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Balancing Act: Managing Bleeding and Thrombosis with Direct Oral Anticoagulants

Disclosure

The program chair and presenters for this continuing education activity have reported no relevant financial relationships, except:

- **Michael Gulseth** - BMS: Consultant, Speaker's Bureau; Boehringer Ingelheim: Consultant; Janssen: Speaker's Bureau; Pfizer: Speaker's Bureau

Case

- **AJ is a 65 year old, 80kg male with a history of unprovoked DVT 1 year ago who was managed on warfarin for 3 months. 2 months ago, he was diagnosed with atrial fibrillation and requested to be on a different oral agent as warfarin was very hard to keep controlled with a lot of lab testing and dosing adjustments done. He takes the agent twice daily, but does not remember what the name is and is very confused. He is now being admitted with bright red blood in his stools that has been going on for several hours and very weak.**
- **PHH: CAD (NSTEMI), GERD, DVT, HTN, AF and CKD IV**
- **Labs: Scr 3.5, Hgb 5.2, INR 2.6**

For AJ – what is your next management step

A Thrombin Time

B Anti-Xa activity

C Bedside assessment of the current bleeding

D All of the above

For AJ – what anticoagulation reversal approach would you initiate

A rFVIIa

B 4 factor PCC/aPCC – 50 units/kg

C Idarucizumab or Andexanet

D Low dose PCC/aPCC – 8-12 units/kg and watch

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Exploring approaches to reversing the DOAC's

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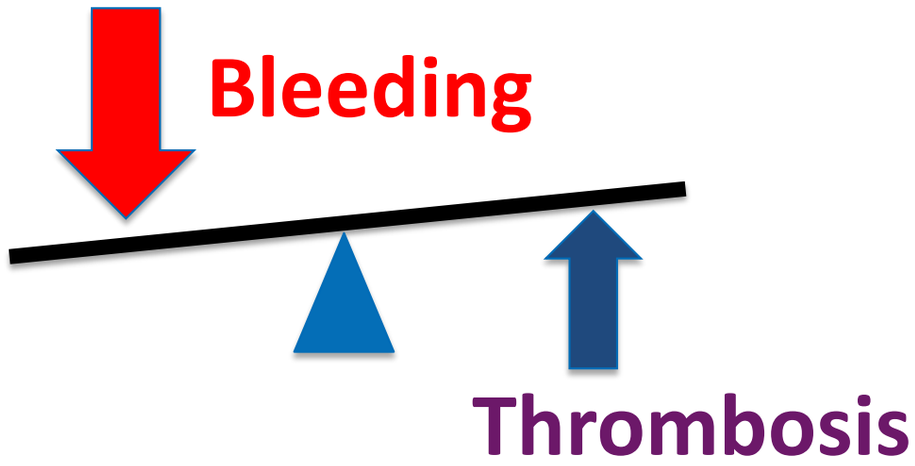
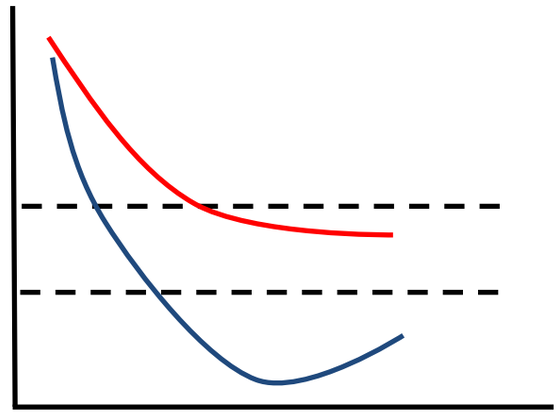
Assess the Situation

- Bleeding?
  - Scan patient
  - Site: risk of a complication
- Assess Urgency of Situation
  - Imminent life threatening vs some time
- Level of anticoagulation
  - Laboratory assay
  - Antiplatelet agents?
- Keep in mind – need to restart anticoagulation



Anticoagulant "Lowering Intensity or Reversal" Strategy

- Hold Anticoagulation
- Bleeding?
  - Site and severity – may influence outcomes
- Create a plan and request necessary follow up
  - Stop or slow it to locate and treat
- Mechanical Intervention (Surgery)
- Pharmacological intervention
  - Topical Agents
  - Neutralize the drug
  - Reverse the effects of the drug independently – Hemostatic agents
- Replace losses
- Optimize management of co-morbid situations

