The Bloody Truth: Anticoagulation Reversal in the Critically Ill

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Disclosure

I have no financial conflicts of interest to disclose

Pharmacist Objectives

1. Explain the basic principles of hemostasis in critical bleeding
2. Discuss the pharmacologic options available for the management of critical bleeds
3. Describe the role of concentrated factors in life-threatening bleeds
4. Identify the new antidotes available for targeted reversal of specific anticoagulants

Technician Objectives

1. Explain the importance of controlling bleeding in the critically ill
2. Identify the pharmacologic options available for the management of critical bleeds
3. Describe the preparation and storage of pharmacologic agents used to control critical bleeds
4. List the new antidotes available for targeted reversal of specific anticoagulants

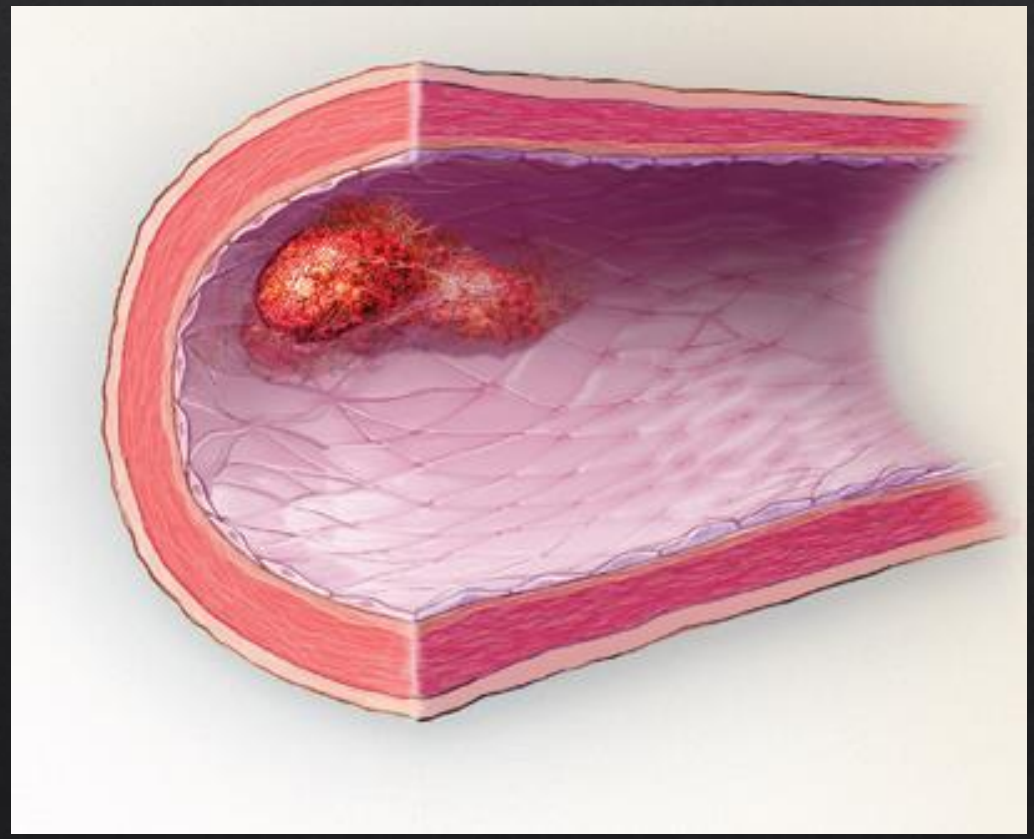
Critical Bleeding

- Acute blood loss = medical or surgical emergency
- May lead to acidosis, shock, arrhythmias, organ failure
- Increased length of stay and cost
- Increased mortality
  - Blood loss >50% often fatal
  - 30-40% of trauma-related deaths
  - Anticoagulant-associated bleeding – 5-fold increase risk of death in first 30 days

N Engl J Med 2007;356:1201-2311.

Pathophysiology of Hemostasis

- Vessel wall injury exposes collagen and tissue factor
- Collagen triggers platelet accumulation and activation
- Tissue factor initiates generation of thrombin
- Thrombin converts fibrinogen to fibrin and activates platelets

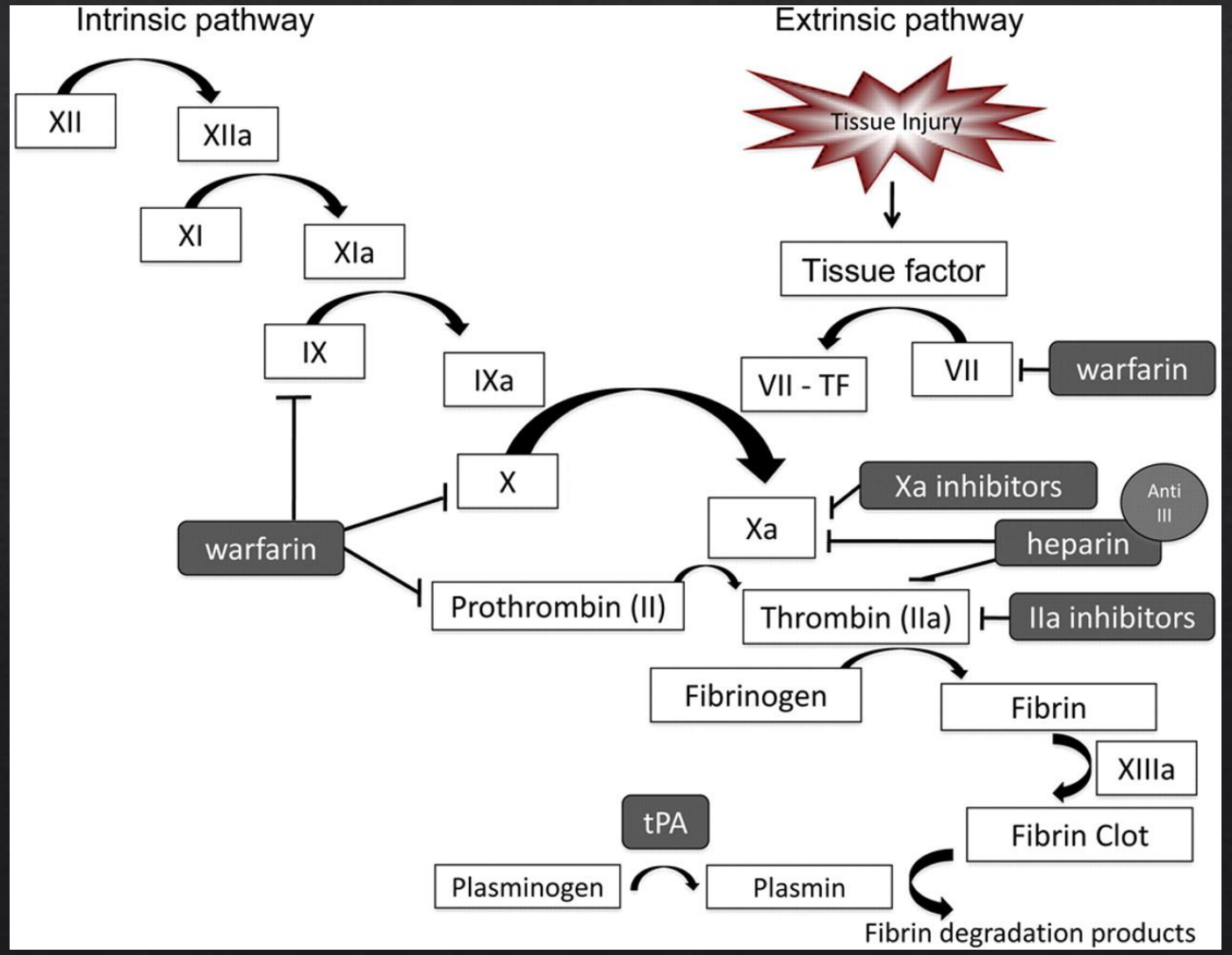


N Engl J Med 2008;359:938-949.

