg)
Loading days 2-4	
INR 1.1-1.3	Repeat initial loading dose
INR 1.4-1.9	50% of initial loading dose
INR 2-3	50% of initial loading dose
INR 3.1-3.5	25% of loading dose
INR > 3.5	Hold until INR < 3.5 then restart at 50% of previous dose

WARFARIN DOSE TITRATION (DAYS ≥ 5)

Table 2. Warfarin Maintenance Dosing Nomogram (≥ day 5) (Lexicomp, adapted from Hadlock 2018)
(See Table 3 for recommendations when to use INR goal 2-3 vs. 2.5-3.5)

As with Loading Dosing nomograms, maintenance therapy nomograms must be used with clinical judgment.

SUBtherapeutic INR

Adjustment(s) for subtherapeutic (low) INR – Note: If the factor causing subtherapeutic INR is transient (eg, missed warfarin dose or temporary change in vitamin K intake), consider resumption of prior maintenance dose following a one-time supplemental dose, if indicated.

INR goal 2-3	INR goal 2.5-3.5	Suggested adjustment(s) to warfarin dose
1.1-1.4	1.1-1.9	• Increase weekly maintenance dose by 20%. Check INR in 72 hours.
INR 1.5-1.7	INR 2-2.2	• Increase weekly maintenance dose by 10%. Check INR in 72 hours.
INR 1.8-1.9	INR 2.3-2.4	• No dosage adjustment may be necessary if the last 2 INRs were in range. If there is no clear explanation for out of range INR, and if clinical judgment does not suggest the INR represents an increased risk of thromboembolism, additional monitoring may be warranted • If dosage adjustment needed, increase weekly maintenance dose by 10%. Check INR in 72 hours.

INR within therapeutic range

INR goal 2-3	INR goal 2.5-3.5	Suggested adjustment(s) to warfarin dose
INR 2-3	INR 2.5-3.5	Desired range; no adjustment needed

WARFARIN DOSE TITRATION (DAYS ≥ 5)

SUPRAtherapeutic INR

Adjustment(s) for supratherapeutic (high) INR – Note: If the factor causing elevated INR is transient (eg, temporary change in vitamin K intake, acute illness), consider resumption of prior maintenance dose following dose(s) held and low-dose oral vitamin K, if indicated.

INR goal 2-3	INR goal 2.5-3.5	Suggested adjustment(s) to warfarin dose
INR 3.1-3.2	INR 3.6-3.7	• No dosage adjustment may be necessary if the last 2 INRs were in range, if there is no clear explanation for the out of range INR, and, if clinical judgment does not suggest the INR represents an increased risk of hemorrhage to patient, additional monitoring may be warranted • If dosage adjustment needed, decrease weekly maintenance dose by 10%. Check INR in 72 hours.
INR 3.3-3.4	INR 3.8-3.9	• Decrease weekly maintenance dose by 10%. Check INR in 72 hours.
INR 3.5-3.9	INR 4- 4.4	• Consider holding 1 dose • Decrease weekly maintenance dose by 20%. Check INR in 72 hours.
INR ≥ 4 but ≤ 10 and no bleeding	INR ≥ 4.5 but ≤ 10 and no bleeding	• Hold until INR below upper limit of therapeutic range • Decrease weekly maintenance dose by 20%. Check INR in 72 hours. • If patient is at significant risk for bleeding, consider Vit. K 2.5mg PO once
INR > 10	INR > 10	See Section Below Management of warfarin-associated supratherapeutic INR with or without bleeding.

WARFARIN – THERAPEUTIC GOALS

INR 1.5 – 2

- Occasional complex care patients with needs for secondary prophylaxis

INR 2 – 3

- Treatment of VTE, SVT, PE or secondary prevention in patients with ongoing risk factors
- Bio-prosthetic mitral valve and no additional risk factors
- Mechanical aortic valve
- Single ventricle physiology or post-Fontan
- Dilated cardiomyopathy
- Giant aneurysm(s) due to Kawasaki disease
- Acute ischemic stroke due cardioembolism or dissection
- Atrial fibrillation

INR 2.5 – 3.5

- Mechanical mitral valve
- VTE, SVT or PE with lupus anticoagulant and/or antiphospholipid syndrome