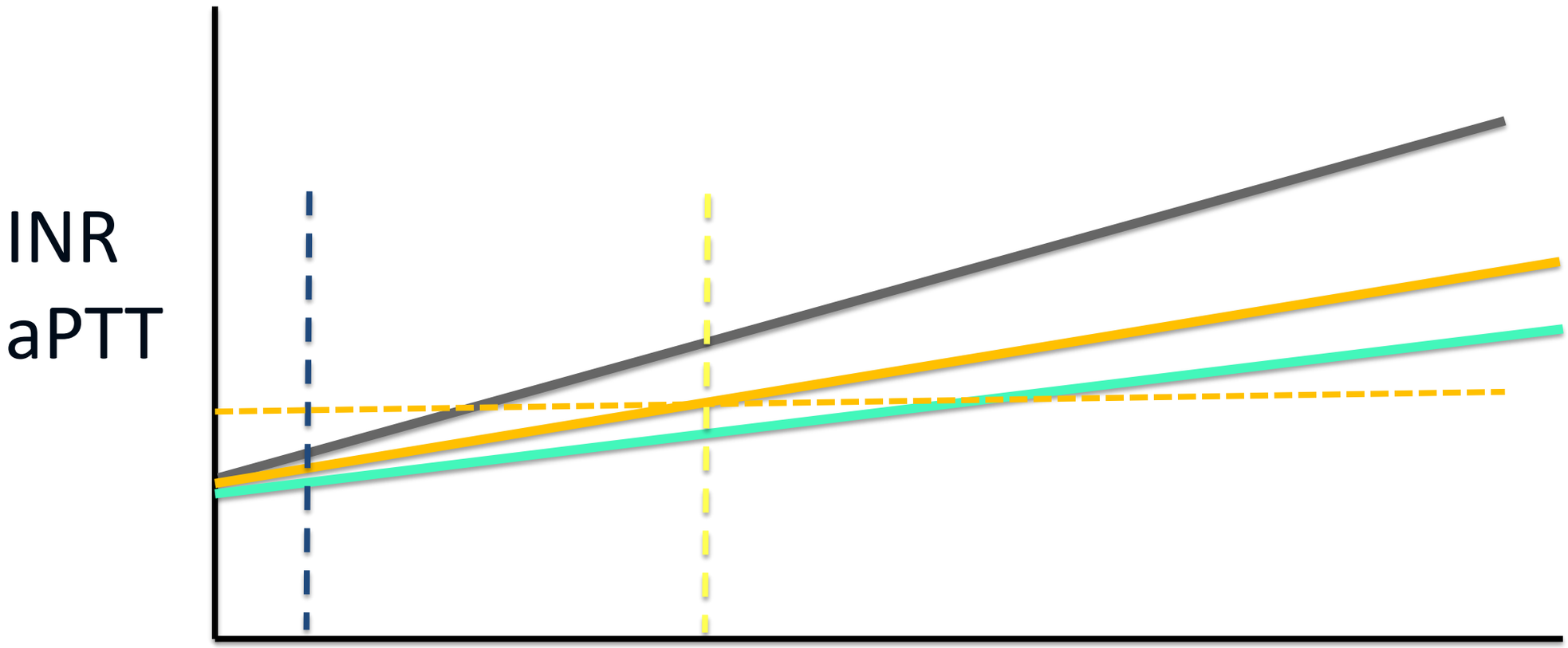


Assessing intensity of anticoagulation effects

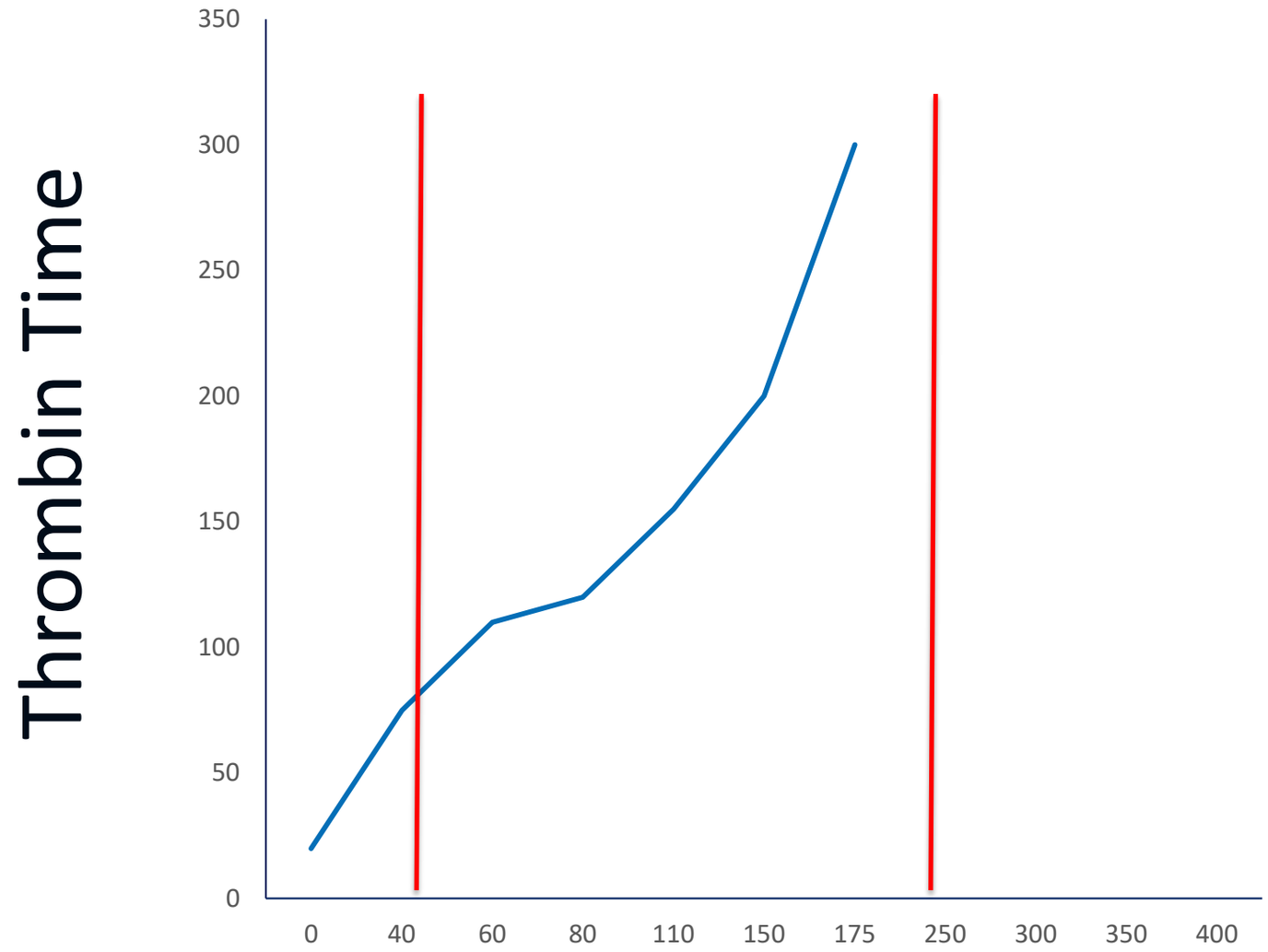
	Dabigatran	Rivaroxaban/Apixaban/ Edoxaban
Drug Present	**Thrombin Time**	**? Chromogenic anti-Factor Xa ? Anti-factor Xa (calibrated to UFH or LMWH)**
Quantitative Test	**? Dilute thrombin time or Chromogenic ECT**	**Chromogenic anti-factor Xa**
Sensitivity: PT vs aPTT	**aPTT > PT (Point-of-Care INR > Central Lab)**	**PT > aPTT. Anti-Xa calibrated to LMWH/UFH – not as predictable or accurate**
No/Limited effect		**ECT, TT**

Lindhoff-Last E et al. *Ther Drug Monit.* 2010; 32:673-9.
Lindahl TL et al. *Thromb Haemost*. 2011; 105:371-8.
van Ryn J et al. *Am J Med*. 2012; 125:417-20.
van Ryn J et al. *Thromb Haemost.* 2010; 103:1116-27.

