Available Strategies to Reverse Anticoagulant Medications

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Objectives

- Describe the pharmacological agents and therapeutic strategies available for use in patients who experience major bleeds
- Discuss the risk and limitations of current agents
 available for reversal
- Construct treatment plans to manage severe bleeds in a patients anticoagulation therapy

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- Anticoagulation is the cornerstone of treatment for thrombosis and thromboembolic complications
- In the United States, over six million patients are on anticoagulation therapy
- Evidence is limited on the management of bleeding and reversal of anticoagulation therapy

 Reversing therapy is a risk (thrombosis) verses risk
 - Reversing therapy is a **risk** (thrombosis) verses **risk** (bleeding) decision
 - Involves fully informed clinical decision making

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Reversal Decision Pathway

- 1. Assess Bleeding
- **2.** Determine Anticoagulation Therapy
- 3. Rapid Laboratory Testing

Assess Bleeding Severity

Major

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- Hemodynamically unstableBleeding in an
- anatomically critical location
- Requires transfusion
 ≥ 2 units of RBCs
- Decrease of hemoglobin – ≥ 2 g/dL drop in Hgb

Non-major

- All other bleeding not classified as major
- Patient may require intervention, transfusions, or hospitalization









- Hgb/HCT
- Platelet count
- Renal function
- Liver function
- DIC tests



Knowledge Check!

- A patient comes into the Emergency Department with a BP of 93/67, abdominal distention and recently was started on anticoagulation therapy
 - What steps would you take to triage this patient?
 - What acronym can you use to remember the decision pathway?
 - What laboratory values would be important to order?







- Indication: alternative reversal agent for patients on warfarin therapy when preferred agents are unavailable
- Mechanism of action: direct plasma transfusion of Vitamin K dependent coagulation factors

Dosing Depends upon the patient's size and clinical situation. The typical 70 kg adult dose is 4 to 6 units infused at 10ml/min. Dose: (10-15 mL/kg)

- Onset and Duration: variable
- Caution: hypervolemia with PE or cardiac failure, disease transmission, transfusion reactions associated with antibody generation, higher incidence of thrombosis, and risk of transfusion-related acute lung injury
 Contraindications: not indicated for volume expansion only, not
- Contraindications: not indicated for volume expansion only, not recommended as a protein or fibrinogen source

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- Indication: bleeding in patients with hemophilia who had inhibitors, suggested for major DOAC- associated bleeding
- Mechanism of action: vitamin K-dependent glycoprotein promotes
 hemostasis through extrinsic pathway
 - 90 ug/kg/dose IV *no clinical studies have evaluated
 - the reversal of DOACs with rFVIIa, avoid use if possible
- Onset varies: administration required every 2 hours until hemostasis is achieved
- Duration: $\frac{1}{2}$ life ~2 to 3 hours
- Contraindications: none listed in manufacturer's labeling
- US Boxed Warning: serious thromboembolic events are associated with use, monitor patients for signs and symptoms of thrombosis
- Warning: antibody formation, hypersensitivity reactions
- vvarning: antibody formation, nypersensitivity re or Vla (Recombinant). Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at https://onlin



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Hemodialysis

- Used in the reversal of dabigatran-associated life-threatening bleeding
 - Dabigatran: protein bound ~35%

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- Hemodialysis removes up to 68% of dabigatran DOAC activity
- Edoxaban is protein bound (~50%)

 trials did not demonstrate hemodialysis as an
- Initials did not demonstrate nemodallysis as an effective method for removal
- Apixaban and rivaroxaban are not dialyzable since they are highly protein bound





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Vitamin K (Phytonadione®)

carboxylase

oxidative deactivation.

Vit K epoxide reductase Biologically active prothrombin

Vit K

(epoxide)

Warfarin

Caution/Warnings

Mechanism of Action:

Precursor

Prothrombin

Vit K

(reduced)

Warfarin

- Infuse at <u>maximum rate of 1mg/min</u>
- Rapid IV push can cause hypotension or anaphylaxis
- Monitor
 - BP, INR, active bleeding
- Contraindications
 - Hypersensitivity to phytonadione or any components of the formulation
- High doses of Vitamin K (>10mg) may cause warfarin resistance for ≥1 week



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Protamine								
Indication: reverses unfractionated heparin, enoxaparin, dalteparin, tinzaparin, nadroparin								
 Mechanism of action: protamine given in the presence of heparin or LMWH forms a stable salt bond and the anticoagulant activity of both drugs is nullified; incompletely reverses the antifactor-Xa activity of LMWH 								
Heparin Last Administered	Dose	Enoxaparin Last Administered	Dose					
Immediate	nediate 1mg to 1.5 mg IV protamine sulfate/100 units of heparin		1mg IV protamine sulfate/1 mg of enoxaparin					
30 to 60 min	0.5 to 0.75mg IV protamine sulfate/100 units of heparin	> 8 hours ago or if aPTT remains	0.5mg IV of protamine/ 1mg of					
> 2 hours	0.25 to 0.375mg IV protamine sulfate/ 100 units of heparin	> 12 hours ago	May not be					
Unknown	25mg to 50mg IV SINGLE dose		required					
***Max dose: 50 mg	Muurullanik in Russende II. Antinia alakan Kalin ku							





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· Warnings/Precautions

- Anti-factor Xa activity re-elevation
- Thromboembolic and ischemic risks
- >10% Immunologic antibody development, infusion related reaction
- 1 to 10% DVT, stroke, MI, cardiac failure, UTI, pneumonia, acute respiratory failure
- Monitor
 - Signs and symptoms of hemostasis or thrombosis **Contraindications**
 - None listed in manufacturer's labeling

