RUSH UNIVERSITY MEDICAL CENTER

Anticoagulation Reversal in the Hemorrhagic Stroke Patient

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The off-label use of Kcentra, Feiba, Novoseven, tranexamic acid and aminocaproic acid will be discussed and I have no actual or potential conflict of interest in regards to this presentation

The planners, editors, faculty and reviewers of this activity have no relevant financial relationships to disclose. This presentation was created without any commercial support.

Learning Objectives

At the conclusion of this course participants will be able to

- Recognize available reversal agents used for the management of anticoagulant induced hemorrhage
- Identify novel agents currently in use or in development for target specific oral anticoagulant reversal
- Develop a strategy to manage tPA induced hemorrhage

Hemorrhagic Stroke

- Multi-factorial injury
  - Caused by a weakened blood vessel that ruptures
  - Brain damage due to compression of tissue from expansion of blood from vessel (hematoma)
- Types
  - Intracerebral hemorrhage (ICH)
  - Subarachnoid hemorrhage (SAH, non-traumatic)

Hemphill JC, et al. Guidelines for the management of sICH. [published online May 28, 2015]. *Stroke.* 2015; 46.
Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet.* 2009; 373: 1632-44.
Connolly ES, et al. Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage. *Stroke*. 2012; 43.

Treatment of Hemorrhagic Stroke

- Evaluation by neurosurgery for possible decompression/drainage of hematoma
- Invasive neurologic monitoring
  - Ventriculostomy, if needed
- Supportive therapies when applicable
  - Blood pressure control
  - Reverse coagulopathy
  - Prevention/management of seizures
  - Prevention/management of cerebral vasospasm

Epidemiology

- Anticoagulant induced intracerebral hemorrhage (aICH)
  - Accounts for 12 – 20% of ICH
  - Increasing in frequency
    - Secondary stroke prophylaxis
    - More elderly patients prescribed anticoagulation
  - Combination therapy with antiplatelet agents
    - Cardiac history

Cervara A, Amaro S, Chamorro A. Oral anticoagulant associated intracerebral hemorrhage. *J Neurol.* 2012; 259: 212-224.
Hemphill JC, et al. Guidelines for the management of sICH. [published online May 28, 2015].*Stroke.* 2015; 46.

"The availability of treatments proven to benefit ICH patients has lagged behind that of ischemic stroke and aneurysmal subarachnoid, and this has resulted in variability in care that ranges from aggressive treatment to a nihilistic approach."

Jauch EC, Pineda JA, Hemphill JC. ENLS: Intracerebral Hemorrhage. 2015.

Guidelines

Guideline	Year Updated
Neurocritical Care Society	2016
AHA/ASA sICH	2015
ACCP	2012

AHA = American Heart Association, ASA = American Stroke Association, sICH = Spontaneous intracerebral hemorrhage, ACCP = American College of Chest Physicians

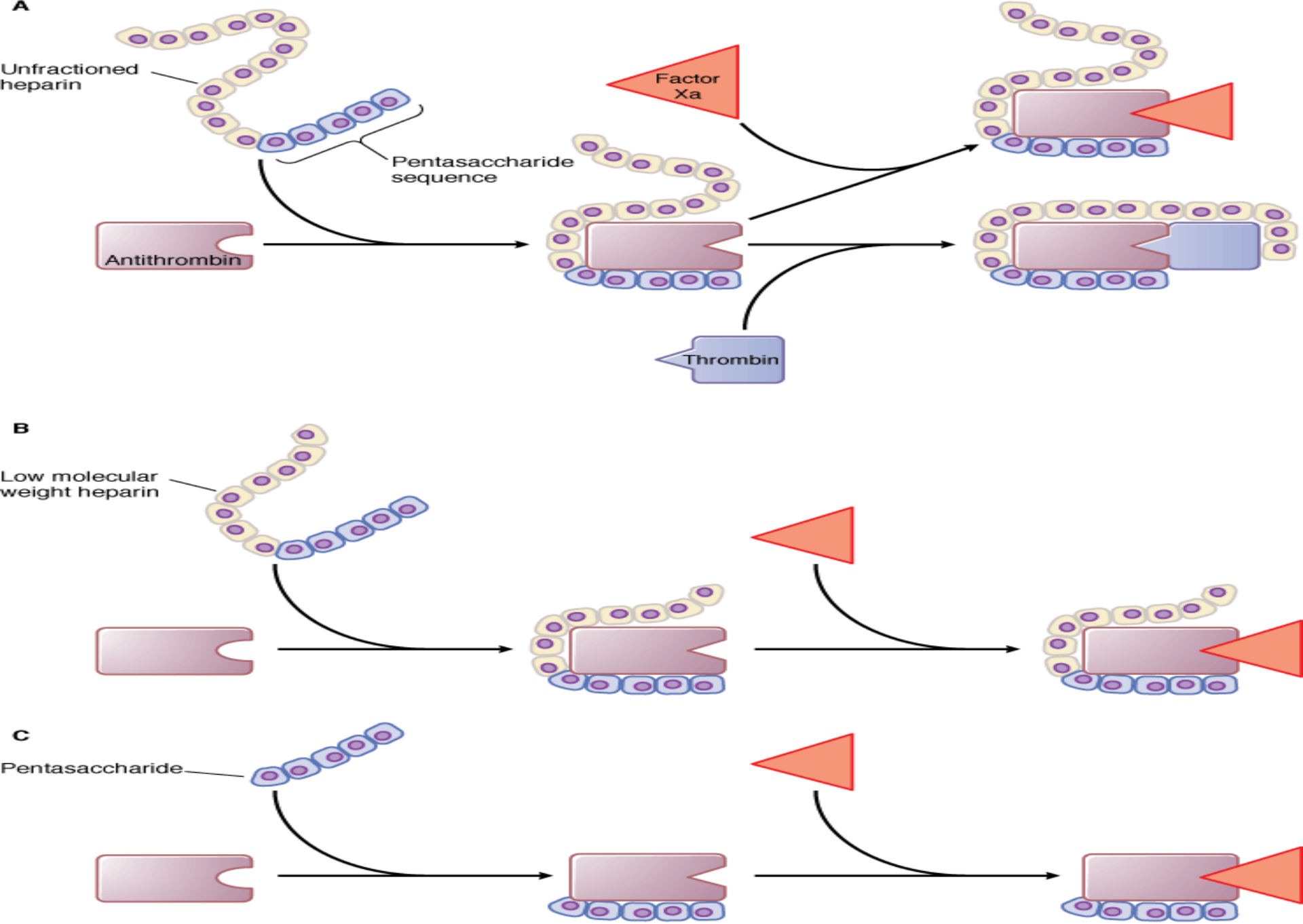
Frontera JA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016 Feb;24(1):6-46.
Hemphill JC, et al. Guidelines for the management of sICH. [published online May 28, 2015].*Stroke.* 2015; 46.
Holbrook A, et al. Evidence based management of anticoagulant therapy. *Chest.* 2012; 141(2)(Supp): e152S–e184S.

