Updates in Treating Emergent Bleeds

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Disclosures

Audience Poll

Learning Objectives

- Review current oral anticoagulation therapies
- Highlight current and emerging data for the treatment of emergent bleeds for patients on anticoagulation
- Apply the use of the new NMMC treatment for emergent bleeds algorithm to a variety of patient cases

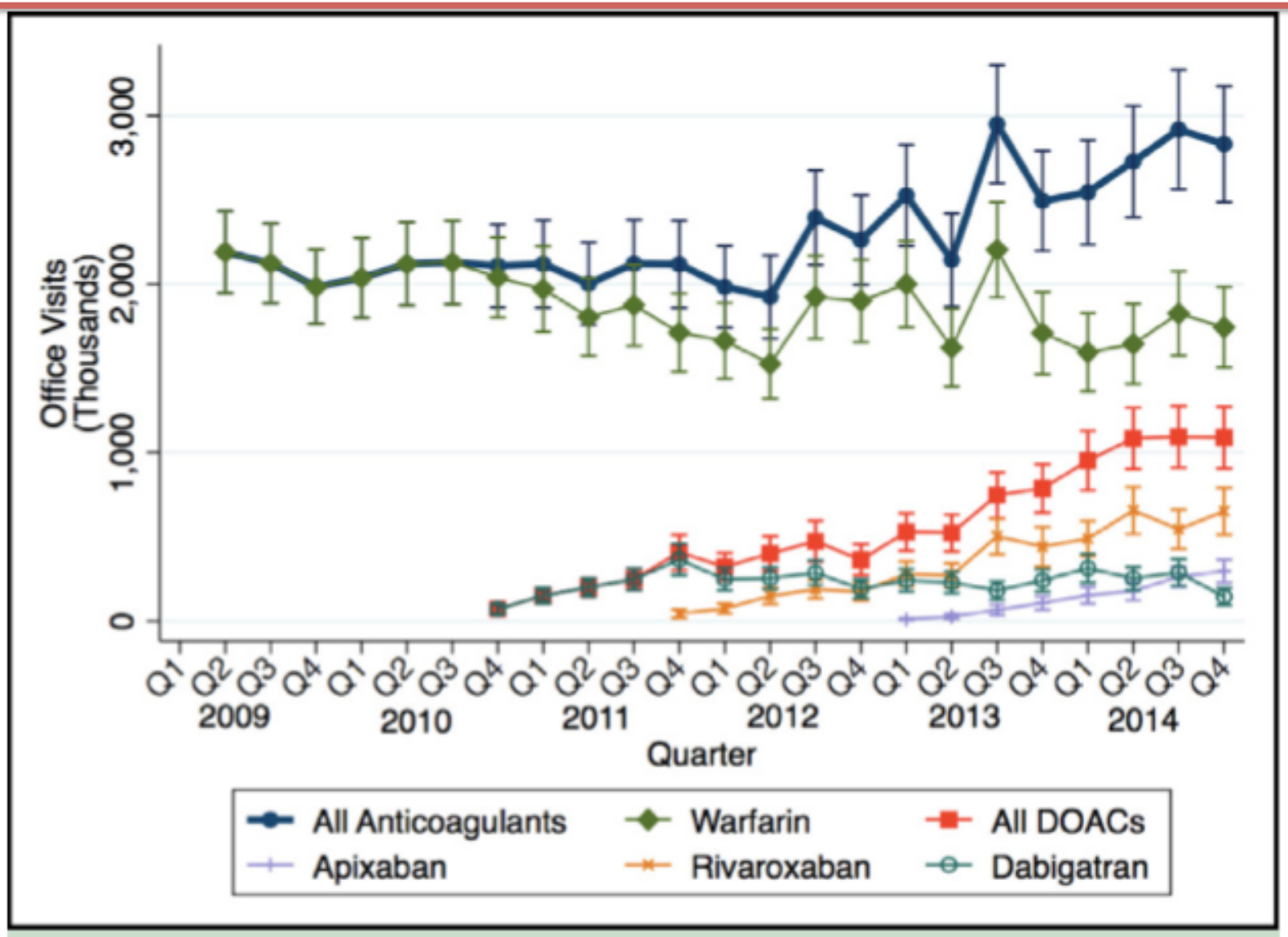
Active Learning

- Which of the following oral anticoagulants is a direct thrombin inhibitor?
  A. Warfarin
  B. Apixaban
  C. Dabigatran
  D. Betrixaban