WARFARIN - MONITORING

- Laboratory Values
  - INR (International Normalized Ratio)
    - Normal INR = 0.9-1.2
  - CBC (Complete Blood Count)
    - Hemoglobin: Normal = 12-16 g/dL (F) and 14-18 g/dL (M)
    - Hematocrit: Normal = 36-45% (F) and 42-50% (M)
- Frequency of monitoring
  - Initial
    - Daily → 2x per week → weekly (once INR consistently within range)
  - Can be prolonged from weekly to monthly (depending on various factors)

WARFARIN - INTERACTIONS

- Potential interactions exist with the following:
  - Disease state
  - Drug-Drug interactions
  - Drug Herbal interactions
  - Food Drug interactions

- Warfarin could be increased, decreased, and/or risk of bleeding affected

WARFARIN - INTERACTIONS

- INR should be checked whenever there has been a change to:
  - Medications and/or supplements
  - Dietary habits
  - New gastrointestinal symptoms and/or reduced oral intake
  - Fever and infection
  - Prolonged antibiotics
  - Hepatic function

WARFARIN - ADVERSE DRUG REACTIONS

- Bruising and bleeding complications
  - May require reversal depending on severity
- Potential teratogenic effects
- Hepatitis
- Purple toe syndrome
- Skin necrosis

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Texas Children's Hospital. (2021). *Initiation and Maintenance of Warfarin in Patients > 9 kg TXCH Best Current Practice Standard.* [Guideline].

WARFARIN – REVERSAL

INR	Bleeding?	Treatment	Reversal Agents
4.5 – 10	No	Monitor more closely Hold warfarin until INR decreases Look for causes and address Restart at a lower dose	Vitamin K not recommended
> 10	No	Hold warfarin until INR decreases Identify causes Restart at lower dose	Give oral Vitamin K
Any	Yes	Hold warfarin	Rapid Reversal required 1. Four-factor prothrombin complex concentrate (PCC) 2. IV Vitamin K

DIRECT ORAL ANTICOAGULANTS (DOACS)