Anticoagulant Review

Heparin and Derivatives

- Unfractionated Heparin
- Low Molecular Weight Heparin
  - Dalteparin
  - Enoxaparin
  - Tinzaparin
- Factor Xa inhibitor (Pentasaccharide)
  - Fondaparinux

Garcia DA, Baglin TP, Weitz JI, et al. Parenteral Anticoagulants. *Chest.* 2012; 141(2) (Supp): e24S-e43s.



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

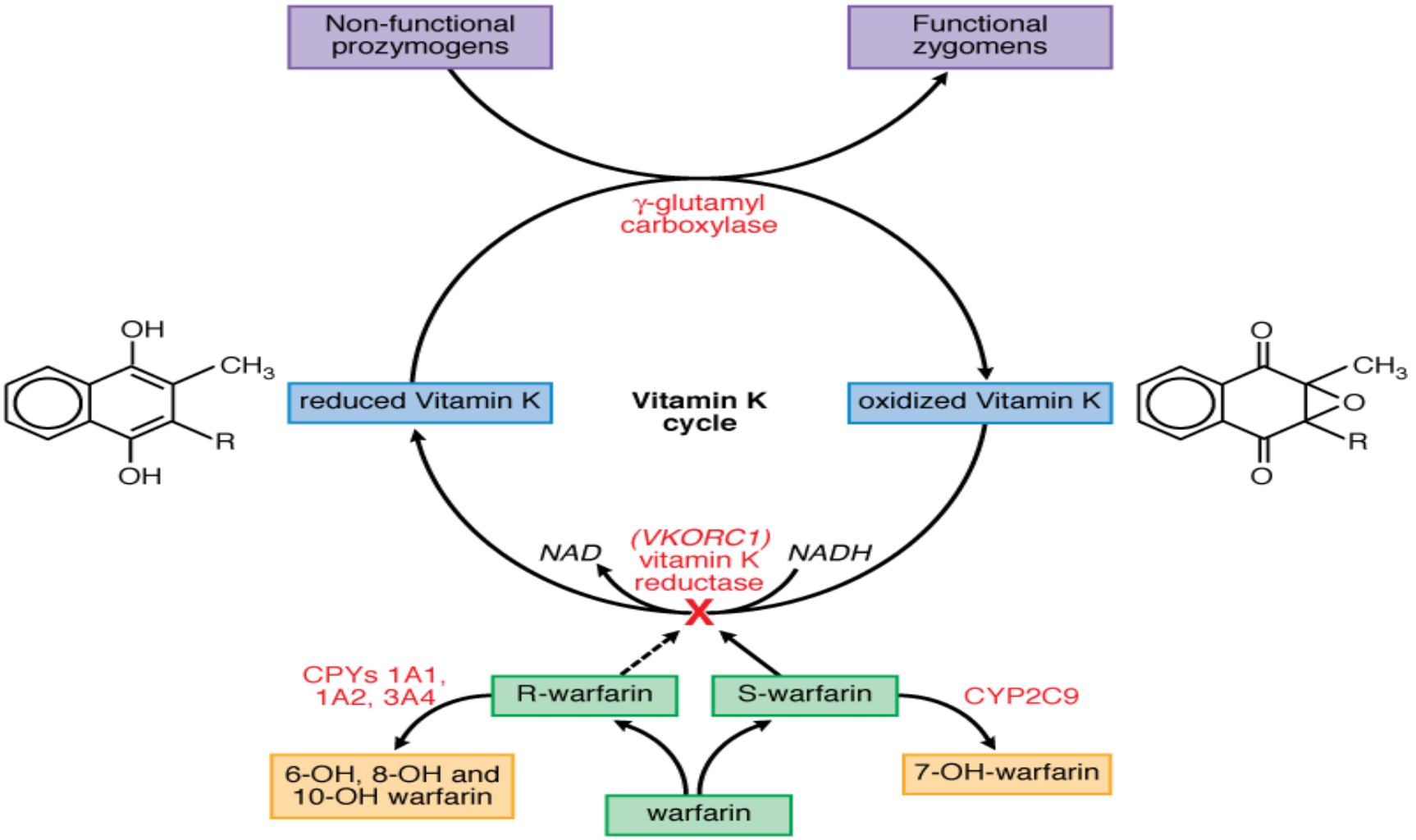
Pharmacokinetics

Drug	Onset	Duration	Elimination	Monitoring
Heparin	IV: Immediate SQ: 20 – 30 minutes	Dose dependent	Renal, hepatic and RES	aPTT, anti-Xa, ACT
Enoxaparin	SQ: 3 – 5 hours	12 – 24 hours	Renal	Anti- Xa
Dalteparin	SQ: 2 hours	12 – 24 hours	Renal	Anti- Xa
Tinzaparin	SQ: 2 – 3 hours	12 – 24 hours	Renal	Anti- Xa
Fondaparinux	SQ: 3 hours	16 – 24 hours	Renal	Anti-Xa (Specific)

ACT = Activated clotting time RES = Reticuloendothelial system

Garcia DA, Baglin TP, Weitz JI, et al. Parenteral Anticoagulants. *Chest.* 2012; 141(2) (Supp): e24S-e43s.
Heparin, Enoxaparin, Dalteparin, Tinzaparin, Fondaparinux. In: DRUGDEX® System [Internet database]. Accessed September 1, 2015.