Review of Anticoagulant Therapy

- For the treatment of thromboembolic disorders
  - Atrial fibrillation
  - Venous thromboembolism
  - Pulmonary embolism
  - Mechanical valves
- Oral Agents
  - Vitamin-K Antagonists (warfarin)
  - Direct thrombin inhibitors (dabigatran)
  - Factor Xa inhibitors (i.e., apixaban, rivaroxaban)

Trends of Anticoagulants



Oral Anticoagulants

***Factor Xa inhibitors not shown here are betrixaban (Bevyxxa) and edoxaban (Savaysa)

	Warfarin (Coumadin)	Dabigatran (Pradaxa)	Apixaban (Eliquis)	Rivaroxaban (Xarelto)
Half-life (Hours)	24-60	17	15	9
Dosing Frequency	Qday	BID	BID	Qday
Renal Excretion	90%	80%	25%	36%
Drug interactions	CYP2C9, 2C8, 2C18, 2C19, 1A2, and 3A4	P-gp	CYP3A4, P-gp	CYP3A4, P-gp

CYP-cytochrome P450; P-gp P Glycoprotein modifiers; hr- hours; Cp=Peak Plasma Concentration

Assessing the Situation

- Patient Q's
  - What do you take?
  - Why do you take it?
  - When did you last take it?
  - How much did you take?
- Clinical Q's
  - Non-major vs. major bleed
  - Acute vs. Chronic
  - Hemodynamic stability

Active Learning

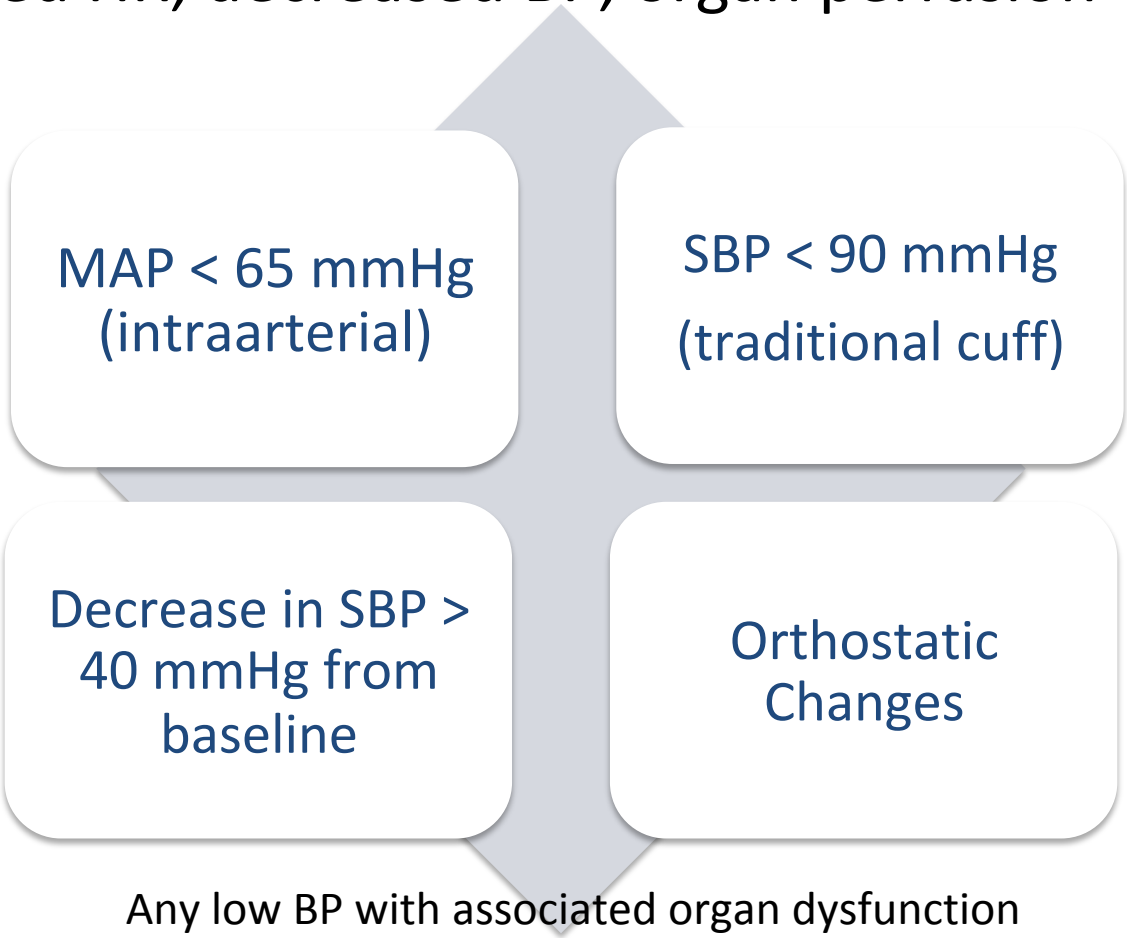
- Which of the following is required to define an anticoagulant associated major bleed?
  A. A decrease in Hemoglobin by 5g/dL
  B. Gastrointestinal bleeding
  C. Requirement of 1 unit of PRBCs
  D. MAP of < 65mmHg