Rivaroxaban

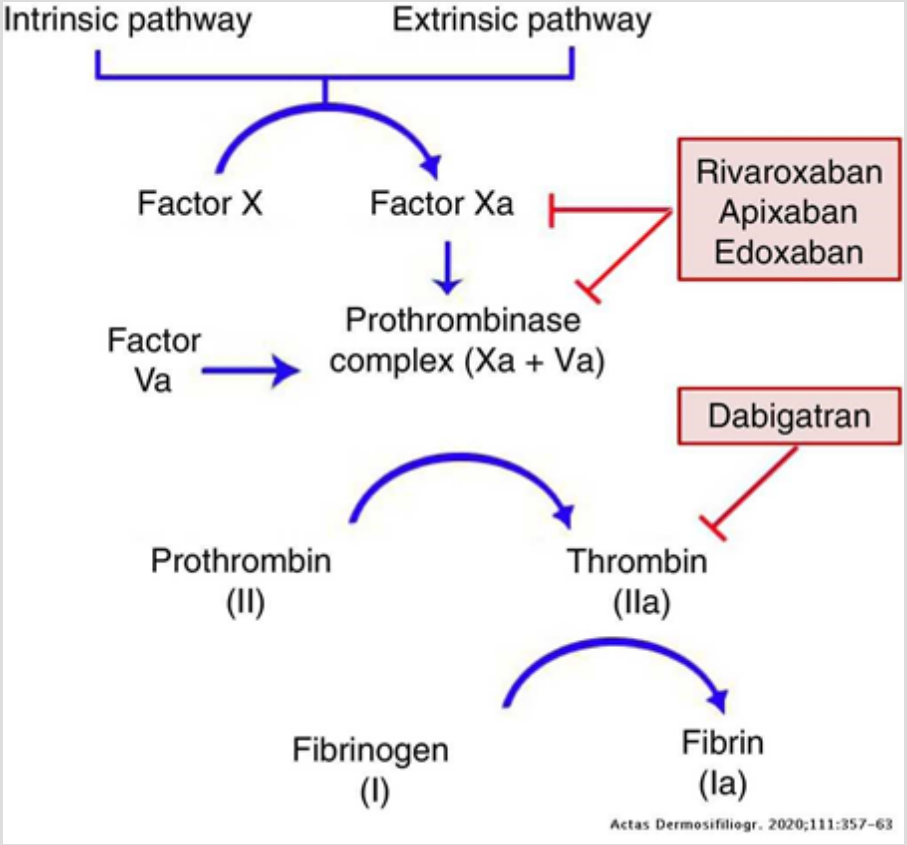
Apixaban

Dabigatran

DOAC MECHANISMS

- Anti-Xa Inhibitors
  - Reversible inhibition of factor Xa
  - Inhibits thrombin induced platelet aggregation

- Direct Thrombin Inhibitors



WHY DOACS?

- No injections
- No therapeutic drug monitoring
- No special diet requirements

RIVAROXABAN – INDICATIONS

- Thromboprophylaxis in patients age ≥ 2 years with congenital heart disease who have undergone Fontan procedure
- Treatment of venous thromboembolism (VTE) in patients < 18 years after ≥ 5 days of initial treatment with a parenteral anticoagulant
- Risk reduction of recurrent VTE in patients < 18 years after ≥ 5 days of initial treatment with a parenteral anticoagulant

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Texas Children's Hospital. (2020). *Rivaroxaban for the Treatment of Acute Venous Thrombosis in Children and Adolescents TXCH Best Current Practice Standard.* [Guideline].

RIVAROXABAN – PROPHYLAXIS DOSING

- GA ≥ 37 weeks
  - 2.6 to 2.9 kg: 0.8 mg/dose every 8 hours
  - 3 to 3.9 kg: 0.9 mg/dose every 8 hours
  - 4 to 4.9 kg: 1.4 mg/dose every 8 hours
  - 5 to 6.9 kg: 1.6 mg/dose every 8 hours

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RIVAROXABAN – PROPHYLAXIS DOSING

Body weight	Once daily dosing	Twice daily dosing	Total daily dose
7 to < 8 kg		1.1 mg	2.2 mg
8 to < 10 kg		1.6 mg	3.2 mg
10 to <12 kg		1.7 mg	3.4 mg
12 to < 20 kg		2 mg	4 mg
20 to < 30 kg		2.5 mg	5 mg
30 to < 50 kg	7.5 mg		7.5 mg
≥ 50 kg	10 mg		10 mg

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RIVAROXABAN – < 18 YRS TREATMENT DOSING

Body weight	Once daily dosing	Twice daily dosing	Three times daily dosing	Total daily dose
2.6 to < 3 kg			0.8 mg	2.4 mg
3 to < 4 kg			0.9 mg	2.7 mg
4 to < 5 kg			1.4 mg	4.2 mg
5 to < 7 kg			1.6 mg	4.8 mg
7 to < 8 kg			1.8 mg	5.4 mg
8 to < 9 kg			2.4 mg	7.2 mg
9 to < 10 kg			2.8 mg	8.4 mg
10 to <12 kg			3 mg	9 mg
12 to < 30 kg		5 mg		10 mg
30 to < 50 kg	15 mg			15 mg
≥ 50 kg	20 mg			20 mg

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RIVAROXABAN – ≥ 18 YRS TREATMENT DOSING

- Days 1 to 21: 15 mg BID
- Day 22+: 20 mg once daily

- Duration based on adult VTE guidelines

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RIVAROXABAN – ORGAN IMPAIRMENT DOSING

- Renal adjustment
  - Avoid use in patients with eGFR < 30 mL/minute

- Hepatic adjustment
  - Avoid use in patients with hepatic disease associated clinically relevant bleeding risk
  - Avoid use if any of the following: ALT > 5x ULN or total bilirubin > 2x ULN with conjugate bilirubin > 20% of total

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RIVAROXABAN – MONITORING

- CBC
- SCr
- Liver function tests
- DIC panel (PT, PTT, fibrinogen, D-dimer)

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RIVAROXABAN – DOSE FORMULATIONS

- Oral tablets
  - 2.5 mg, 10 mg, 15 mg, 20 mg
    - 15 mg and 20 mg tablets should be taken with food
    - Tablets may be crushed and mixed with water or applesauce. Consume within 4 hours