Anticoagulants

- Heparin
- Low molecular weight heparin
- Warfarin
- Direct thrombin inhibitors
- Factor Xa inhibitors

Coagulation Cascade

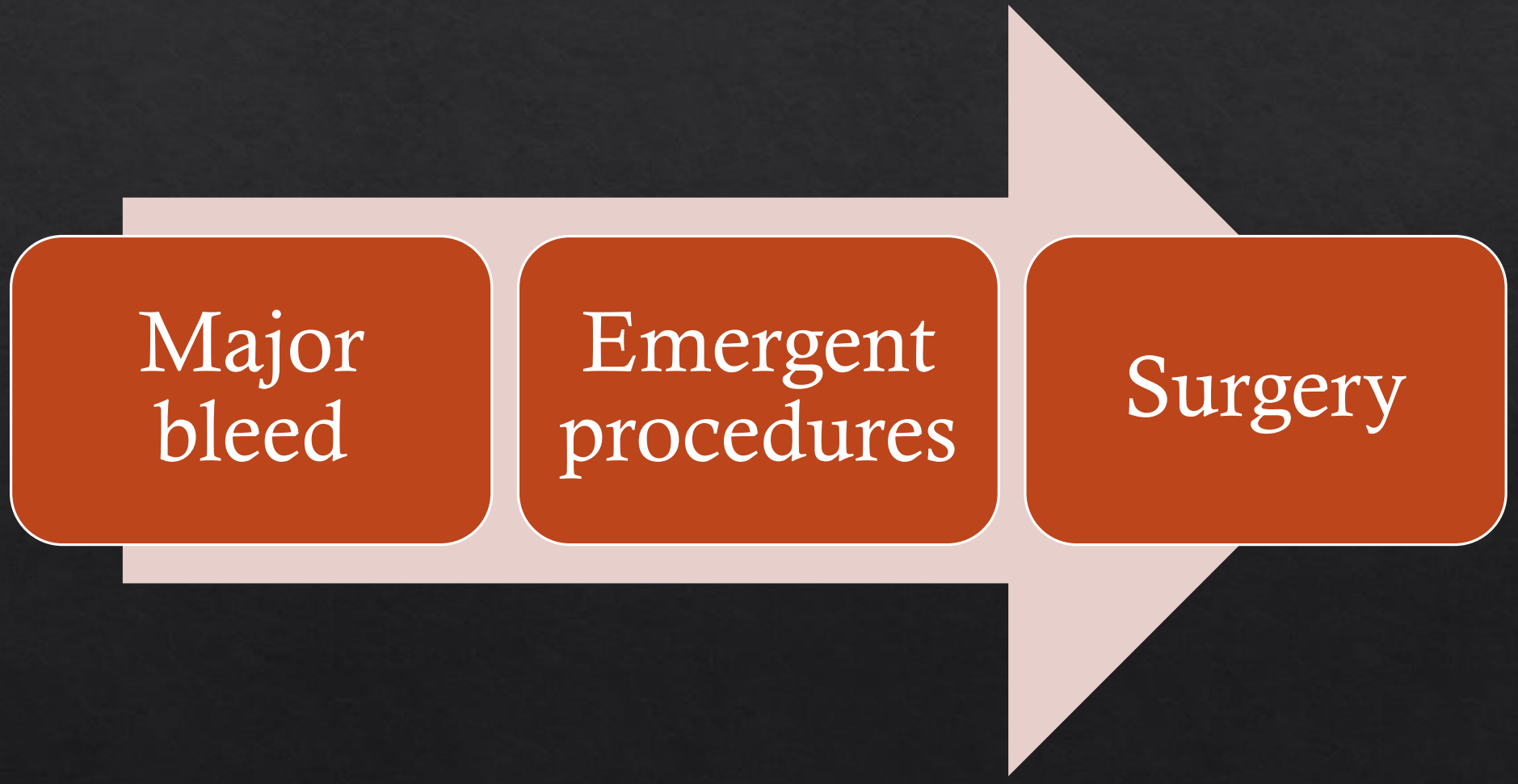


Anticoagulant Pharmacokinetics

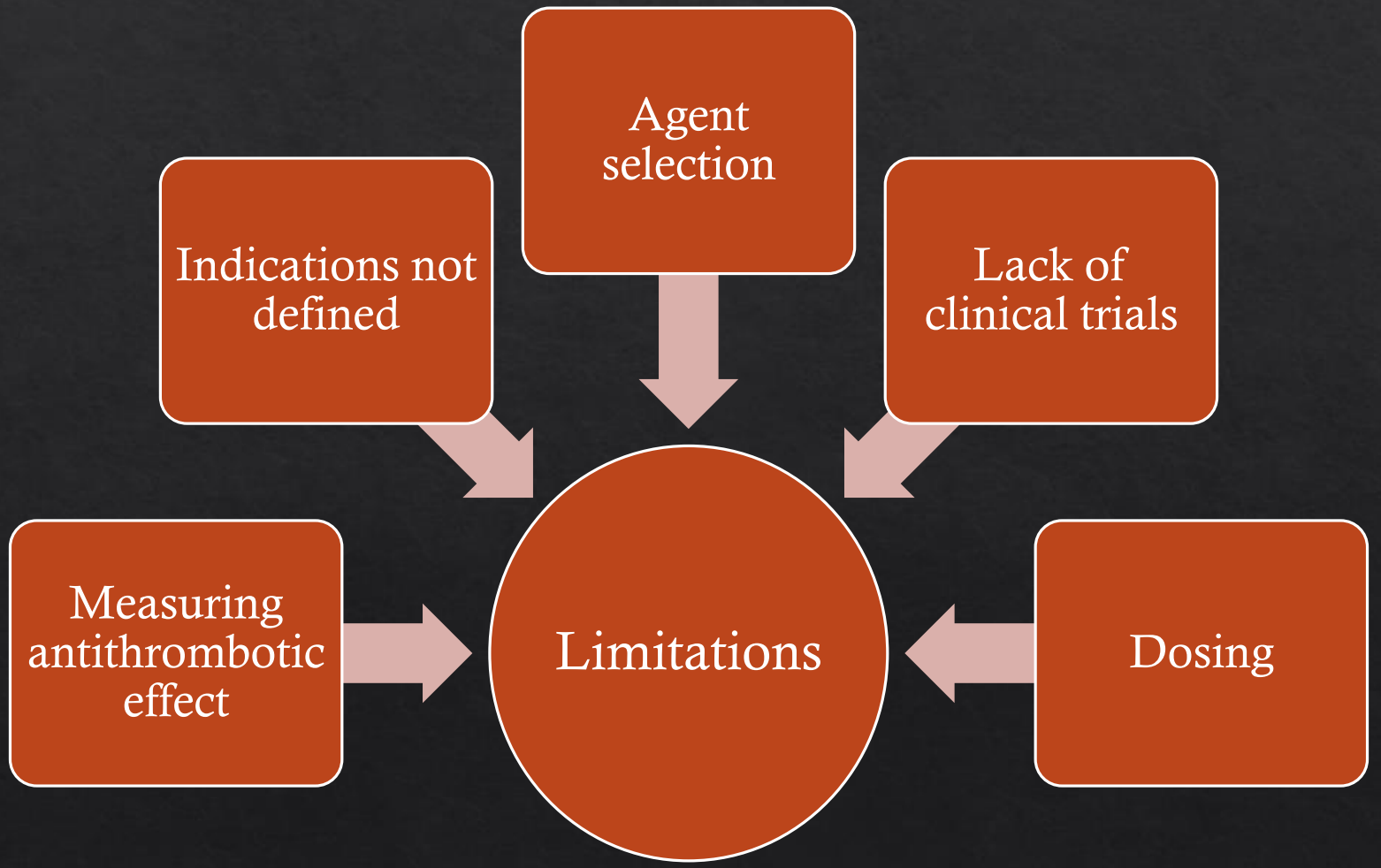
	Heparin	Low molecular weight heparin	Warfarin	Dabigatran	Rivaroxaban/ Apixaban
Target	II, X	II, X	II, VII, IX, X	II	Xa
Route of Administration	IV	SC	PO	PO	PO
Bioavailability	100%	100%	79-100%	6%	50-80%
Metabolism	Hepatic	Hepatic	Primarily CYP2C9	Conjugation	Oxidation (CYP3A4)
Renal Excretion	Minimal	40%	Minimal	80%	~30%
Half-life	1-2 hr	5-7 hr	20-60 hr	12-17 hr	5-9 hr