Defining Bleed Severity

- 1. Location of bleed
  - Critical site: location in which impairment of organ function occurs when bleeding develops
    - Intracranial hemorrhage (ICH)
    - Central nervous system sites (e.g., intraocular, intra-extra-spinal)
    - Thoracic
    - Intrabdominal
    - Retroperitoneal hemorrhage (RPH)
    - Intraarticular
    - Intramuscular
  - Note: Intraluminal GI bleeding is NOT considered a critical site bleed

Defining Bleed Severity

- 2. Hemodynamic compromise, any of the following; increased HR, decreased BP, organ perfusion



Defining Bleed Severity

- 3. Apparent Bleeding
  - Causes a drop in Hemoglobin by > 2g/dL
  - Necessitates 2 or more units of packed red blood cells (PRBCs)

Management of Bleeds

- Supportive Care
- Blood products
- Local hemostatic control
- Avoidance of hypothermia and acidosis
- Surgical intervention
- Target specific reversal agents

Supportive Care and Resuscitation

- HOLD the anticoagulant!
- Aggressive volume replacement
  - No benefit of colloids
  - Lactated Ringers may be better than 0.9% NaCl
    - Lower events of renal dysfunction
    - Potential to avoid metabolic acidosis
- Blood Products
  - Activate massive blood transfusion protocol if needed

Role of Comorbid Conditions

- Heart Failure
  - Decreased perfusion to kidneys and liver
  - Decreased clearance of DOACs
- Renal Failure
  - Decreased platelet aggregation
  - Decreased clearance of DOACs
- Cirrhosis
  - Decreased clotting factors
  - Decreased platelets
- Underlying clotting disorders (e.g., trauma, DIC, pregnancy, etc.)

Active Learning

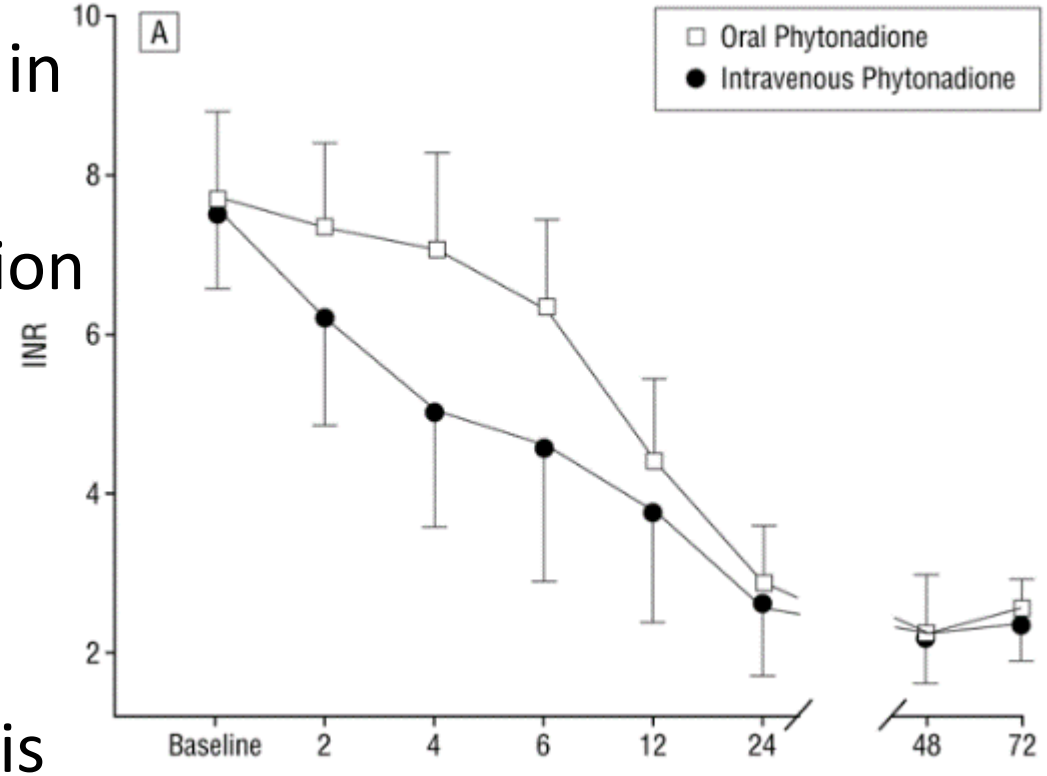
- ET is a 45 y/o F with a PMH of DM, HLD,HTN, and Afib on dabigatran who slipped on the ice during tryouts for a spot the USA Olympic Curling Team. What FDA approved reversal option is available for the reversal of the anticoagulant effects of dabigatran?
  A. Andexanet alpha
  B. aFPCC
  C. Idarucizumab
  D. 4FPCC