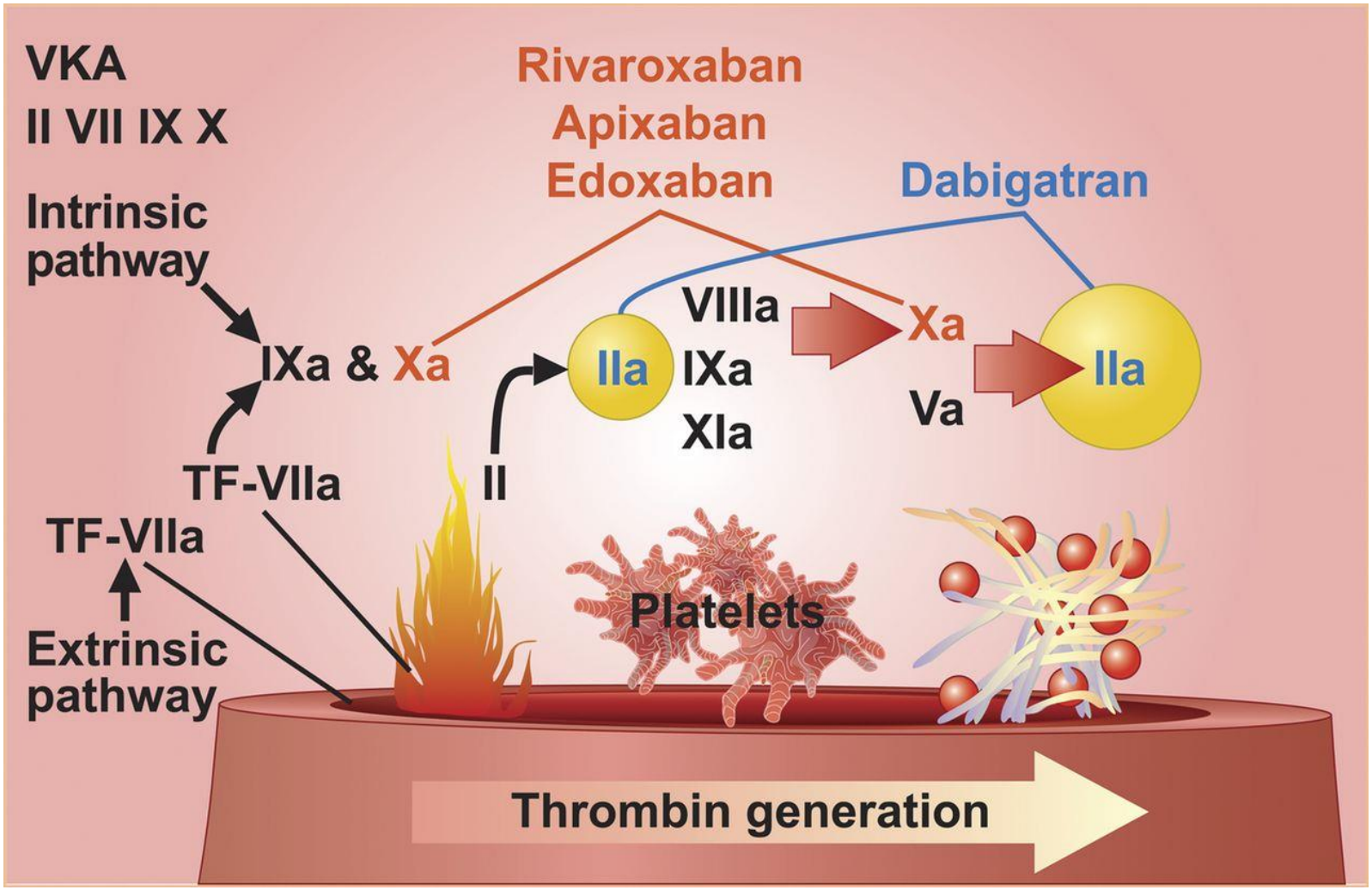
Warfarin



Half-life of Clotting Factors

Factor	Time (hours)
Factor II	50 hours
Factor VII	6 hours
Factor IX	24 hours
Factor X	36 hours
Protein C	6 hours
Protein S	30 hours

Coagulation process and targets of direct oral anticoagulants (DOACs).



Pierre Fontana et al. Eur Heart J 2014;eurheartj.ehu027

European Heart Journal

Direct Thrombin Inhibitors

Drug	Administration	Half Life	Elimination	Monitoring
Dabigatran	Oral	12 hours	Renal	Not required (aPTT, TT, ECT)
Argatroban	Parenteral	30 – 60 minutes	Hepatic	aPTT, ACT
Bivalirudin	Parenteral	25 minutes	Renal	aPTT, ACT

aPTT = Activated partial thromboplastin time, TT = Thrombin time, ECT = Ecarin clotting time, ACT = Activated clotting time

Dabigatran, Argatroban, Bivalirudin. In: DRUGDEX® System [Internet database]. Accessed September 1, 2015.
Hankey GJ, Eikelboom JW. Dabigatran Etexilate: A new oral thrombin inhibitor. *Circulation.* 2011;123:1436-1450.

Factor Xa Inhibitors

Drug	Half Life	Elimination	Monitoring
Rivaroxaban	6 – 13 hours	Fecal/Renal	Not required (aPTT, PT)
Apixaban	12 – 15 hours	Fecal/Renal	Not required (aPTT, PT)
Edoxaban	10 – 14 hours	Renal	Not required (aPTT, PT)

aPTT = Activated partial thromboplastin time, PT = Prothrombin time

Kubitza D, Becka M, Wensing G, et al. *Eur J Clin Pharmacol.* 2005; 61(12):873–80.
Abrams PJ, Emerson CR. Rivaroxaban. *Pharmacotherapy* .2009;29(2):167–181.
Nutescu E. Apixaban. *Am J Health-Syst Pharm.* 2012; 69: 1113-26.
Edoxaban. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; Version 2.3.2

Thrombolytics

Drug	Plasma half life	Elimination
Alteplase	5 min	Hepatic
Tenecteplase	20 min	Hepatic
Reteplase	15 min	Feces, urine

1 Recombinant t-PA (alteplase) binds to fibrin in thrombus 2 converts entrapped plasminogen to plasmin 3 that initiates local fibrinolysis

Alteplase, Tenecteplase, Reteplase. In: DRUGDEX® System [Internet database]. Accessed July 1, 2012.

Alteplase [Package Insert]. San Fransisco, CA: Genentech, Inc: 2005.

Reversal Agents

- Blood Products
  - Fresh Frozen Plasma
  - Platelets
  - Cryoprecipitate
- Pharmacological
  - Prothrombin Complex Concentrates (PCCs)
    - Activated
    - Non-activated
  - Recombinant Factor VIIa (rFVIIa)
  - Phytonadione (Vitamin K)
  - Antifibrinolytics
    - Aminocaproic Acid
    - Tranexamic Acid
  - Desmopressin (DDAVP)
  - Idarucizumab

Prothrombin Complex Concentrates (PCC)

- **Activated**
  - FEIBA (aPCC)
    - II, VIIa, IX, X, Protein C
- **Non-activated**
  - Three factor
    - II, IX, X
      - Profilnine SD
      - Bebulin VH
  - Four factor
    - II, VII, IX, X
      - Kcentra

- Advantages
  - Less volume
  - Rapid administration
  - Quicker reversal
- Disadvantages
  - Heparin induced thrombocytopenia
    - Bebulin
    - Kcentra
  - Thrombosis

Frontera JA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016 Feb;24(1):6-46.