Chest 2012;141(2_suppl):e419S-e494S.

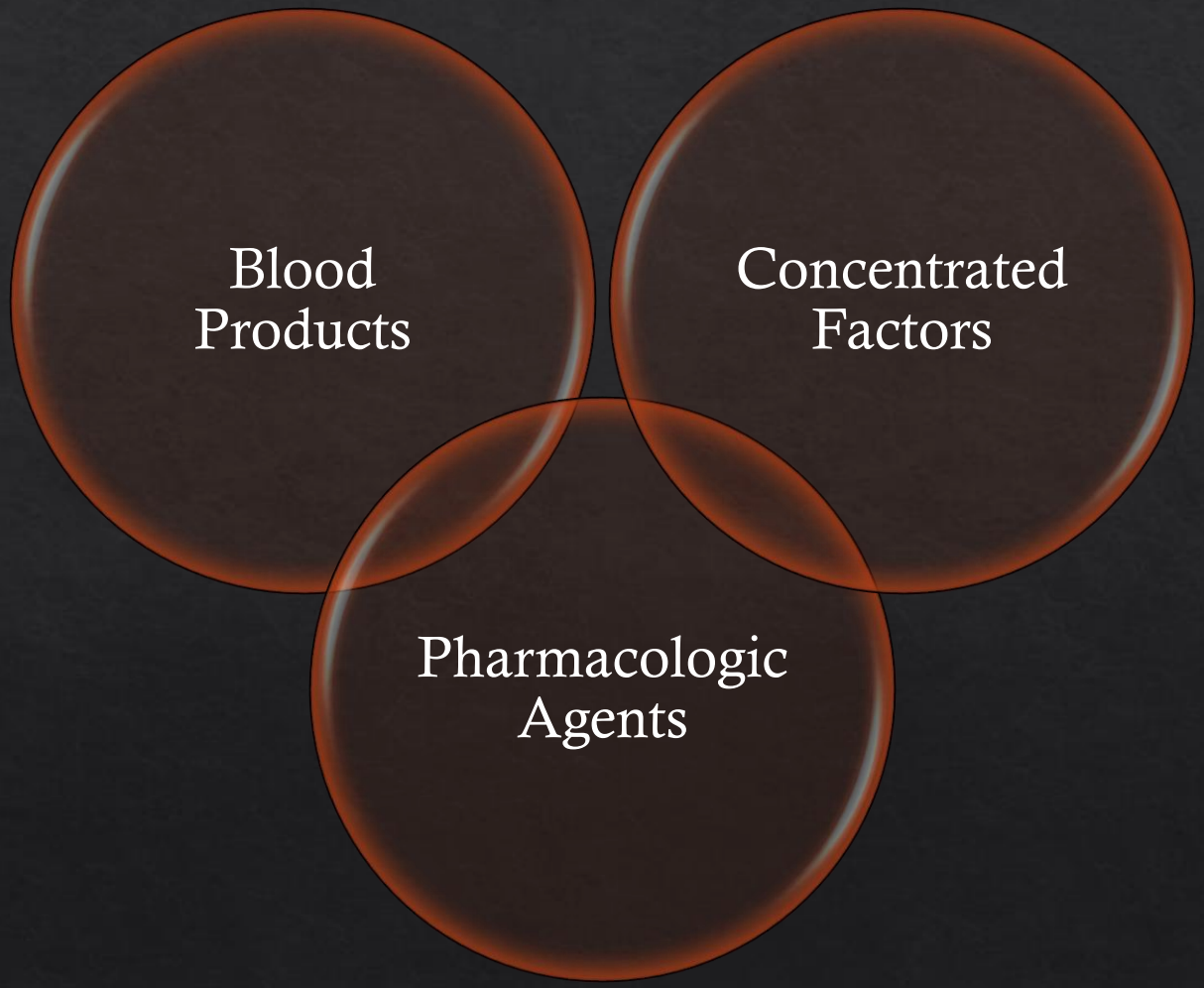
Acute Reversal Indications



Limitations of Reversal Agents

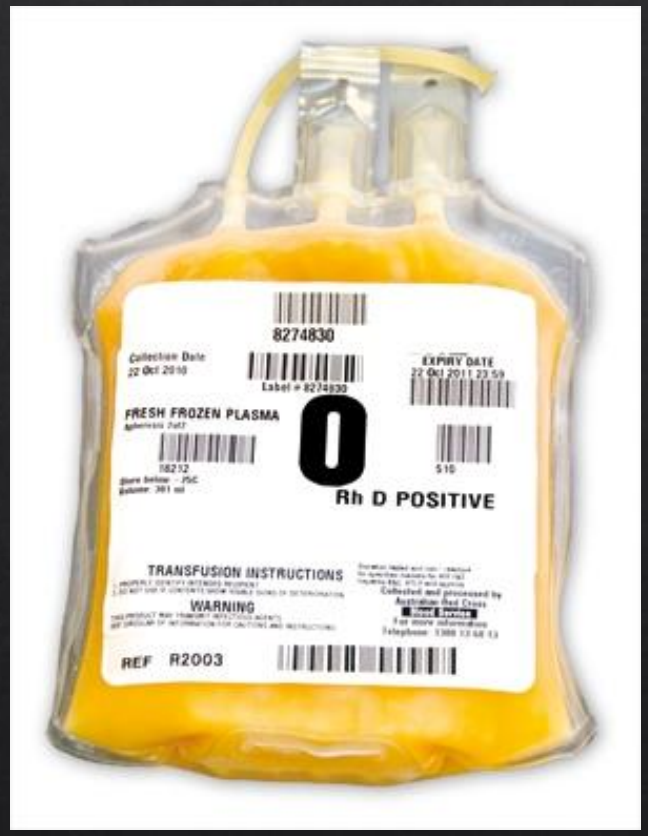


Reversal Options



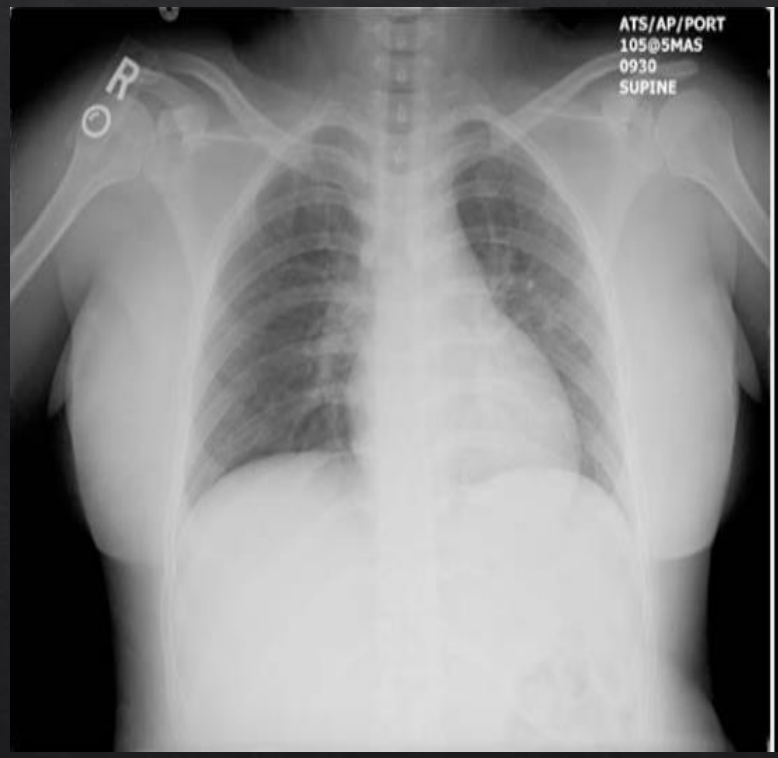
Blood Products

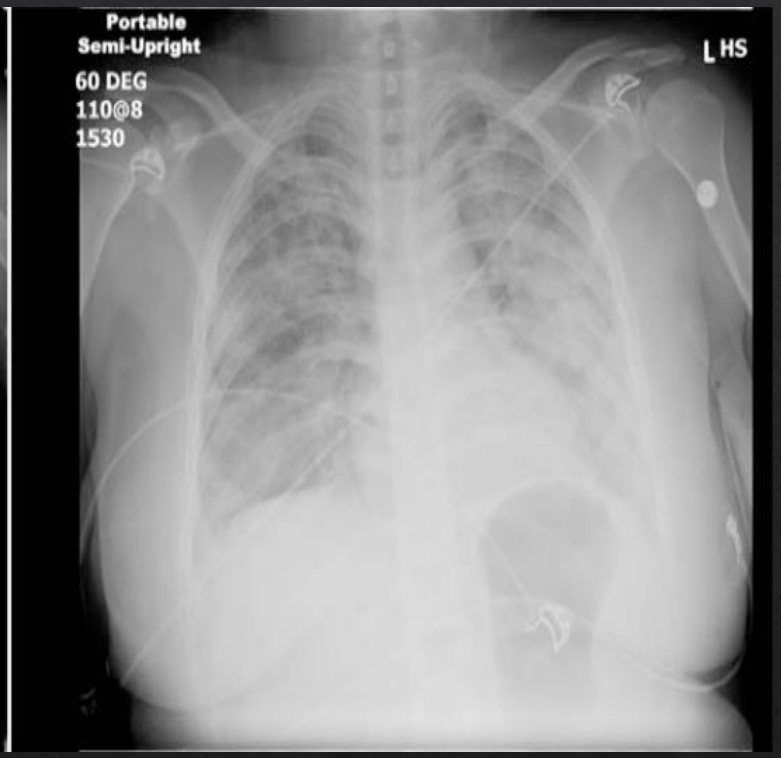
- Fresh frozen plasma
- Red blood cells
- Platelets