Knowing Your Options

Anticoagulant	FDA-Approved Reversal Agent
Warfarin (Coumadin)	4F-PCC (Kcentra)
Dabigatran (Pradaxa)	Idarucizumab (Praxbind)
Apixaban (Eliquis) Rivaroxaban (Xarelto)	Andexanet alpha (Andexxa)

Warfarin Reversal

- Vitamin K
  - Single agent used in minor bleeds
  - Used in combination for treating emergent bleeds
  - Effects are dose-dependent
  - IV administration is preferred



Baseline INR 6-10
IV vs PO at 6 hours: $p < 0.001$
12 hours: $p=0.03$

Arch Intern Med. 2006;166:391-397
Arch Intern Med 2003;163;2469-73

Fresh Frozen Plasma (FFP)

- Plasma
  - Doses range from 10-20mL/kg required for reversal
  - Requires ABO blood type matching
  - Disadvantages
    - Time to procurement
    - Volume overload
    - Allergic reactions
    - Transfusion-related acute lung injury

Prothrombin Complex Concentrates

- Four-factor Prothrombin Complex Concentrate (4F-PCC)
  - Inactivated (Kcentra®)
    - Contains inactivated factors II, VII, IX, X, and Protein C and S
    - Indicated for the emergent reversal of VKA life threatening bleeding or needing urgent/invasive interventions
  - Activated (FEIBA®)
    - Contains factors II, VII (activated), IX, and X
    - Indicated for use in hemophilia

4F-PCC

- Dosed based on INR and patient weight

Pre-Tx INR	2 - < 4	4 - 6	> 6
Dose	25 units/kg	35 units/kg	50 units/kg
Max Dose	2500 units	3500 units	5000 units

- Must be administered with 5-10mg of IV vitamin K
- Boxed warning for thromboembolic complications

Fixed-Dose 4F-PCC

Design	Retrospective chart review post-implementation of fixed-dose protocol
Patients	77 patients with acute major bleed within 18 hours of administration of a Factor Xa inhibitor • Mean age=77 years • Bleeding= GI (49%), ICH (42%) and other (9%)
Treatment	• 1500 units of 4F-PCC prior to INR resulting

Results	• Median dose=20.1units/kg
	• Median pre-tx INR=3.06
	• Median post-tx INR=1.32
	  • 100% of patient with INR ≤ 2
	  • 75% of patients with INR ≤ 1.5

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Astrup, et al. *J Thromb Thrombolysis* 2018; 45(2): 300-305

NMMC's Reversal Strategy

- Obtain pre-treatment INR
  - Do not wait for INR to obtain reversal agent
- Fixed-dose Protocol
  - 1500units of 4FPCC **with** 10mg IV vitamin K
  - Obtain INR 15-30 post infusion
  - If homeostasis is not achieved after first dose, rebolus with 500 units of 4FPCC

Drug		Strategies for Reversal	Monitoring Parameters
Vitamin K Antagonist	**Warfarin** *(Coumadin)* $T_{1/2}$=24-60h	1. Obtain INR-Do NOT wait for pretreatment INR **2. Administer 1500 IU of 4FPCC (Kcentra) with 10mg IV vitamin K** 3. Recheck INR 15-30 minutes after 4FPCC has ended 4. If homeostasis is not achieved after first dose, **rebolus with 500 IU of 4FPCC (Kcentra)**	**Do NOT wait for pretreatment INR** • Pre-Kcentra INR • Post-Kcentra INR, 15-30 minutes post infusion