Potential INR or aPTT response with higher DOAC serum concentrations



Dabigatran and Thrombin Time



Use of PCC or aPCC with DOACS: Bleeding

- In-Vitro and Ex Vivo data inconsistent
  - Dose used may not mimic clinical approach
- No randomized comparisons
- Doses variable (8 – 100 units/kg)
- Single doses and low doses in GI Bleeds have worked
  - Rare need to repeat doses; Onset seems to be rapid.
  - Some failures
- Any advantage: aPCC over PCC with Anti-Factor Xa agents unclear.
- Thrombosis has been reported
- Mortality Rates Vary
- Neurocritical Care Society ICH Guidelines: 50 units/kg PCC or aPCC
  - If no Idarucizumab given
  - Some success in case reports

Dibu JR et al. *Neurocrit Care*. 2015 Nov 6. [Epub ahead of print].
Frontera JA et al. Neurocrit Care. 2016; 24:6-46.
Dager W et al Am J Health System Pharm 2016

Reversing Newer Oral Anticoagulants: Bleeding Patients

- **Activated charcoal if recent ingestion**
- **Concentrated clotting factor may depend on what is available – Reassess 5-10 min post administration - If time available, start with lower doses and repeat if necessary**

	Dabigatran	Rivaroxaban/Apixaban/Edoxaban
No rush, minor bleeding	• Monitor – re-check labs	• Monitor – re-check labs
Expedited (1-24 hr), major bleeding	• Idarucizumab 5g • Consider PCC4 (25 units/kg) or low dose factor VIII inhibitor bypassing activity (aPCC)	• Evaluate if PCC needed. Consider PCC4 or PCC3 if clinically necessary • Option: low dose aPCC (8-12 units/kg)
Emergent (< 1 hr), major bleeding	• Idarucizumab 5gm • Option - Add: aPCC 10-25 units/kg, have next dose ready (or PCC4 25-50 units/kg) or TXA (bolus + Infusion)	• aPCC 25 - 50 units/kg or • PCC4 or PCC3 25-50 units/kg

Nutescu EA et al. *Am J Health-Syst Pharm*. 2013; 70:1914-29.
https://www.ucdmc.ucdavis.edu/anticoag/pdf/AnticoagReversal.pdf

For the use of PCC's to reverse DOACs, a single dose of 25units/kg or higher should be used (True or False)

A TRUE

B FALSE

Case

XZ is on a DOAC for AF PTA

(Not currently on the Med profile - not ordered on admission)

- **PMH: AF, HFrEF, CKD (Scr 2.0), CAD**
- **Meds: Amiodarone, ASA – 81mg**
- **He was admitted yesterday and no bleeding issues**
- **You find out XZ now in route to OR for a procedure with bleeding related risks**

For XZ – what is your next management step

A. Since Anesthesia has already taken the patient to the OR – no action

B. Call Anesthesia - Check coags STAT – put temp hold for incision

DOAC – Agent Unclear

Bleeding or need for Urgent Reversal

Assessment
-Amount of Drug (↑ INR/PT etc)
- Thrombin Time/Anti-Xa
- Bleeding Risk
- Charcoal if ingestion recent
- Med Rec: Dosing QD/BID

Thrombin Time **High**
Anti-Xa **Low**
? ↑ aPTT > PT (assay dependent)

Thrombin Time **Low**
Anti-Xa **High**
? ↑ PT > aPTT (assay dependent)

Dabigatran

Rivaroxaban
Apixaban
Edoxaban

Bleeding

Supportive Management
- Underlying Condition
- Transfuse
- Need for invasive procedure