- Cryoprecipitate



Disadvantages of Blood Products

- Infection
- Large volume
- Allergic reactions
- Transfusion reaction
- Acute lung injury
- Cross-matching
- Limited resource





N Engl J Med 2008;359:938-949.
Pharmacotherapy 2007;27:575-685.

Concentrated Factors

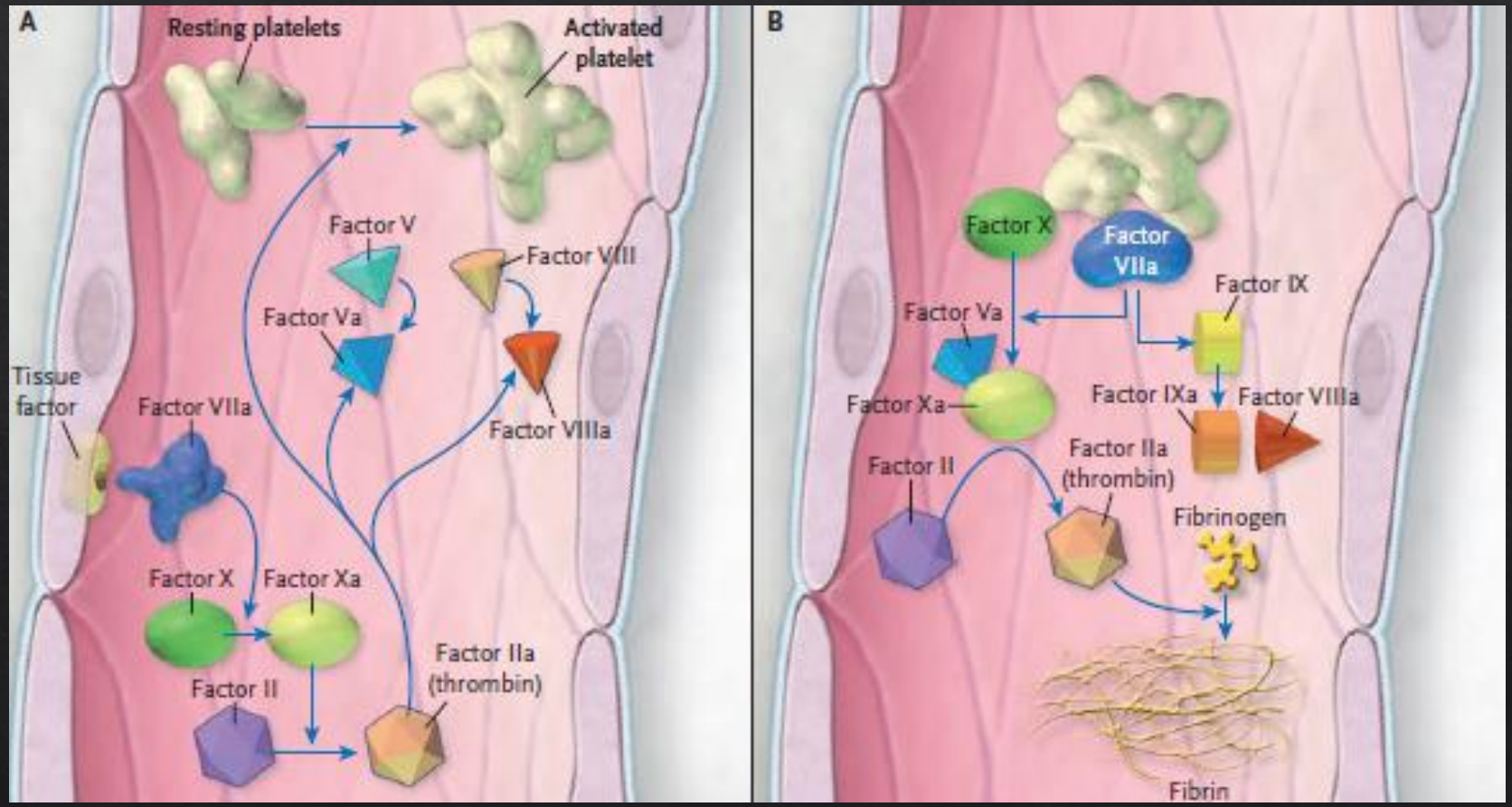
Recombinant factor VIIa (rFVIIa)