Table 4 Prothrombin complex concentrates composition[a]

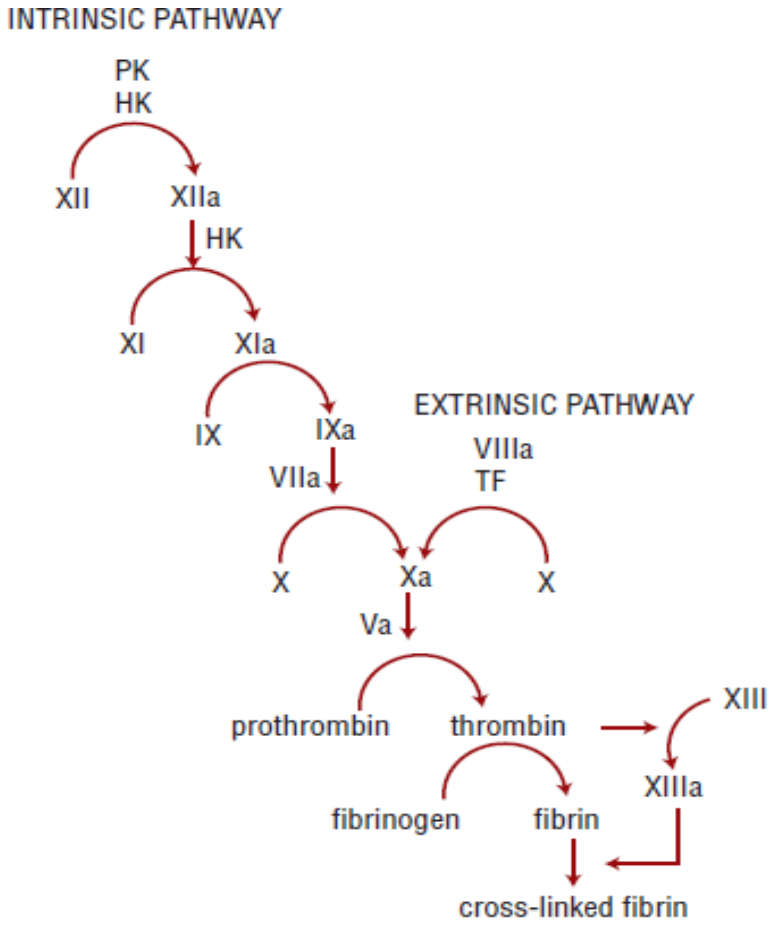
Prothrombin complex concentrate	Factor levels (IU/ml)				Protein levels (IU/ml)			Other	
	II	VII	IX	X	C	S	Z	ATIII	Heparin
3 Factor									
Bebulin	24-37	< 5	24-37	24-37	NA	NA	NO	None	< 0.15/IU FIX
Profilnine	NMT 150/ U/100 Factor IX U	NMT 35/ U/100 Factor IX U	100 unit	NMT 100/ U/100 Factor IX U	NA	NA	NA	None	None
4 Factor									
Beriplex	20-48	10-25	20-31	22-60	22-31	17-19	Yes	Yes	Yes
Cofact	30	13	23	26	4	21	Yes	Yes	None
Kcentra	19-40	10-25	20-31	25-51	21-41	12-23	No	Yes	Yes
Octaplex	31	16	22	24	12	24	Yes	No	Yes
Activated PCC									
FEIBA*	1.3 IU/IU	0.9 IU/IU	1.4 IU/IU	1.1 IU/IU	1.1 IU/IU	NA	NA	No	No

[a]All concentrations are approximate and vary from one lot to another.
NMT = not more than, IU = international units.
*IU/IU = IU/FEIBA unit.

Babilonia K, Trujillo T. The role of prothrombin complex concentrates in reversal of target specific anticoagulants. *Thrombosis Journal*. 2014; 12.

Recombinant Factor VIIa

- Extrinsic pathway activation
- Used with 3 factor PCC to "build" a 4 factor PCC
- Advantages
  - Quick onset
- Disadvantages
  - Thrombosis
  - Short acting



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

Coagulation Factor VIIA. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Pharmacotherapy: A Pathophysiologic Approach, 8e: http://www.accesspharmacy.com. Accessed September 2, 2015.

Phytonadione (Vitamin K_1)

- Promotes liver synthesis of clotting factors
  - VII, IX, X, II
  - Protein C and S
- Warfarin
  - Inhibits Vitamin K reductase
  - Warfarin insensitive pathway for reduction of phytonadione
    - NADPH dehydrogenases

Goldfrank's Toxicologic Emergencies, 9e: : http://www.accesspharmacy.com. Accessed August 25, 2015.

Role of Phytonadione

- Reversal of vitamin K antagonists
- Administration
  - ~~Subcutaneous~~
  - Intravenous
  - Oral
- Delayed onset
- Anaphylaxis/Anaphylactoid reactions
  - Low risk
  - Castor oil vehicle in solution

Beshay JE, et al. Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. *J Neurosurg.* 2010; 112:307-318.