Management of 4F-PCC

- Storage and Preparation
  - Stored and prepared in pharmacy IV lab
  - Doses are based on the amount of clotting factor IX present in each vial
- Administration
  - 0.12 mL/kg/min (~3 units/kg/min)
  - Max rate of 8.4 mL/min
- Cost
  - $1.76/unit
    - 1500 unit fixed dose ~$2640
    - FDA dosing at 25units/kg (2500units) ~$4400

Idarucizumab (Praxbind®)

- Monoclonal antibody that binds to dabigatran
  - Binds both free and thrombin-bound dabigatran to neutralize anticoagulation
- FDA-Approved indications
  - Emergent surgery or urgent procedure
  - Life-threatening bleeding
- No procoagulant effects

Idarucizumab (Praxbind®)

- REVERSE-AD Trial
  - Primary endpoint: Max % reversal of anticoagulant effects of dabigatran within 4 hours post- administration of Idarucizumab
  - Compared outcomes of two groups
    - Uncontrolled bleeding + dabigatran
    - Emergent surgery/procedure +dabigatran
  - Results
    - Idarucizumab administration resulted in immediate, complete and sustained reversal of dabigatran
    - No severe adverse events

NMMC's Reversal Strategy

- If ingested within the last 2 hours, give charcoal PO/NG
- Administer Idarucizumab (Praxbind®) 2.5g IV x 2 doses (Total dose= 5g)
- Alternative approaches
  - aFPCC (Feiba) 50-100 unit/kg IV
  - Hemodialysis

Direct Thrombin Inhibitors	**Dabigatran** *(Pradaxa)* $T_{1/2}$=17h	1. If ingested **within last 2 hours**, give charcoal 50mg PO/NG 2. **Administer Idarucizumab (Praxbind) 2.5g IV x 2 doses (total dose= 5g)** **OR** **Administer aFPCC (Feiba) 50-100 units/kg IV** Note: Outcomes of repeat Praxbind doses are not known	• aPTT • Thrombin

Management of Idarucizumab

- Stored in pharmacy
  - 5 g dose = two 2.5g vials
  - Refrigerated
- Preparation
  - No compounding required
- Administration
  - Give 2.5g/50ml IVP, repeat with 2.5g/50ml IVP 15 minutes apart
- Cost
  - AWP=$4200 per 5g dose

Active Learning

- What is the recommended dose of Andexanet alpha for a patient presenting with ICH whose last dose of Rivaroxaban 10mg was 10 hours ago?
  A. Bolus 200mg, then a 2 hour infusion of 480mg infusion
  B. Bolus 400mg, then a 2 hour infusion of 480mg
  C. Bolus 480mg, then a 2 hour infusion of 400mg infusion
  D. Bolus 800mg, then a 2 hour infusion of 960mg

Reversal of Xa Inhibitors

- Andexanet alpha (Andexxa®)
  - Humanized, monoclonal antibody that binds and sequesters Factor Xa inhibitors
  - Indications
    - Reversal of apixaban (Eliquis®) and rivaroxaban (Xarelto®) in life-threatening or uncontrolled bleeding
  - Boxed warnings
    - Thromboembolic risks, ischemic risk
    - Cardiac arrest and sudden death

Andexanet Alpha

- Two dosing regimens: low and high dose
- Dosing is based on time of last dose taken and the prescribed dose

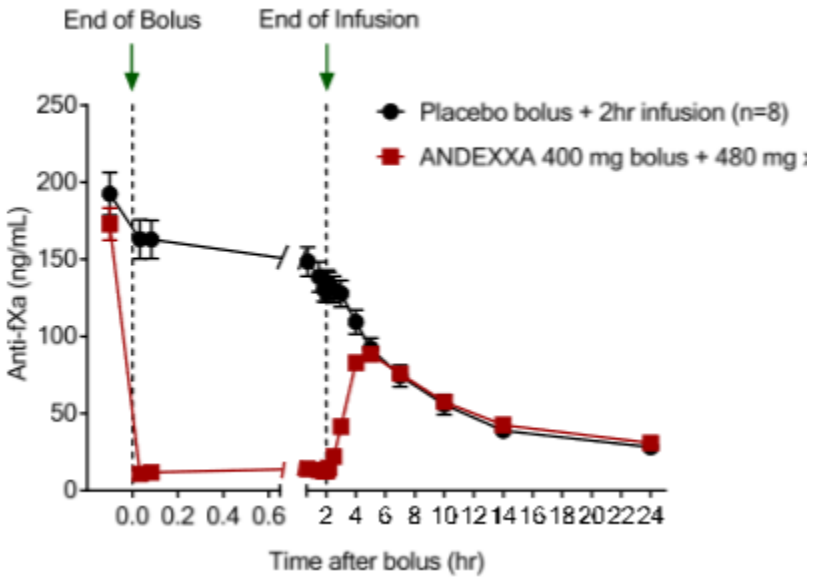
Dose	Initial IV bolus	Continuous IV infusion
Low dose	400 mg IV over 15 minutes	4 mg/min for up to 120 minutes (480 mg total)
High dose	800 mg IV over 30 minutes	8 mg/min for up to 120 minutes (960 mg total)