- Only activated factor VII

Prothrombin Complex Concentrate (PCC)

- 3-factor (II, IX, X)
- 4-factor (II, VII, IX, X)
- Activated 4-factor (II, VIIa, IX, X)

Recombinant FVIIa (rFVIIa)



N Engl J Med 2007;356:1201-2311.

rFVIIa – Off-label Uses

Populations with Severe Bleeds

- Trauma
- Neurosurgery
- Cardiac surgery
- Liver transplantation

Anticoagulation Reversal

- Warfarin
- Heparin
- Direct thrombin inhibitors

Pharmacotherapy 2007;27:695-845.

Prothrombin Complex Concentrate (PCC)

	Coagulation Factors in Each Product (IU relative to Factor IX)			
	II	**VII**	**IX**	**X**
3-Factor PCCs				
Profilnine	148	11	100	64
Bebulin VH	120	13	100	100
4-Factor PCCs				
Kcentra	118	70	100	152
Activated 4-Factor PCCs				
FEIBA	1.3 IU/IU	0.9 IU/IU	1.4 IU/IU	1.1 IU/IU

Crit Care 2011;15:201.
Ann Pharmacother 2013;47:841-855.
Kcentra package insert. Kankakee, IL: CSL Behring; 2013.

Reversal with PCC

- Warfarin
- Dabigatran
- Factor Xa inhibitors

Outcomes with 4F-PCC for Reversal

Warfarin

- INR "normalizes" in minutes to hours
- Effective for reducing INR without FFP
- Bleeding is similar to FFP
- Infrequent thromboembolic events have occurred

Dabigatran

- In vitro PCC significantly increase thrombin generation
- In vivo PCC did not correct coagulation assays
- Activated PCC significantly increased thrombin generation in vitro

Factor Xa Inhibitors

- PCC normalized PT and endogenous thrombin potential
- PCC only partially increased peak thrombin generation
- Activated PCC normalized thrombin generation ex vivo

Transfus Med 2011;21:116-123.
Thromb Res 2012;129:526-529.
Circulation 2011;124:1573-1579.
Thrombosis Journal 2014;12(8):1-9.

Dosing Recommendations for 4F-PCC

Agent	Dose (units)
Warfarin **INR 2-4** **INR 4-6** **INR >6**	 25 units/kg (max 2500 units) 35 units/kg (max 3500 units) 50 units/kg (max 5000 units)
Dabigatran	25-50 units/kg (max 5000 units)
Rivaroxaban **Apixaban**	25-50 units/kg (max 5000 units) 25-50 units/kg (max 5000 units)

Pharmacologic Reversal Options

- Protamine
  - Unfractionated Heparin
  - Low molecular weight heparin
- Vitamin K
  - Warfarin
- Idarucizumab
  - Dabigatran
- Andexanet
  - Rivaroxaban
  - Apixaban

Protamine for Heparin Reversal

- Mix of cations and basic peptides derived from fish sperm
- Combines with heparin to form a stable complex neutralizing the anticoagulant activity of heparin and protamine
- Available in intravenous formulation only
- Onset: 5 min, half-life: 7 min
- Adverse effects
  - Anaphylaxis, pulmonary hypertension, hypotension, paradoxical bleeding

Time Elapsed	Dose of Protamine (mg) to Neutralize 100 units of Heparin
Immediate	1-1.5
30-60 min	0.5-0.75
>2 hr	0.25-0.375
Maximum Dose	50 mg

Intern Emerg Med 2009;4:137-145.

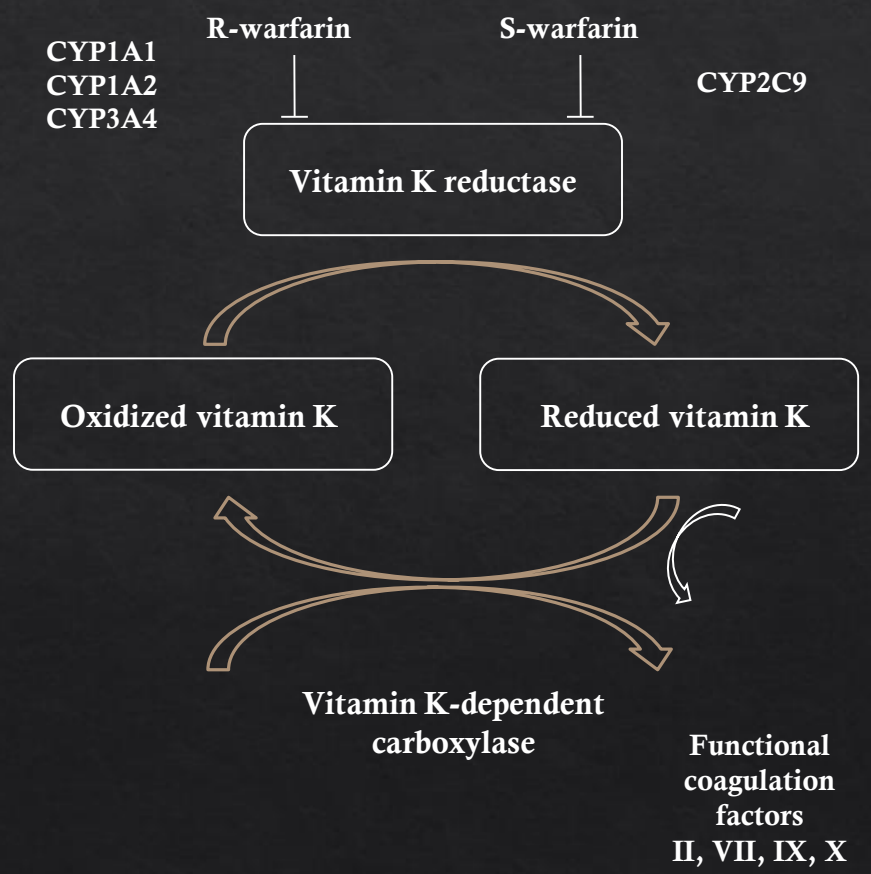
Protamine for LMWH Reversal

- Protamine neutralizes anti-factor IIa (not Xa)
  - Incomplete reversal of LMWH (40-50%)
- Dose: 1 mg protamine/100 anti-factor Xa units of LMWH in last 8 hours
  - 1 mg protamine/1 mg enoxaparin
- Maximum Dose: 50 mg

Intern Emerg Med 2009;4:137-145.
J Neurosurg 2010;112:307-318.