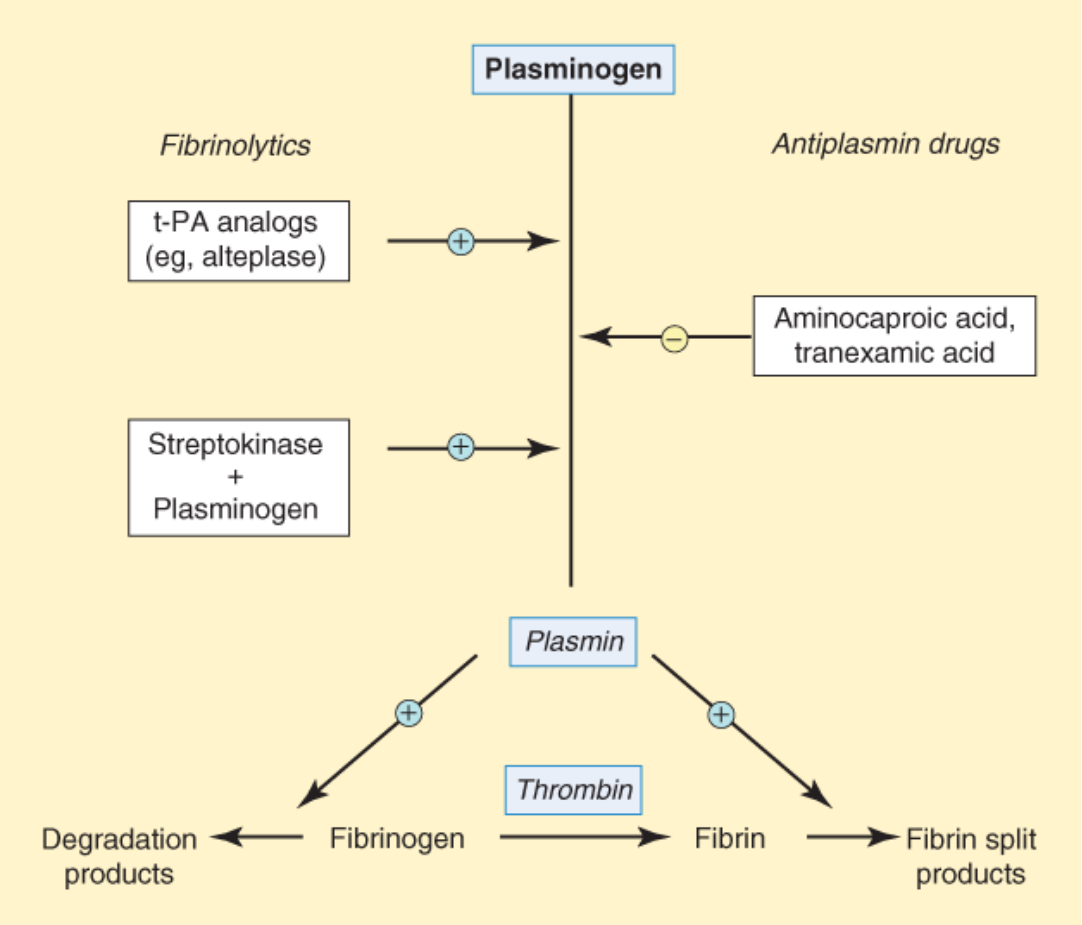
Protamine

- Cationic peptides derived from fish sperm nuclei
  - Inactivates heparin
  - Can be used for LMWH reversal
- Use with caution
  - Too much = more bleeding
  - Too fast = anaphylactoid reaction