Urgent

Non-Urgent

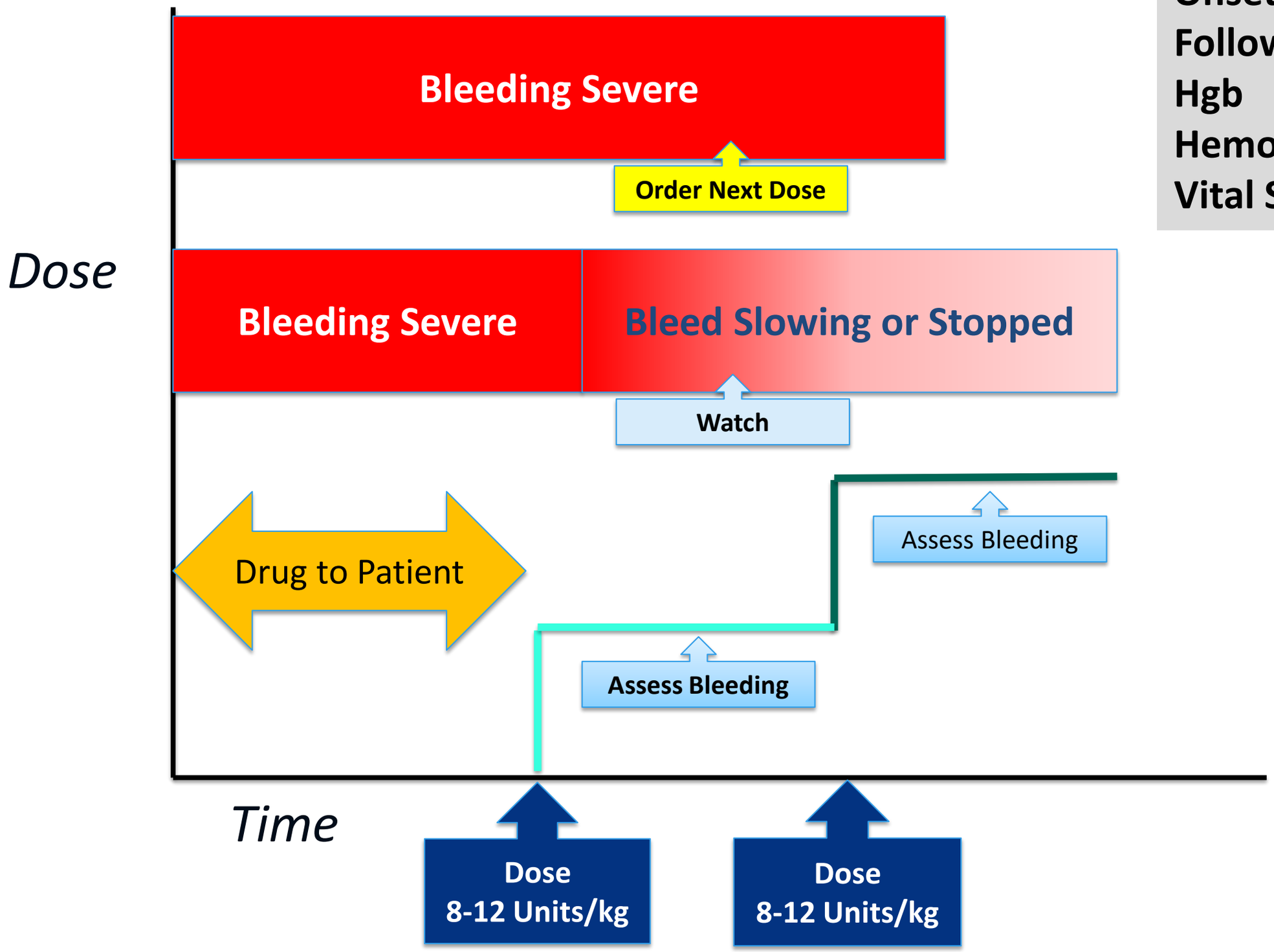
Watch

Semi Urgent

Administer Antidote
Consider Adding Hemostatic Agent if urgent – life threatening bleed

Consider Antidote
Hemostatic Agent if clinically necessary (low dose titrate to effect)

Low Dose Titration Strategy (non-ICH)



Onset Rapid in Minutes
Follow S/S Bleeding
Hgb
Hemodynamics
Vital Signs

Idarucizumab – Dabigatran Reversal

Humanized Fab fragment specific to dabigatran

- Affinity: Dabigatran 350 times > Thrombin
- No evidence of prothrombotic effect
- Renal elimination
- Rapid onset and dose dependent effect
  - Sustained > 24 hours with dose > 2 g
- aPTT, TT and ECT normalized

Van Ryn J et al. *Circulation*. 2012; 126:A9928. Schiele F et al. *Blood*. 2013; 121:3554-62. Siegal DM et al. *N Engl J Med*. 2015; 373:2413-24. Boehringer Ingelheim. Praxbind (idarucizumab) prescribing information. www.accessdata. fda.gov/drugsatfda_docs/ label/2015/761025lbl.pdf (accessed 2016 April).

Idarucizumab – Interim Phase III analysis

RE-VERSE AD **Prospective – 5g dose**

- Most had atrial fibrillation taking 110mg twice daily of dabigatran
- 15 to 16 hours post last dabigatran dose
- 2/3 had CrCl > 50ml/min
- 5 thrombotic events secondary to not restarting anticoagulation
- 18 Deaths (Index evet or underlying clinical condition)

A (n=51) Serious Bleeding	B (n=39) Urgent Procedure
Mean Dabigatran Cp = 132ng/ml	Mean Dabigatran Cp = 114ng/ml
Reversed (Cp < 20ng/ml) in minutes	Reversed (Cp < 20 ng/ml) in minutes
Hemostatic effect at 11.4 hr (median) [Dependent on time of assessment]	Acceptable procedure hemostasis

<u>Most</u> remained reversed at 24 hours

Pollack CV et al. *N Engl J Med*. 2015; 373:511-20.