Vitamin K (Phytonadione)

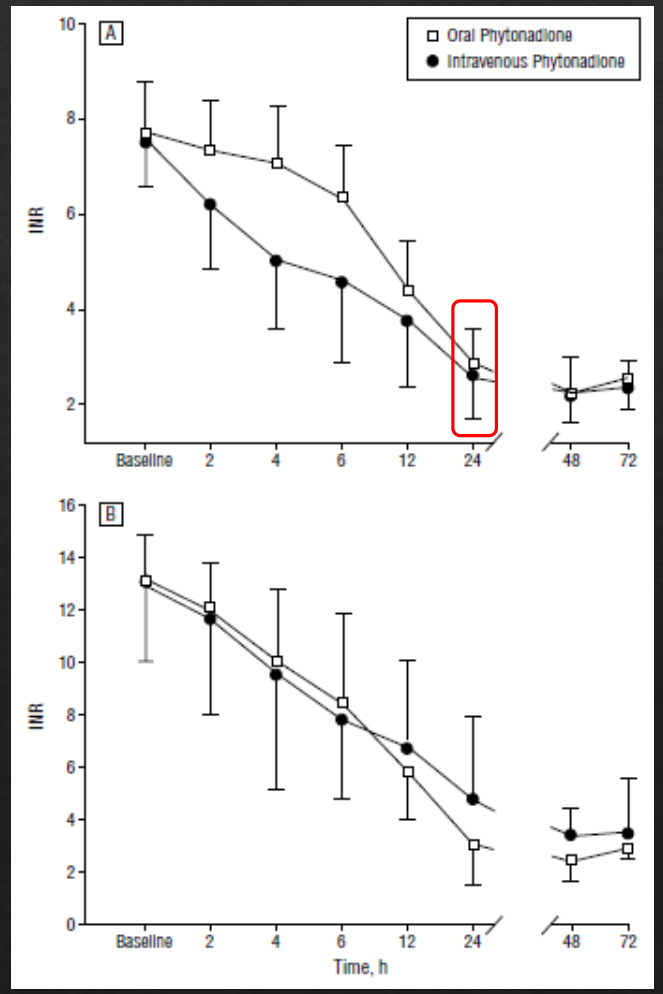
- Reversal of warfarin-related bleeds
- Available as oral and intravenous
- Reversal dose: 5-10 mg IVPB
- Onset: Oral: 6-10 hr, IV: 1-2 hr
- Peak: Oral: 24-48 hr, IV: 12-16 hr
- Adverse effects
  - Anaphylaxis (IV), injection site reactions



J Thromb Haemost 2011;9:1705-1712.

Vitamin K: PO vs IV

- Graph A
  - INR 6-10
  - Rate of response higher with IV
  - Median time to INR 2-4: 6 hr (IV) vs 24 hr (PO)
  - At 24 hr: no difference in INR between IV and PO
- Graph B
  - INR >10
  - No difference in rate of response between IV and PO



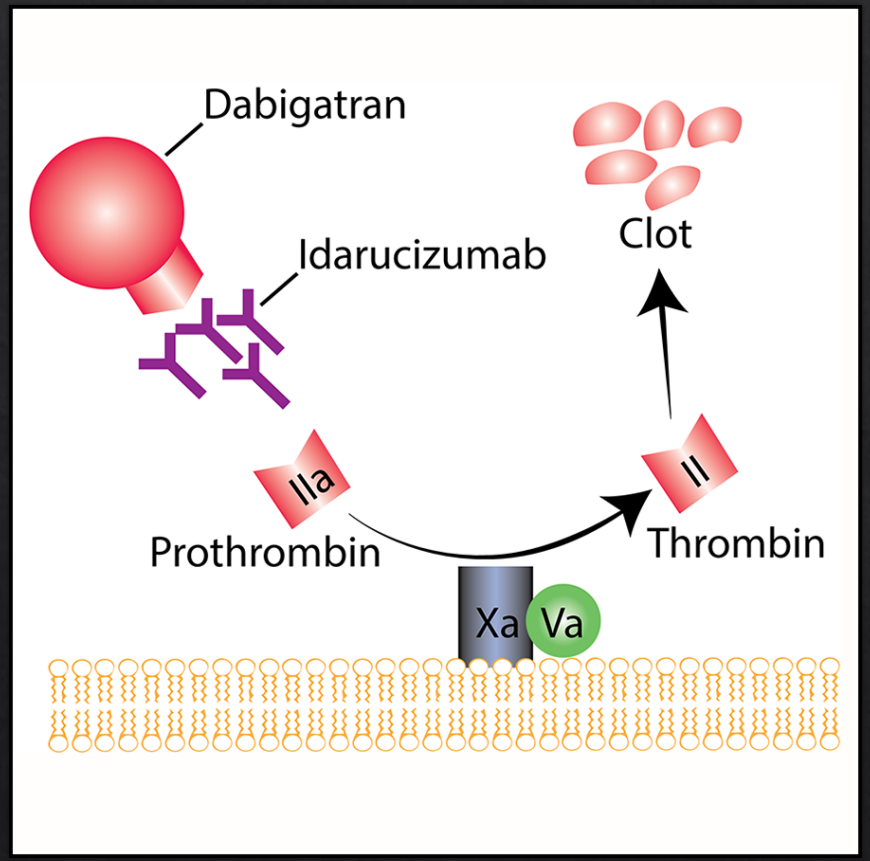
Arch Intern Med 2003;163:2469-2473.

Considerations for Vitamin K

- Indicated for pharmacologic reversal of warfarin
- IV route preferred over PO and SQ for acute bleeds
- IVPB administration recommended to prevent anaphylaxis
- Administer with plasma product due to delayed response
  - FFP, PCC, or rFVIIa

Pharmacotherapy 2007;27:695-845.

Idaracuzimab (Praxbind)