Goldfrank's Toxicologic Emergencies, 9e: : http://www.accesspharmacy.com. Accessed August 25, 2015.

Antifibrinolytics

- Aminocaproic acid
- Tranexamic acid



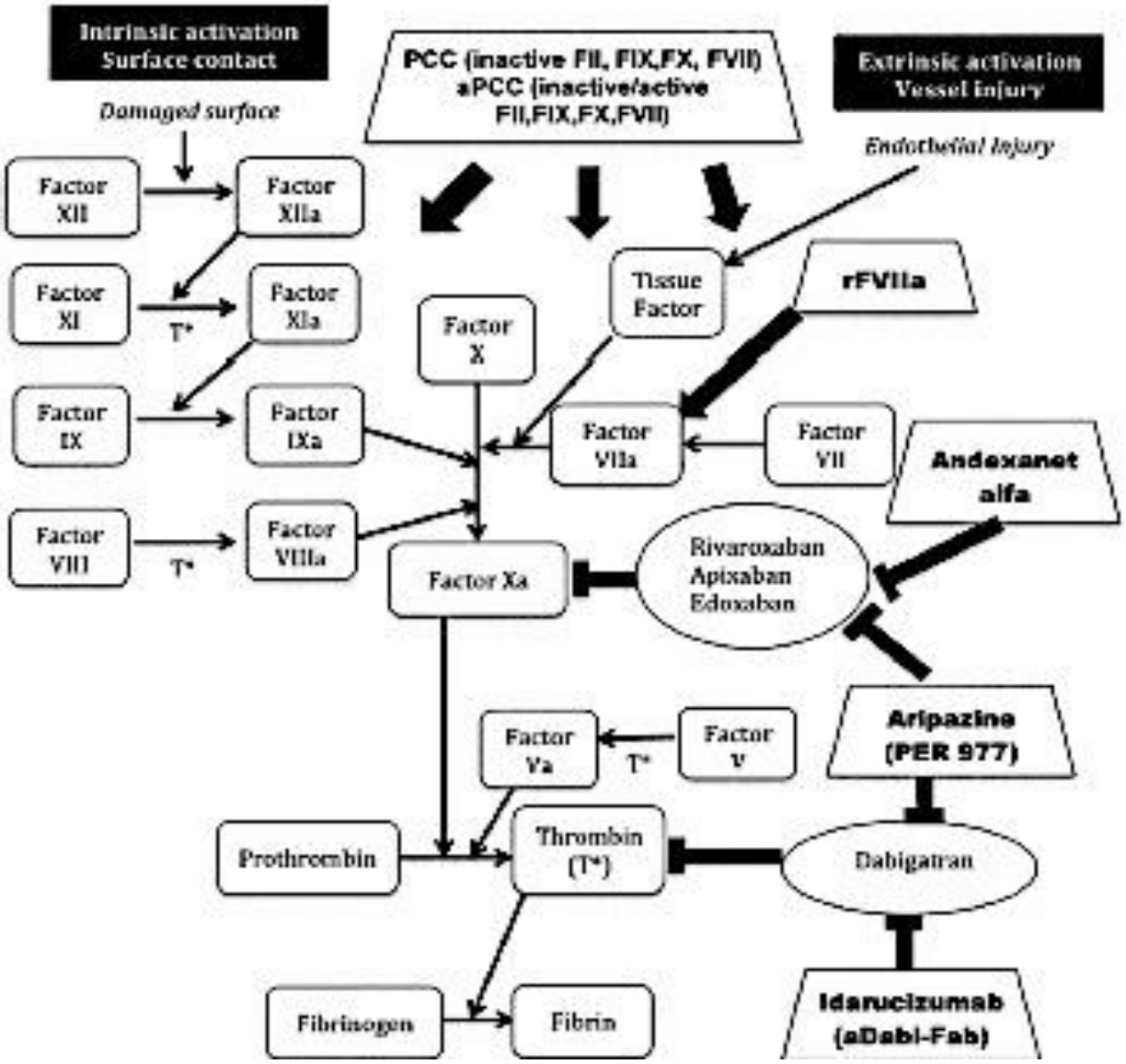
Source: Trevor AJ, Katzung BG, Masters SB: *Pharmacology Examination & Board Review, 9th Edition:* www.accesspharmacy.com