Andexanet

Factor Xa inhibitor Antidote PRT4445

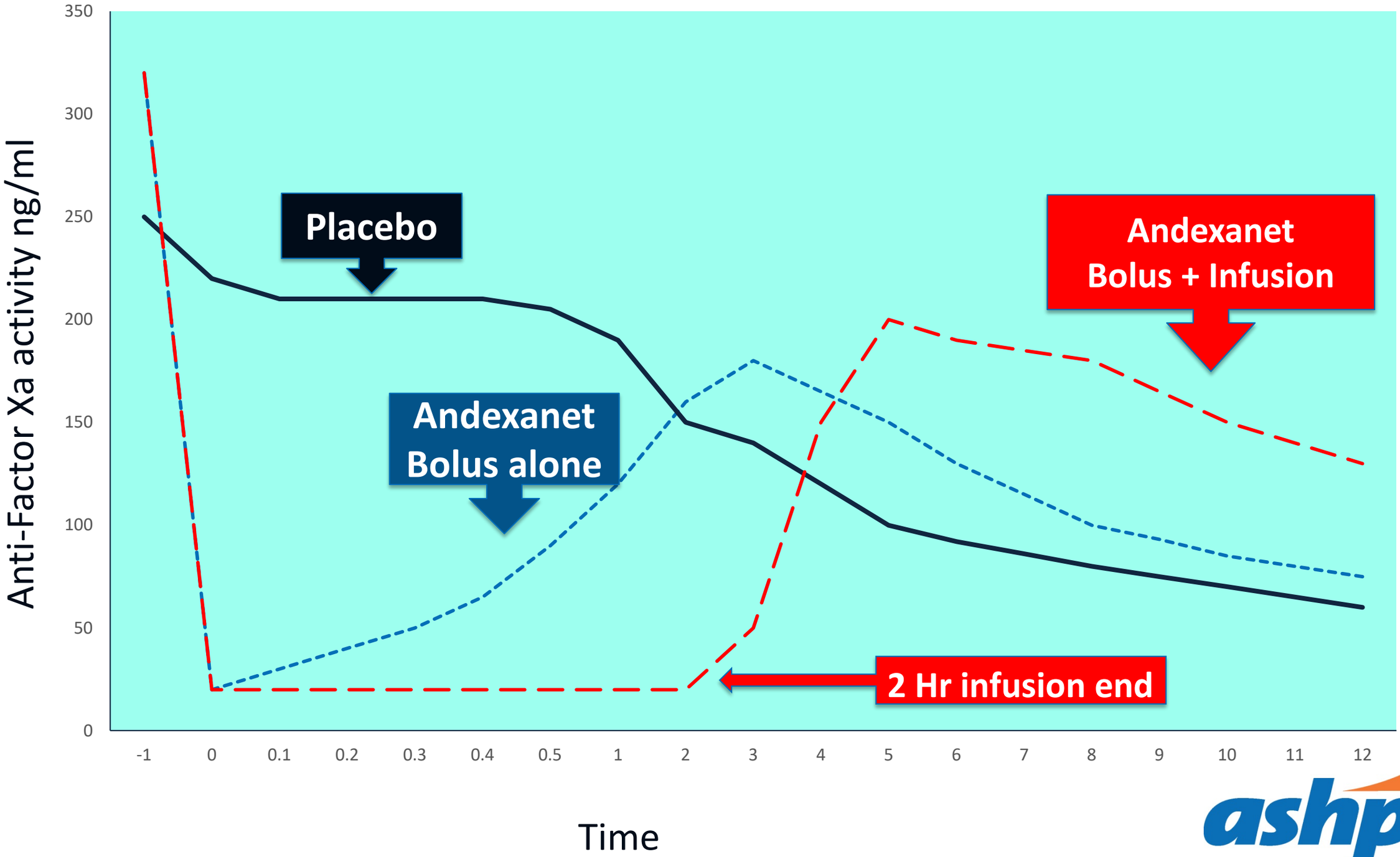
Phase III Trial	Agent	Phase 1	Phase 2
ANNEXA-A	Apixaban 5mg	400mg IV x 1	400mg IV + 4mg/min for 2 hrs
ANNEXA-R	Rivaroxaban 20mg	800mg IV x 1	800mg IV + 8mg/min for 2 hrs

ANNEXA-4 (Open – single group) *N: Safety = 67; Efficacy = 47*	Bolus Dose	2 hr Infusion
Apixaban, Rivaroxaban > 7 hr post dose	400mg (30mg/min)	480mg (4mg/min)
Enoxaparin, Edoxaban or Rivaroxaban ≤ 7 hr post dose	800mg (30mg/min)	960mg (8mg/min)

- ANNEXA 4: Substantial anti-Factor Xa activity reduction; 79% effective hemostasis
- Andexanet administered at 4.8 +/-1.8 hours
- Limited Data for Enoxaparin or Edoxaban
- Similar Curves as ANNEXA – A and ANNEXA - R

Lu G et al. *Nat Med*. 2013;19:446-51; Siegal DM et al. N Engl J Med. 2015; 373: 2413-24; Crowther M et al. *Circulation.* 2014; 130:2105-2126; Crowther M et al. *J AM Coll Cardiol*. 2015; 65. 10S; Connolly SJ et al. N Engl J Med 2016:1131-41

Andexanet: Reversing Oral Anti-Xa agents



Siegal DM et al. *N Engl J Med*. 2015; 373: 2413-24.

Ciraparantag

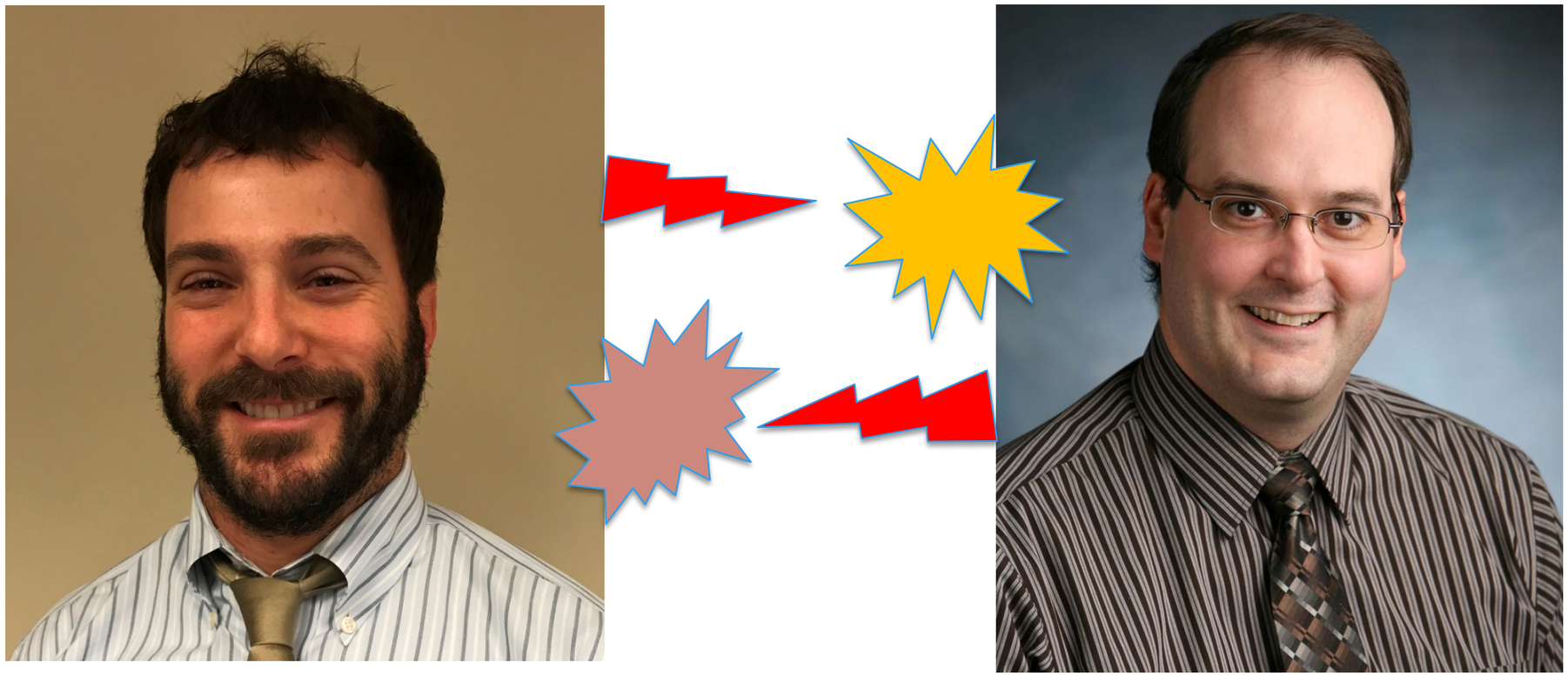
"Universal"Factor Xa and IIa inhibitor Antidote: PER977