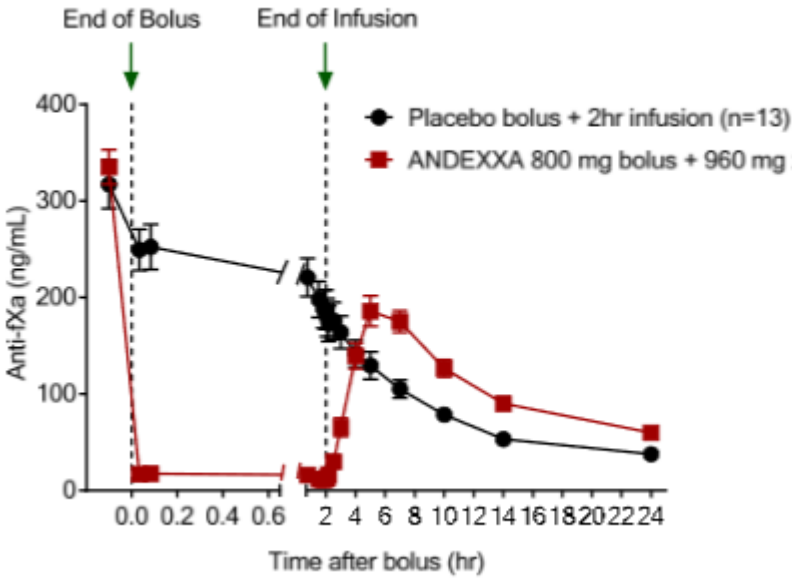
Andexanet Alpha

Xa Inhibitor	Xa Inhibitor Last Dose	Timing of Xa inhibitor (Last dose before Andexanet Alpha)	
		< 8 hours or unknown	≥ 8 hours
Rivaroxaban (Xarelto®)	≤ 10 mg	Low	Low
	> 10 mg or unknown	High	
Apixaban (Eliquis®)	≤ 5 mg	Low	
	> 5 mg or unknown	High	

Andexanet Alpha Trials

- Andexxa-A and Andexxa-R studies
  - Both studies enrolled healthy, adult patients
    - Volunteers were given either Apixaban or Rivaroxaban for 3-4 days before receiving andexanet
    - N=50





Anexxa-4

- Ongoing, open label trial
- Enrolled patients presenting with major bleeds and had taken a FXa inhibitors within 18 hours
- Preliminary data suggest that;
  - Anti-Xa activity is reduced by 90%
  - Homeostasis was achieved in 79% of patients
  - 18% of patients experienced a thrombotic event within 30 days
- Full publication expected within the year

Additional Considerations

- Rebound in Anti-Xa 2-4 hours post infusion
  - Monitor for bleeding and anti-Xa levels
- Not studied in patients going to surgery
- Use of andexanet after administration of PCC
- Restarting anticoagulation
  - Currently no recommendations
  - Prescriber variability
- Cost!
  - Low dose~$25,000
  - High dose~$50,000

4F-PCC

- Tao et al (2018)
  - Retrospective, single center, chart review
    - 4F-PCC given to reverse apixaban or rivaroxaban
    - n=43
  - Primary Endpoint
    - Hemostatic efficacy determined by treating physician
      - 6.9% of patients continued to have active bleeding
  - Secondary Endpoint
    - 2.1% of patients had a thromboemobolic event by day 14