New Antidotes Approved or in the Pipeline

Agents	Target	Structure	Route	MOA
Idarucizumab (Praxbind)	Dabigatran	Fab	IV	Binds to dabigatran with greater affinity than thrombin
Andexanet alpha (PRT064445)	Direct and indirect Fxa inhibitors	Modified recombinant FXa	IV	Binds to FXa inhibitors
Aripazine (PER977)	Universal	Small synthetic molecule	IV	Binds directly to UFH and other anticoagulants

Fab = Human monoclonal antibody, IV = Intravenous, Fxa = Factor Xa, UFH = Unfractionated heparin, MOA = Mechanism of action

Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy.* 2015; 35:198-207.



Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy.* 2015; 35:198-207.

Idarucizumab

- FDA approved October 2015
- Phase III study (REVERSE-AD)
  - Idarucizumab 5 g total dose given to 2 groups
    - Life-threatening bleed defined by treating physician
    - Require surgery or other invasive procedure that cannot be delayed for at least 8 hours
- Supplied as 2 x 2.5 g vials
  - Can be give rapid IV push
  - Total of 5 g given within 15 minutes

Pollack CV, et al. Idarucizumab for dabigatran reversal. *N Eng J Med.* 2015; 373: 511-20.
Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy.* 2015; 35: 198-207.

Andexanet Alfa

- Breakthrough Therapy Designation by FDA
- 3 Phase III studies
  - Reversal of rivaroxaban and apixaban in older healthy adults 50-75 years old
    - Rivaroxaban (ANNEXA-R)
      - Andexanet alfa 800 mg IV bolus, then 4 mg/min for 2 hours
    - Apixaban (ANNEXA-A)
      - Andexanet alfa 400 mg IV bolus, then 4 mg/min for 2 hours
  - Reversal of factor Xa inhibitors in acute major bleeding

Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy.* 2015; 35: 198-207.
Siegal DM, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med* 2015; 373:2413-2424.
NCT02329327. www.clinicaltrials.gov. Accessed April 3rd, 2016.

Aripazine

- Fast Track Designation granted by FDA
- Phase I and II studies
  - Edoxaban
  - Heparin
  - Enoxaparin
- Greatest potential as a universal reversal agent

Mo Y, Yam FK. Recent advances in the development of specific antidotes for TSOACs. *Pharmacotherapy.* 2015; 35: 198-207.
PER977. www.clinicaltrials.gov. Accessed September 9, 2015.

KEEP CALM AND STOP THE ANTICOAGULATION

Clinical Considerations for Reversal

- Indication
  - Intensity of anticoagulation and risk of hematoma expansion
  - Surgical intervention
- Choice of reversal agent
  - Past medical history
  - Thromboembolic events
  - Adverse reactions/Allergies
- Outcomes
  - Morbidity
  - Mortality

Nutescu EA, et al. *Am J Health-Syst Pharm.* 2013; 70:1914-29

Warfarin Reversal

- Blood Products
  - FFP 10-15 mL/kg
- Pharmacological
  - Phytonadione
    - 10 mg IVPB x 1
  - 4 factor PCC or aPCC
    - 25 – 50 units/kg
      - Dose based on presenting INR
    - 3 factor PCC
      - FVIIa
  - rFVIIa
    - 1 mg IVP + FFP
- Supportive care
  - Monitoring for adverse reactions
    - Thromboembolism
    - Anaphylaxis and anaphylactoid reactions
  - Efficacy
    - Decrease in PT/INR

Frontera JA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016 Feb;24(1):6-46.