- **Synthetic small molecule - directly binds and reverses heparins, direct factor Xa- and IIa-inhibitors. Does not bind to blood coagulation factors/other blood proteins.**
- **Reverses anticoagulant activity: ~10-30 minutes after IV dose.**
- **Dose Dependent - Effects last at least 24 hours in most cases**
  - **Complete reversal: Rivaroxaban/Apixaban anti-Xa activity ex vivo in human plasma. May reverse Enoxaparin/Fondaparinux**
- **Phase I – 3 hr post Edoxaban 60mg**
- **No prothrombotic effects**
- **Phase III underway**

Laulicht B et al. *Circulation*. 2012; 126:A11395.
Ansell JE et al. *N Eng J Med*. 2014; 371:2141-2.

Additional Considerations

- Rebound Activity when Object drug effects outlast Antibody
- Bleeding may persist despite antidote alone



- Antidote to Neutralize Anticoagulant for AF and now acute stroke
  - Can Check a Thrombin Time (Dabigatran and post Idarucizumab)

Thorborg C et al. Br J Anaesth 2016;117:407-9; Alhashem HM et al Am J Emerg Med 2016; Berrouschot J et al Stroke 2016;47:1936-8; Kafke W et al Cae Rep Neurol 2016;8:140-4

Getting Drug to the patient

- rFVIIa
- PCC 3or 4
- aPCC

Patient Arrives

↓

Situation assessed, Medication History, Labs

↓

Decision to treat

↓

Medications Ordered

↓

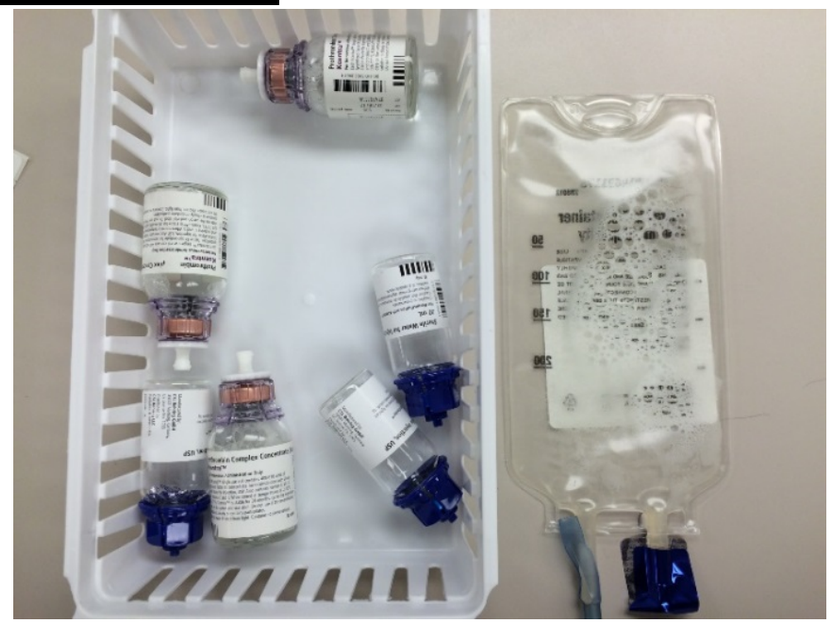
Pharmacy Processes Order

↓

Ordered Medications sent to patient

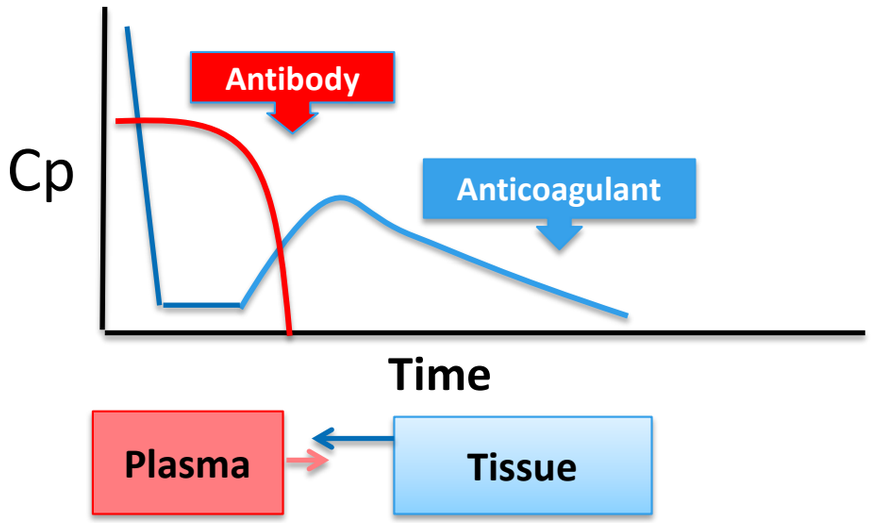
↓

Medication Infused



Potential Challenges with DOAC Antidotes

- **Tissue rebound of either the anticoagulant or antidote**



- **Need for emergent hemostasis – when is a hemostatic agent necessary, which agent and what dose – risk for thrombosis**