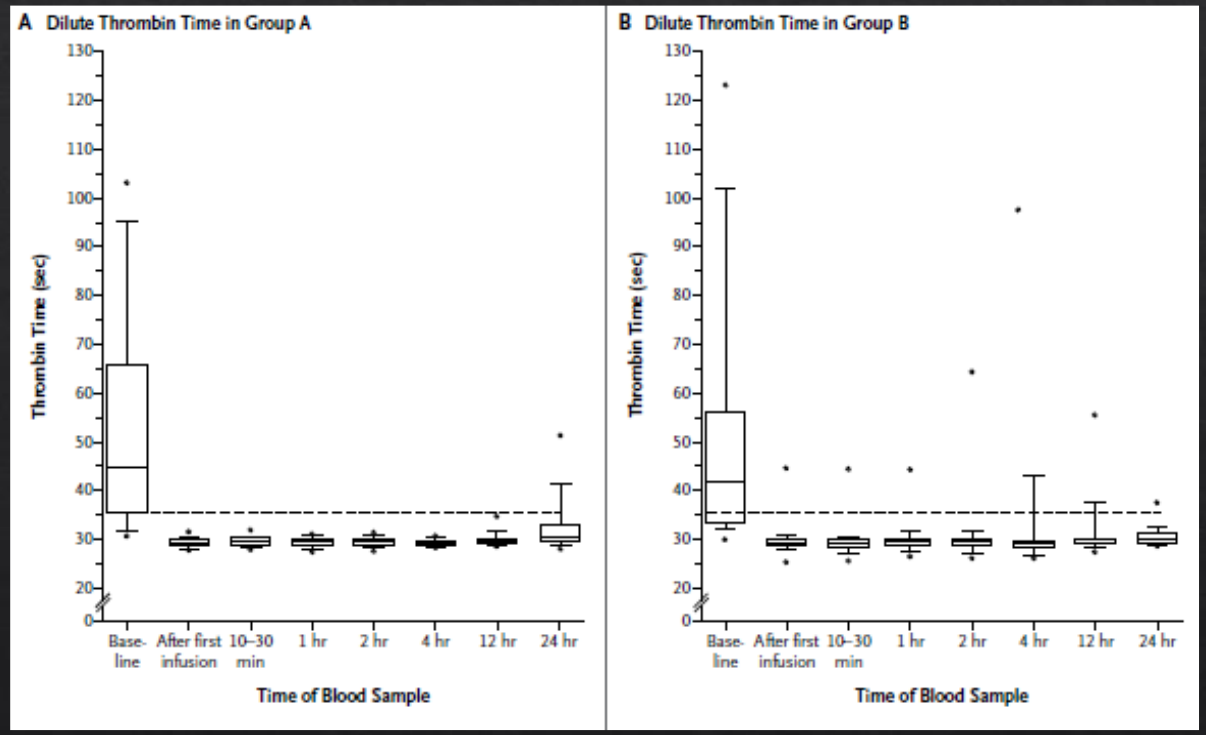


- Monoclonal antibody fragment that binds dabigatran causing neutralization
- Reversal of anticoagulant effects of dabigatran
- Available dosage form: 2.5 g vial
- Dose: 5 g IVPB

N Engl J Med 2015;373:511-520.
Circulation 2015;132:2412-2422.

REVERSE-AD

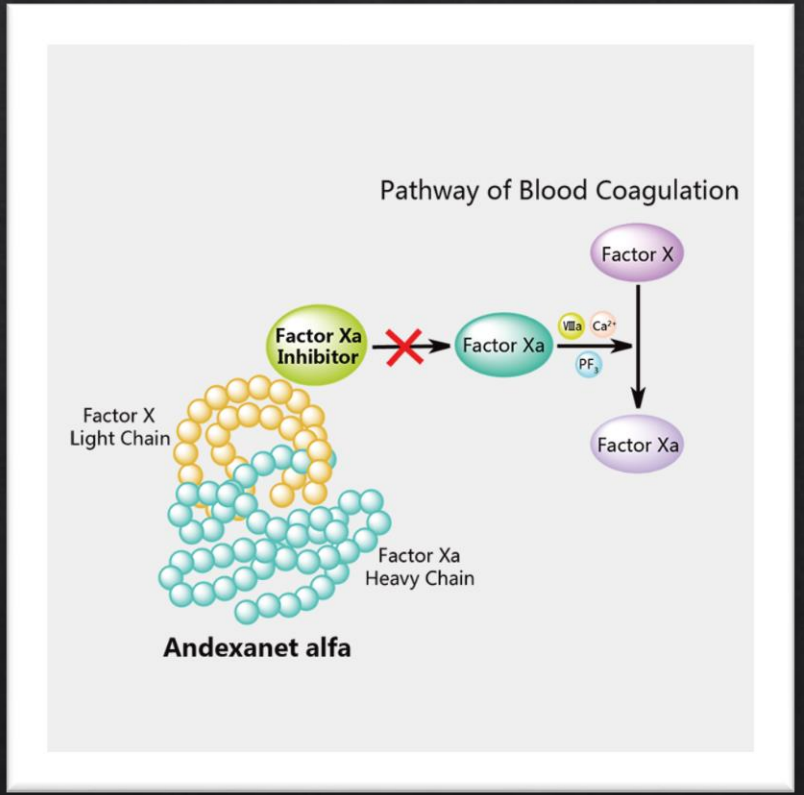
- Prospective, cohort study
- 90 patients enrolled (taking dabigatran)
  - Group A – Severe bleeding
  - Group B – Required reversal for urgent intervention
- Two idarucizumab 2.5 g IV infusions administered no more than 15 min apart
- Primary endpoint – maximal reversal within 4 hours



N Engl J Med 2015;373:511-520.

Andexanet Alfa (AndexXa)

- Recombinant modified human factor Xa decoy protein that binds factor Xa inhibitors causing neutralization
- Reversal of anticoagulant effects of direct and indirect factor Xa inhibitors
- Dose depends on factor Xa inhibitor
- Not approved by FDA



N Engl J Med 2015;373:2413-2424.
N Engl J Med 2016;375:1131-1141.

ANNEXA-A and ANNEXA-R

- Randomized, double-blind, placebo-controlled studies
- Evaluated the ability of andexanet alfa to reverse apixaban (ANNEXA-A) and rivaroxaban (ANNEXA-R) in healthy volunteers

	ANNEXA-A	ANNEXA-R
Anticoagulant	Apixaban 5 mg BID	Rivaroxaban 20 mg daily
Dose of andexanet	400 mg bolus ± 4 mg/min infusion	800 mg bolus ± 8 mg/min infusion
Reduction in anti-FXa	~92%	92-97%
Unbound anticoagulant	<3.5 ng/mL	<4.0 ng/mL

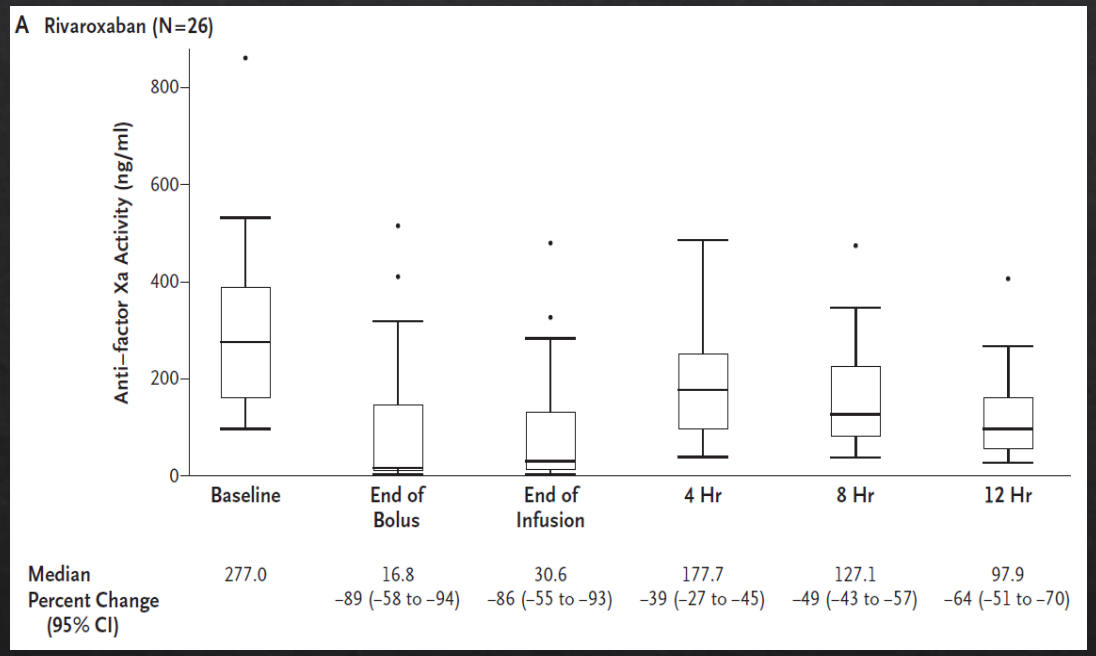
N Engl J Med 2015;373:2413-2424.