Dabigatran Reversal

- Activated Charcoal
  - Acute ingestion (1-2H)
  - 25-50 g dose without sorbitol
- Fluids
  - NS 1 L bolus
  - NS 1 mL/kg/hr
- Idarucizumab
  - 5 gram x 1 dose
- aPCC or 4 factor PCC
  - 50 units/kg x 1 dose
- Hemodialysis
  - 62% removal at 2 hours
- Lab Monitoring
  - Thrombin time
  - aPTT

Van Ryn J, et al. Effect of dabigatran on coagulation assays and reversal strategies. *Thromb Haemost.* 2010; 103:1116-1127.
Kaatz S, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol.* 2012; 87:S141–S145.
Frontera JA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016 Feb;24(1):6-46.

Intravenous DTIs

- Hirudin analogues and argatroban
  - Shut off drip
  - Fluids
- aPCC or 4 factor PCC
  - 50 units/kg x 1 dose
- Lab Monitoring
  - aPTT

Beshay JE, et al. Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. *J Neurosurg.* 2010; 112:307-318.
Irani MS, et al. Reversal of hirudin-induced bleeding dithesis by PCC. *Am J Cardiol.* 1995; 75: 422-423.
Frontera JA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016 Feb;24(1):6-46.

Oral Factor Xa Reversal

- Activated charcoal
  - Not studied, but recommended
- Fluids
  - NS 1 L bolus
  - NS 1 mL/kg/hr
- aPCC or 4 factor PCC
  - 50 units/kg x 1 dose
- Hemodialysis
  - May not be as effective
  - Highly protein bound
- Lab monitoring
  - PT
  - aPTT

Kaatz S, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol.* 2012; 87:S141–S145.
Miyares MA, Davis K. A review of laboratory monitoring options and reversal agents. *Am J Health-Syst Pharm.* 2012; 69:1473-84.
Frontera JA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016 Feb;24(1):6-46.

Fondaparinux Reversal

- First line agent
  - aPCC 20 units/kg x 1 dose increased thrombin generation time in plasma from healthy volunteers
- If aPCC is contraindicated
  - rFVIIa 90 mcg/kg x 1 dose
  - Immediate normalization of thrombin generation time, aPTT and PT
- Monitoring
  - Anti-factor Xa for fondaparinux

Desmurs-Clavel H, et al. Reversal of the inhibitory effect of fondaparinux on thrombin generation by rFVIIa. *Thromb Res.* 2009; 123:796-8.
Bijsterveld NR, et al. Ability of rFVIIa to reverse antiooagulant effect of fondaparinux in healthy volunteers. *Circulation.* 2002; 106: 2550-4.

Heparin Product Reversal

Unfractionated heparin

- Protamine
  - Immediate reversal
    - 1 mg/100 units heparin
  - Delayed reversal (30-60 min)
    - 0.5 mg/100 units heparin
- DO NOT GIVE FFP
- Monitor
  - aPTT
  - ACT

Low molecular weight heparin

- Protamine
  - Enoxaparin
    - Within 8 hours
      - 1 mg/1 mg
    - Within 8-12 hours
      - 0.5 mg/1 mg
  - Dalteparin (within 3-5 half lives)
    - 1 mg/100 units
  - rFVIIA 90 mcg/kg x 1 dose if protamine contraindicated
- Monitor
  - Anti-Xa level

Frontera JA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016 Feb;24(1):6-46.

tPA Reversal

- Stop infusion
- Give 10 units cryoprecipitate STAT
  - Goal fibrinogen > 150 mg/dL
- Consider aminocaproic acid or tranexamic acid when cryoprecipitate is contraindicated
  - Aminocaproic acid 5 g IVBP x 1 dose
  - Tranexamic acid 10-15 mg/kg IVPB x 1 dose
- Lab Monitoring
  - Fibrinogen

French KF, et al. Treatment of intracerebral hemorrhage with tranexamic acid After thrombolysis. *Neurocrit Care.* 2012; 17:107-111.
Neidech A. Intracranial Hemorrhage. *Am J Respir Crit Care Med.* 2011;184: 998-1006.
Frontera JA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016 Feb;24(1):6-46.

Nursing Clinical Pearls

- Vitamin K
  - Do not give subcutaneously for life threatening bleeds
  - Monitor for anaphylaxis/anaphylactoid reactions
    - Risk is less than 1%
- Prothrombin Complex Concentrates
  - Flush IV line with normal saline
  - Monitor for infusion related reactions
  - Coags must be drawn 30 minutes after dose complete
  - Monitor for new onset thromboembolism
- Factor VIIa
  - Flush line with NS before and after administration
    - Give over 2 minutes
  - Monitor for new onset thromboembolism
  - Coags must be drawn within 30 minutes of administration
- Protamine
  - Too much = more bleeding
  - Too fast = anaphylactoid reaction

Conclusion

- Early recognition and reversal of anticoagulant or thrombolytic associated hemorrhagic stroke with the appropriate agent is the cornerstone of treatment
- New antidotes will replace PCCs and rFVIIa for DOAC reversal when they are approved by the FDA