J of Intensive Care. 2018; 6:34

4F-PCC

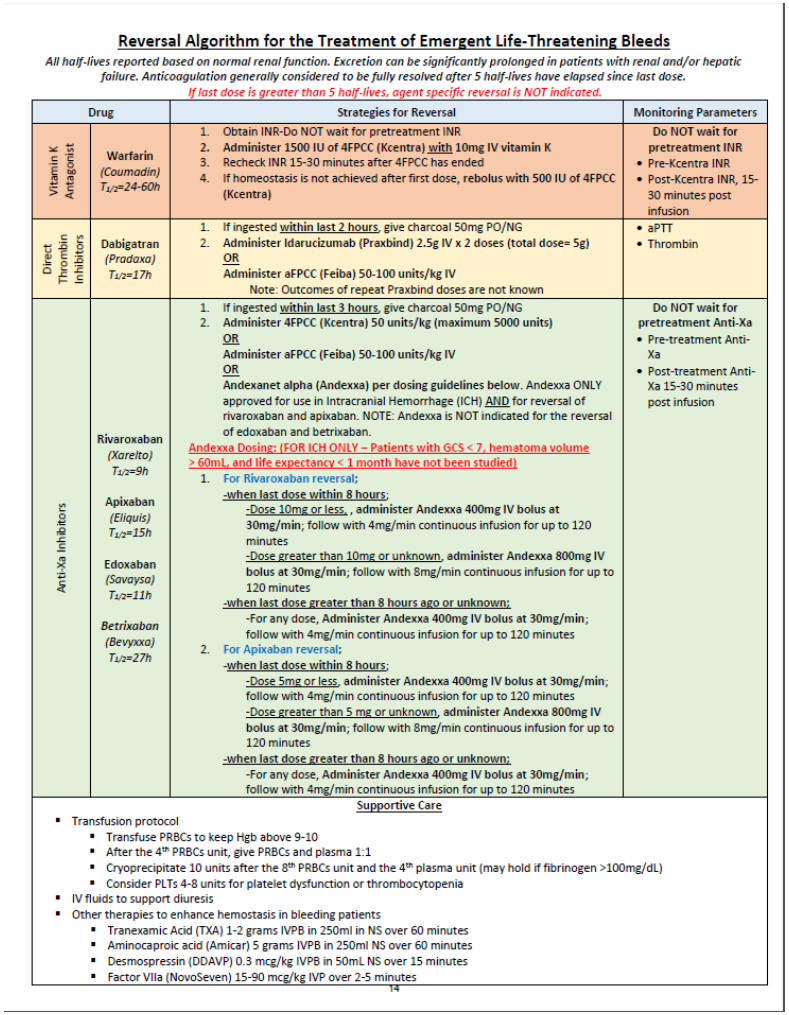
- Kaplan et al (2018)
  - Single center retrospective chart review
    - 4F-PCC given to reverse apixaban or rivaroxaban
    - n=22
  - Primary Endpoint
    - Hemostasis
      - 90.9% of patients
        - » 27.3% also received FFP
    - Safety
      - 9% experience deep vein thrombosis
      - In-hospital mortality was 9%

Crit Care Med. 2018; 46(1):259

NMMC's Reversal Strategy

- For ICH ONLY
  - Andexanet alpha per dosing regimen
- For all other major bleeds
  - If dose was last taken within 3 hours, charcoal 50 g PO/NG
  - 4FPCC (Kcentra) 50 units/kg IV (max dose=5000 units)

    OR
  - aFPCC (Feiba) 50-100 units/kg IV



Reversal Algorithm for the Treatment of Emergent Life-Threatening Bleeds

All half-lives reported based on normal renal function. Excretion can be significantly prolonged in patients with renal and/or hepatic failure. Anticoagulation generally considered to be fully resolved after 5 half-lives have elapsed since last dose.

If last dose is greater than 5 half-lives, agent specific reversal is NOT indicated.