- Oral suspension
  - 1 mg/mL

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RIVAROXABAN – ADVERSE DRUG REACTIONS

- Bleeding
- Gastroenteritis
- Vomiting
- Cough
- Skin rash
- Fatigue
- Back pain

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RIVAROXABAN – TRANSITIONING

- Transitioning from another anticoagulant **TO** rivaroxaban
  - If previously on UH or LMWH, rivaroxaban should be initiated at the time that the UH
  - infusion is discontinued or within 2 hours of the next scheduled LMWH dose.
  - 2. If previously on warfarin, discontinue warfarin and start rivaroxaban when the INR is <3.

- Transitioning to another anticoagulant **FROM** rivaroxaban
  - Switching from rivaroxaban to LMWH: discontinue rivaroxaban and give the first dose of LMWH at the time that the next rivaroxaban dose is due.
  - Switching from rivaroxaban to warfarin: as rivaroxaban affects INR, INR measurements
  - during coadministration of the two medications will not be useful. Discontinue rivaroxaban and begin warfarin at the next scheduled dose of rivaroxaban. Use LMWH to bridge to therapeutic warfarin using standard practice.

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APIXABAN– INDICATIONS

- Age ≤ 18 yrs
  - Currently being investigated in children for prevention of VTE in cardiac disease and pediatric acute lymphoblastic leukemia (ALL)*
- Age ≥ 18 yrs
  - Treatment of DVT and PE
  - Reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation
  - Prophylaxis of DVT in those who have undergone hip or knee replacement surgery
  - Risk reduction of recurrent DVT or PE following initial therapy

*Consider in scenarios where use of standard anticoagulation is challenging or contraindicated

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APIXABAN– TREATMENT DOSING

- Nonvalvular atrial fibrillation
  - Initial: 5 mg twice daily
    - 2.5 mg twice daily if: body weight ≤ 60 kg and SCr ≥ 1.5 mg/dL

- Venous thromboembolism
  - 10 mg twice daily x 7 days, followed by 5 mg twice daily
    - Treatment duration:
      - Provoked PE/DVT with transient risk factor: 3-6 months provided risk factor is no longer present
      - Provoked PE/DVT with chronic risk factor: 3-6 months; indefinite courses are considered depending on risk of VTE recurrence and bleeding
      - Unprovoked PE/DVT: 3-6 months; indefinite courses are considered depending on risk of VTE recurrence and bleeding

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APIXABAN– MONITORING

- CBC
- SCr
- Liver function tests
- DIC panel (PT, PTT, fibrinogen, D-dimer)

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APIXABAN– DOSE FORMULATIONS

- Oral tablets
  - 2.5 mg, 5 mg

- Apixaban tablets may be swallowed whole or crushed and mixed with applesauce immediately prior to use and administered orally. Crushed tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours. For delivery through an NG tube, crushed tablets may be suspended in 60mL of water or D5W.

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APIXABAN– ADVERSE DRUG REACTIONS

- Bleeding
- Gastroenteritis
- Vomiting
- Cough
- Skin rash
- Fatigue
- Limb pain

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APIXABAN– TRANSITIONING

- Transitioning from another anticoagulant **TO** apixaban
  - If previously on UH or LMWH, apixaban should be initiated at the time that the UH infusion is discontinued or at the same time of the next scheduled LMWH dose.
  - If previously on warfarin, discontinue warfarin and start apixaban when the INR is <2.

- Transitioning to another anticoagulant **FROM** apixaban
  - Switching from apixaban to LMWH: discontinue apixaban and give the first dose of LMWH at the time that the next apixaban dose is due.
  - Switching from apixaban to warfarin: as apixaban affects INR, INR measurements during coadministration of the two medications will not be useful. Discontinue apixaban and begin warfarin at the next scheduled dose of apixaban. Use LMWH to bridge to therapeutic warfarin using standard practice.

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RIVAROXABAN AND APIXABAN REVERSAL

- First line
  - Non-activated prothrombin concentrate (KCentra)

- Second line
  - Andexanet Alpha

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Texas Children's Hospital. (2020). *Rivaroxaban for the Treatment of Acute Venous Thrombosis in Children and Adolescents TXCH Best Current Practice Standard.* [Guideline].