- **Need for subsequent device/procedure anticoagulation**

- **Will a PCC/aPCC be necessary if a antidote is given?**
  - **If so, can a lower dose be used initially?**

DOAC - Overdose or very high concentrations

Overdose

Assessment
- Amount of Drug
- Bleeding Risk
- Charcoal if ingestion recent

Non-Super High Levels

Not Bleeding

Watch
Consider Antidote if clinically necessary

Bleeding

Administer Antidote
Consider Adding Hemostatic Agent if urgent – life threatening bleed

Super-High Levels

Bleeding

Administer Antidote
Consider Adding Hemostatic Agent if urgent – life threatening bleed

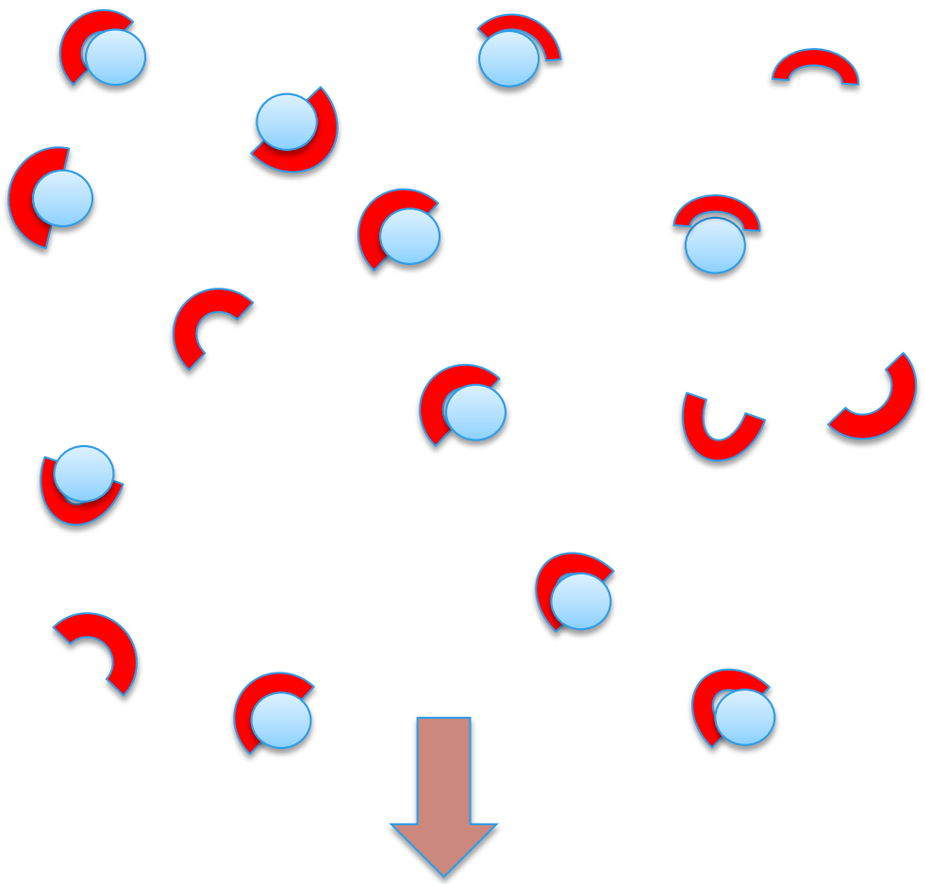
Not Bleeding

Consider Antidote if clinically necessary

May require a higher antidote dose if very high and full DOAC neutralization desired – partial reversal with standard dose may meet goals if not bleeding