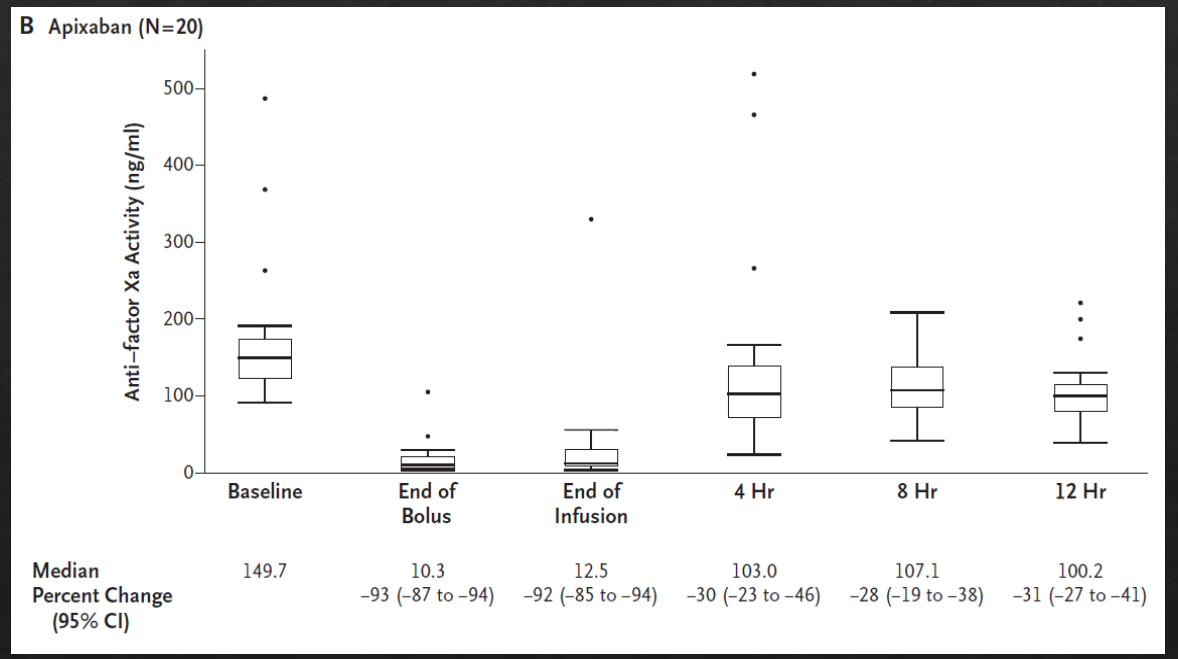
Andexanet Alfa in Acute Major Bleeding

- Multicenter, prospective, open-label, single-group study
- Enrolled 67 patients who were taking either rivaroxaban or apixaban and experienced acute major bleeding
- Intervention: Andexanet IV bolus followed by 2-hour infusion (dose depended on the anticoagulant)
- Median factor Xa activity after bolus
  - Rivaroxaban – decrease by 89%
  - Apixaban – decrease by 93%
- Minimal adverse effects

N Engl J Med 2016;375:1131-1141.

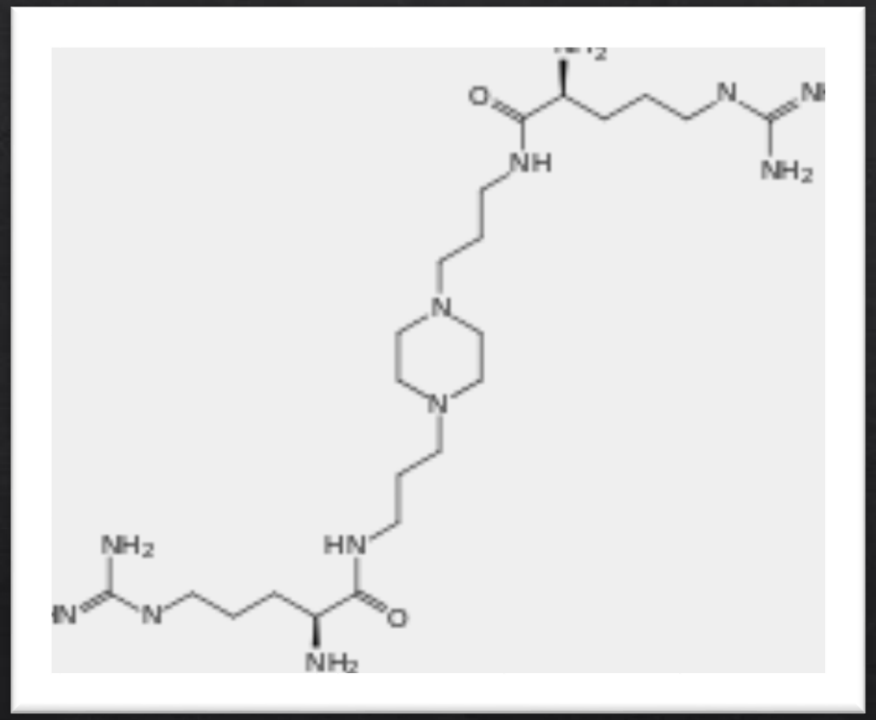
ANNEXA-4





N Engl J Med 2016;375:1131-1141.

Ciraparantag



- Synthetic molecule that binds to anticoagulants by forming a strong noncovalent hydrogen bond
- Targets unfractionated heparin, low molecular weight heparin, direct thrombin inhibitors, and factor Xa inhibitors
- Animal studies demonstrate reversal of bleeding after receiving ciraparantag
- Currently in phase I and II studies

Cardiology in Review 2016;24:310-315.

Comparison Table by Reversal Agents

	Anticoagulant Reversal	Usual Dose	Admixture Considerations	Storage	Cost ($)	Unit
Activated factor VII	Heparin Warfarin Dabigatran	1-5 mg	Reconstituted with histidine diluent Given over 2-5 min	Room temperature or refrigerated	$8000	5 mg vial
4-factor Prothrombin Complex Concentrate	Warfarin Dabigatran Factor Xa inhibitors	25-50 units/kg	Do not infuse faster than 8.4 mL/min	Room temperature	$800	500 unit vial
Activated Prothrombin Complex Concentrate	Warfarin Dabigatran Factor Xa inhibitors	25-50 units/kg	Do not infuse faster than 2 units/kg/min	Room temperature Protect from light	$1000	500 unit vial
Vitamin K	Warfarin	5-10 mg	10 mg in 50 mL IVPB over 20 min	Room temperature Protect from light	$7	10 mg vial
Protamine	Heparin LMWH	50 mg	Max: 50 mg in 50 mL over 10 min	Room temperature	$150	50 mg vial
Idarucizumab	Dabigatran	5 g	Infuse premix vial over no more than 5-10 min	Room temperature x 48 hr Protect from light	$1800	2.5 g vial

Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; November 3, 2016.

Summary

- Critical bleeding is associated with increased mortality in critically ill patients
- The indication for anticoagulant reversal depends on the acuity and severity of the bleed
- Concentrated factors and blood products may be useful when no pharmacologic reversal agent exists or as an adjunct
- A direct pharmacologic antidote is available for the reversal of dabigatran and other antidotes are currently in phase II trials for factor Xa inhibitor reversal demonstrating promising results

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