ANDEXANET ALPHA

- Binds and sequesters factor Xa inhibitors; inhibits activity of tissue factor pathway inhibitor, increasing tissue factor-initiated thrombin generation

- Dosing:

FXa inhibitor	FXa inhibitor dose	< 8H or unknown since last dose	> 8H since last dose
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg or unknown	High dose	
Apixaban	≤ 5 mg	Low dose	
	> 5 mg or unknown	High dose	

  - Low dose: 400 mg IV bolus, followed by IV infusion of 4 mg/min for up to 120 minutes
  - High dose: 800 mg IV bolus, followed by IV infusion of 8 mg/min for up to 120 minutes

- ADR: infusion site reaction, thromboembolic events, cardiac arrest

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DABIGATRAN – INDICATIONS

- Thromboprophylaxis to prevent recurrent clots in patients 3 months to < 12 years who have completed treatment for 1st VTE

- Treatment of VTE in patients 8 to < 18 years who have been treated with a parenteral anticoagulant for at least 5 days

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DABIGATRAN – CAPSULE DOSING FOR 8 TO <18 YRS

Weight	Dose
11 to < 16 kg	75 mg BID
16 to <26 kg	110 mg BID
26 to < 41 kg	150 mg BID
41 to < 61 kg	185 mg BID
61 to < 81 kg	220 mg BID
≥ 81 kg	260 mg BID

- Avoid use in patients with eGFR < 50 ml/min/1.73 m2

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DABIGATRAN– MONITORING

- CBC
- SCr
- DIC panel (PT, PTT, fibrinogen, D-dimer)
- Ecarin clotting test, thrombin time

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DABIGATRAN– DOSE FORMULATIONS

- Oral capsule
  - 75 mg, 110 mg, and 150 mg

- Oral pellets coming in June 2024
  - For patients age 3 months+

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DABIGATRAN– ADVERSE DRUG REACTIONS

- Bleeding
- Gastrointestinal irritation (indigestion, stomach upset, diarrhea)
- Abdominal pain
- Heartburn
- Nausea
- Skin rash

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DABIGATRAN– TRANSITIONING

- Transitioning **TO** dabigatran from:
  - LMWH or fondaparinux: Start dabigatran 0-2 hours prior to next scheduled dose of parenteral anticoagulant
  - Continuously administered parenteral anticoagulant: Start dabigatran when parenteral anticoagulant is discontinued
  - Warfarin: Start dabigatran when INR is < 2

- Transitioning **FROM** dabigatran to:
  - LMWH or fondaparinux: Wait 12 hours from last dose of dabigatran to start parenteral anticoagulant
  - Warfarin:
    - eGFR ≥ 50 mL/min/1.73 m2: Start warfarin 3 days after stopping dabigatran
    - EGFR < 50 mL/min/1.73 m2: Do not use dabigatran

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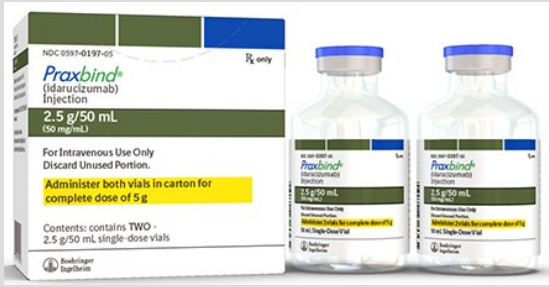
DABIGATRAN REVERSAL – IDARUCIZUMAB (PRAXBIND®)

- Humanized monoclonal antibody fragment that binds to dabigatran and its metabolites to neutralize the anticoagulant effect
- For life-threatening bleeding, bleeding into a critical organ or prior to an urgent or emergent procedure if other supportive measures are ineffective

- Dose:
  - 5 g IV dose given as 2 separate 2.5 g infusion

- ADR: headache, constipation, nausea



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Texas Children's Hospital®

COMMENTS/QUESTIONS?

ACUTE & CHRONIC ANTICOAGULATION THERAPY IN THE PEDIATRIC POPULATION

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