Drug		Strategies for Reversal	Monitoring Parameters
Vitamin K Antagonist	Warfarin (Coumadin) $T_{1/2}$=24-60h	1. Obtain INR-Do NOT wait for pretreatment INR 2. Administer 1500 IU of 4FPCC (Kcentra) with 10mg IV vitamin K 3. Recheck INR 15-30 minutes after 4FPCC has ended 4. If homeostasis is not achieved after first dose, rebolus with 500 IU of 4FPCC (Kcentra)	Do NOT wait for pretreatment INR • Pre-Kcentra INR • Post-Kcentra INR, 15-30 minutes post infusion
Direct Thrombin Inhibitors	Dabigatran (Pradaxa) $T_{1/2}$=17h	1. If ingested within last 2 hours, give charcoal 50mg PO/NG 2. Administer Idarucizumab (Praxbind) 2.5g IV x 2 doses (total dose= 5g) OR Administer aFPCC (Feiba) 50-100 units/kg IV Note: Outcomes of repeat Praxbind doses are not known	• aPTT • Thrombin
Anti-Xa Inhibitors	Rivaroxaban (Xarelto) $T_{1/2}$=9h Apixaban (Eliquis) $T_{1/2}$=15h Edoxaban (Savaysa) $T_{1/2}$=11h Betrixaban (Bevyxxa) $T_{1/2}$=27h	1. If ingested within last 3 hours, give charcoal 50mg PO/NG 2. Administer 4FPCC (Kcentra) 50 units/kg (maximum 5000 units) OR Administer aFPCC (Feiba) 50-100 units/kg IV OR Andexanet alpha (Andexxa) per dosing guidelines below. Andexxa ONLY approved for use in Intracranial Hemorrhage (ICH) AND for reversal of rivaroxaban and apixaban. NOTE: Andexxa is NOT indicated for the reversal of edoxaban and betrixaban. Andexxa Dosing: (FOR ICH ONLY – Patients with GCS < 7, hematoma volume > 60mL, and life expectancy < 1 month have not been studied) 1. For Rivaroxaban reversal; -when last dose within 8 hours; -Dose 10mg or less, , administer Andexxa 400mg IV bolus at 30mg/min; follow with 4mg/min continuous infusion for up to 120 minutes -Dose greater than 10mg or unknown, administer Andexxa 800mg IV bolus at 30mg/min; follow with 8mg/min continuous infusion for up to 120 minutes -when last dose greater than 8 hours ago or unknown; -For any dose, Administer Andexxa 400mg IV bolus at 30mg/min; follow with 4mg/min continuous infusion for up to 120 minutes 2. For Apixaban reversal; -when last dose within 8 hours; -Dose 5mg or less, administer Andexxa 400mg IV bolus at 30mg/min; follow with 4mg/min continuous infusion for up to 120 minutes -Dose greater than 5 mg or unknown, administer Andexxa 800mg IV bolus at 30mg/min; follow with 8mg/min continuous infusion for up to 120 minutes -when last dose greater than 8 hours ago or unknown; -For any dose, Administer Andexxa 400mg IV bolus at 30mg/min; follow with 4mg/min continuous infusion for up to 120 minutes	Do NOT wait for pretreatment Anti-Xa • Pre-treatment Anti-Xa • Post-treatment Anti-Xa 15-30 minutes post infusion

Supportive Care

- Transfusion protocol
  - Transfuse PRBCs to keep Hgb above 9-10
  - After the 4th PRBCs unit, give PRBCs and plasma 1:1
  - Cryoprecipitate 10 units after the 8th PRBCs unit and the 4th plasma unit (may hold if fibrinogen >100mg/dL)
  - Consider PLTs 4-8 units for platelet dysfunction or thrombocytopenia
- IV fluids to support diuresis
- Other therapies to enhance hemostasis in bleeding patients
  - Tranexamic Acid (TXA) 1-2 grams IVPB in 250ml in NS over 60 minutes
  - Aminocaproic acid (Amicar) 5 grams IVPB in 250ml NS over 60 minutes
  - Desmospressin (DDAVP) 0.3 mcg/kg IVPB in 50mL NS over 15 minutes
  - Factor VIIa (NovoSeven) 15-90 mcg/kg IVP over 2-5 minutes

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Management of Andexanet Alpha

- Stored in pharmacy
  - 100 mg vials
  - 200 mg vials in the pipeline
- Preparation
  - Takes ~3 min to dissolve each vial
  - Low dose= 9 vials
  - High dose= 18 vials
- Administration
  - Requires a 0.22 micron filter for administration
  - Half of the dose remains in the line if not flushed post bolus and infusion

Access to Algorithm

Active Learning

- MS is a 73 y/o M with PMH of stroke (2017), HTN, and Afib presents with sudden onset of abdominal pain with N,V,D
- Medications: ASA 81mg, metoprolol 25mg, atorvastatin 40mg, and rivaroxaban 10mg (last dose 24 hours ago)
- Vitals and labs: BP=103/98, HR=120, H/H=8/27, SCr=0.8mg/dL
- Dx=Concern for mesenteric ischemia requires emergent exploratory surgery
- What do you recommend?
  A. 4FPCC 25units/kg
  B. aPCC 50units/kg
  C. Andexanet alpha 400mg followed by 480mg infusion
  D. Nothing

Learning Objectives

- Review current oral anticoagulation therapies
- Highlight current and emerging data for the treatment of emergent bleeds for patients on anticoagulation
- Apply the use of the new NMMC treatment for emergent bleeds algorithm to a patient case

Acknowledgments

- NMMC pharmacy team
- Stephanie Tesseneer, PharmD, BCCCP