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Ciraparantag (Aripazine-PER977)

- Direct sequestering of heparin, direct factor Xa, and thrombin inhibitors
- Small synthetic water-soluable molecule
- Forms strong ionic, noncovalent bonds and large complex molecules that bind anticoagulation agents
- · Under evaluation in Phase II clinical trials

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Summary of Reversal Agents								
	Heparin or	Warfarin	Factor IIa	FXa Inhibitors		\$		
		(100)	(dabigatran)	Apixaban	Rivaroxaban	Edoxaban		
1 st line	Protamine	Vitamin K + 4F-PCC	Idarucizumab	Andexanet alfa				
Dose	Heparin Dose: 1 mg protamine / 100 units of heparin LMWH Dose: 1 mg IV protamine/1 mg of enoxaparin or 1 mg IV protamine / 100	Vitamin K Dose: 1-10 mg 4F-PCC Dose: 1500 units IV x 1 (or based on INR)	Dose: 2 x 2.5 g IV	Low dose: 400 mg IV bolus + 4 mg/minute IV influsion if apixaban < 5 mg or rivaroxaban < 10mg, or ≥ 8 hours since last dose High dose: 800 mg IV bolus + 8 mg/minute IV influsion if apixaban > 5mg or rivaroxaban > 10mg, or < 8 hours or unknown since last dose		800 mg IV bolus + 8 mg/minute IV infusion		
lf 1 st line is not available	anti-Xa units for dalteparin, tinzaparin,	Vitamin K + Plasma	PCC or aPCC	4F-PCC or aPCC				
Dose nad	nadroparin	Vitamin K Dose: 1-10 mg Plasma Dose:	Dose: 50 units/kg	4F-PCC: Dose: 25-50 units/kg IV aPCC: Dose: Dose: 50 units/kg IV		its/kg IV iits/kg IV		

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Resumption of Anticoagulation

- Benefits of resuming anticoagulation vs. the risk of recurrent bleeding
- Risk assessment of recurrent thrombosis
 - Utilize guidelines based on underlying indication for anticoagulation
 - Assess specific patient risk factors
 - Site of bleeding
 - Past medical history
 - · Clotting disorders, etc.

FXa^{I16L} (PF-05230907)

- A recombinant zymogen-like variant of activated factor X (FXa) that introduces an amino acid substitution of isoleucine for leucine at position 16
- Becomes activated when it encounters activated Factor V on damaged cellular surfaces
- · Restores hemostasis selectively at the site of bleeding
- Phase 1 clinical trial of FXa^{116L} conducted in healthy adults studying the effect on rivaroxaban or dabigatran

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Conclusion

- Evidence is limited on the reversal of anticoagulation agents
 - Many agents are available and pharmacist are a key promoter for the <u>right reversal agent</u>
 - Each agent comes with risks and limitations that are important to inform the patients and providers
- Utilize practice-based guidelines when developing treatment plans to manage severe bleeds

Knowledge Check!

• A 87 yo male reports to the anticoagulation clinic. You see him on a monthly basis and his INR is always within goal of 2-3. Today is the day after St. Patrick's Day. He reports of increased alcohol intake yesterday, and his INR comes back at 3.8. How would you manage this patient?

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Knowledge Check!

 A 76 yo female reports to the anticoagulation clinic with complaints of abdominal pain and distension. She reports feeling dizzy and weak the past 24 hours and has apparent tachypnea. Her INR comes back >4 and you are unable to detect it on a POCT, what is your clinical suspicion, how should you proceed?

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Knowledge Check!

- A 54 yo male is hospitalized status post coronary artery bypass grafting (CABG)
 - Heparin infusion at 1200 u/hr is administer for 3 hours
 - Patient begins complaining of lower extremity swelling and pain
 - A Doppler is ordered to rule out DVT and extremity bleeding is suspected
 - The provider wants to reverse the heparin, what do you recommend?

Knowledge Check!

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 - Assess for active bleeding
 - Hold Warfarin dose x 1; decrease weekly dose
- Counsel on signs and symptoms of bleeding
- Follow up with patient within the week

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Knowledge Check!

- A 76 yo female reports to the clinic with complaints of abdominal pain and distension. She reports feeling dizzy and weak the past 24 hours and has apparent tachypnea. Her INR comes back >4 and you are unable to detect it on a POCT. What is your clinical suspicion, how should you proceed?
 - Immediately refer to the Emergency Room
 - Intravenous INR draw
 - High clinical suspicion for intra-abdominal bleed
 - Select appropriate agent based on reversals available at your institution

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Knowledge Check!

- The provider wants to reverse the heparin, what do you recommend?
 - Stop heparin drip
 - Recommend Protamine 1mg/100units of heparin
 1200 units heparin x 3 hours = 3,600 units / 100 units
 36mg of Protamine
 - If bleeding persists consider another dose of protamine
 - Monitor for additional signs and symptoms of thrombosis

Knowledge Check!

- A 67yo male comes into the Emergency Department at 10:36am on Rivaroxaban 20mg nightly for nonvalvular atrial fibrillation. Upon CT scan, the patient shows evidence of an intracranial hemorrhage. Assuming the patient took the medication last night and all available reversal agents are available at your institution, what medication and dose would you recommend as the most effective agent?
 - KCentra 1500 units IV once
 - Andexxa 400 mg IV bolus followed by 4 mg/minute IV infusion for up to 120 minutes
 - Vitamin K 10mg IV once
 - Andexxa 800 mg IV bolus followed by 8 mg/minute IV infusion for up to 120 minutes

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