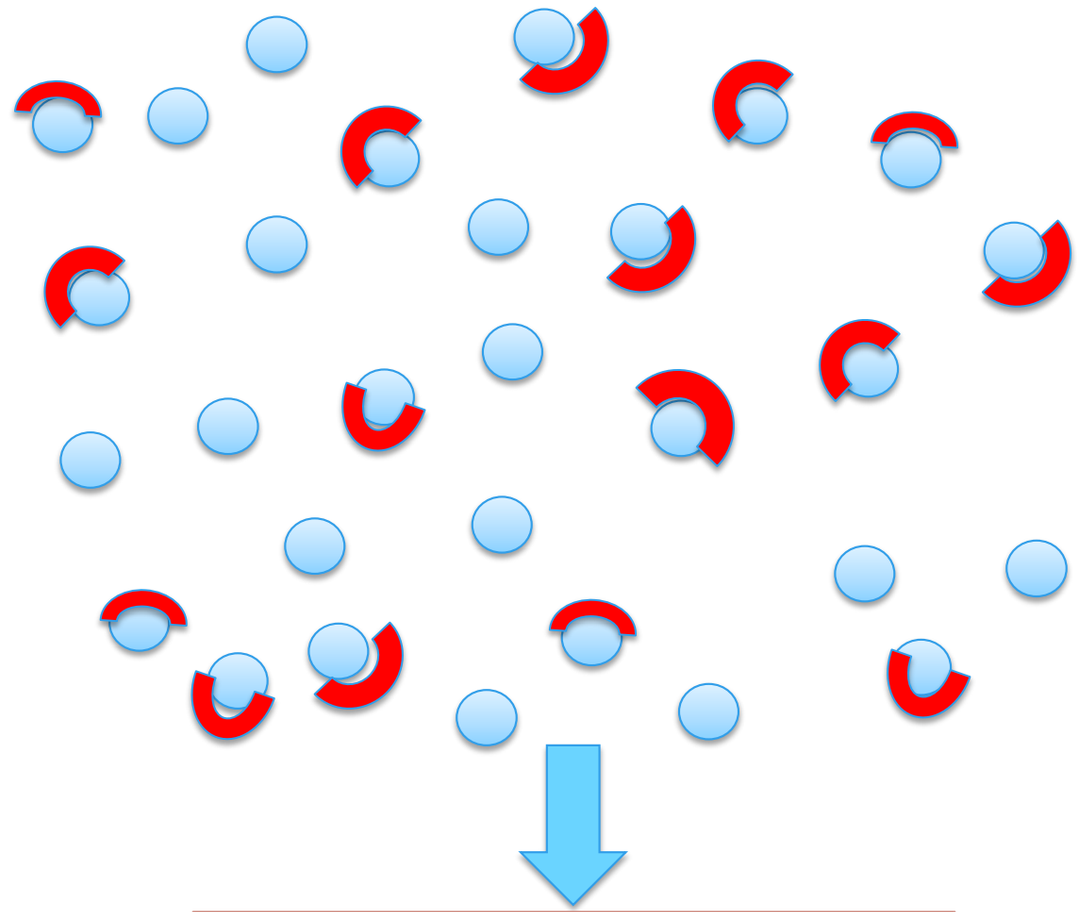
Antibody Maximal Effect

Antibody > Target Agent



Drug Neutralized

Target Agent > Antibody



Drug Effects Persist

Rottenstreich A et al Thromb Res 2016:103-4; Marino KK et al Pharmacotherapy 2016

Restarting Anticoagulation

Assessment of Thrombosis vs Bleeding

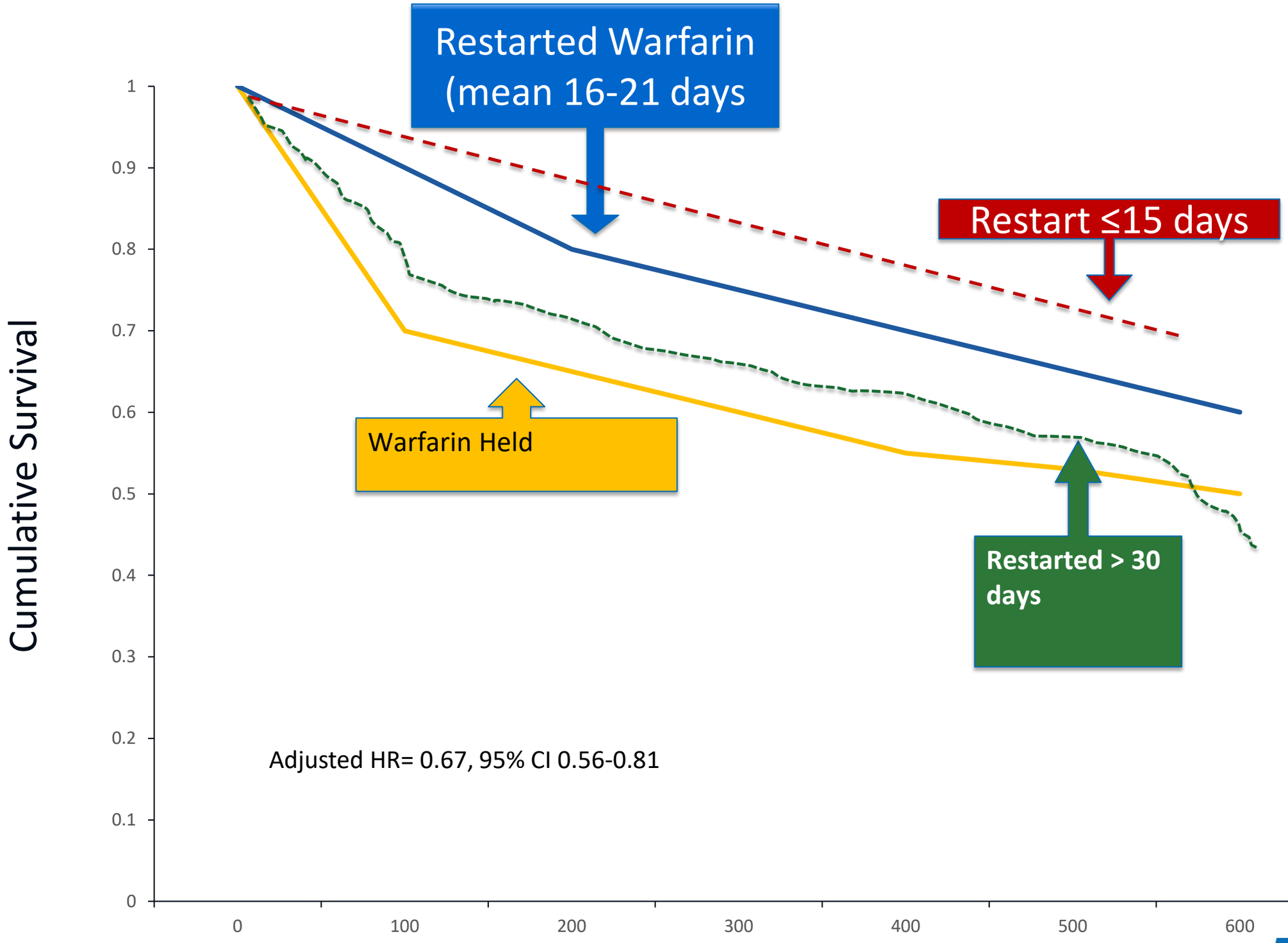
↑Thrombosis Risk: Surgery, PCC, Acutely Ill

Will there be a change in the anticoagulant?

- GIB and ICH: (Pts on warfarin)
  - Higher long term survival and lower incidence of thrombosis with minimal risk of recurrent bleeding events
  - Potential Exceptions (CNS bleeds):
    - Cerebral amyloid angiopathy (lobar)
    - Microvascular risk
    - Microbleeds on gradient-echo MRI
    - Indication: Primary prevention; Atrial fibrillation, low CHADS2 < 4 or CHA2DS2-VASc < 5; Anticipated difficulty managing anticoagulation

Witt DM et al. *Arch Intern Med.* 2012; 172:1484-91; Kuramatsu JB et al. *JAMA.* 2015; 313:824-36; Qureshi W et al. *Am J Cardiol*. 2014; 113:662-8; Goldstein JN, Greenberg SM. *Cleve Clin J Med*. 2010; 77:791-9.

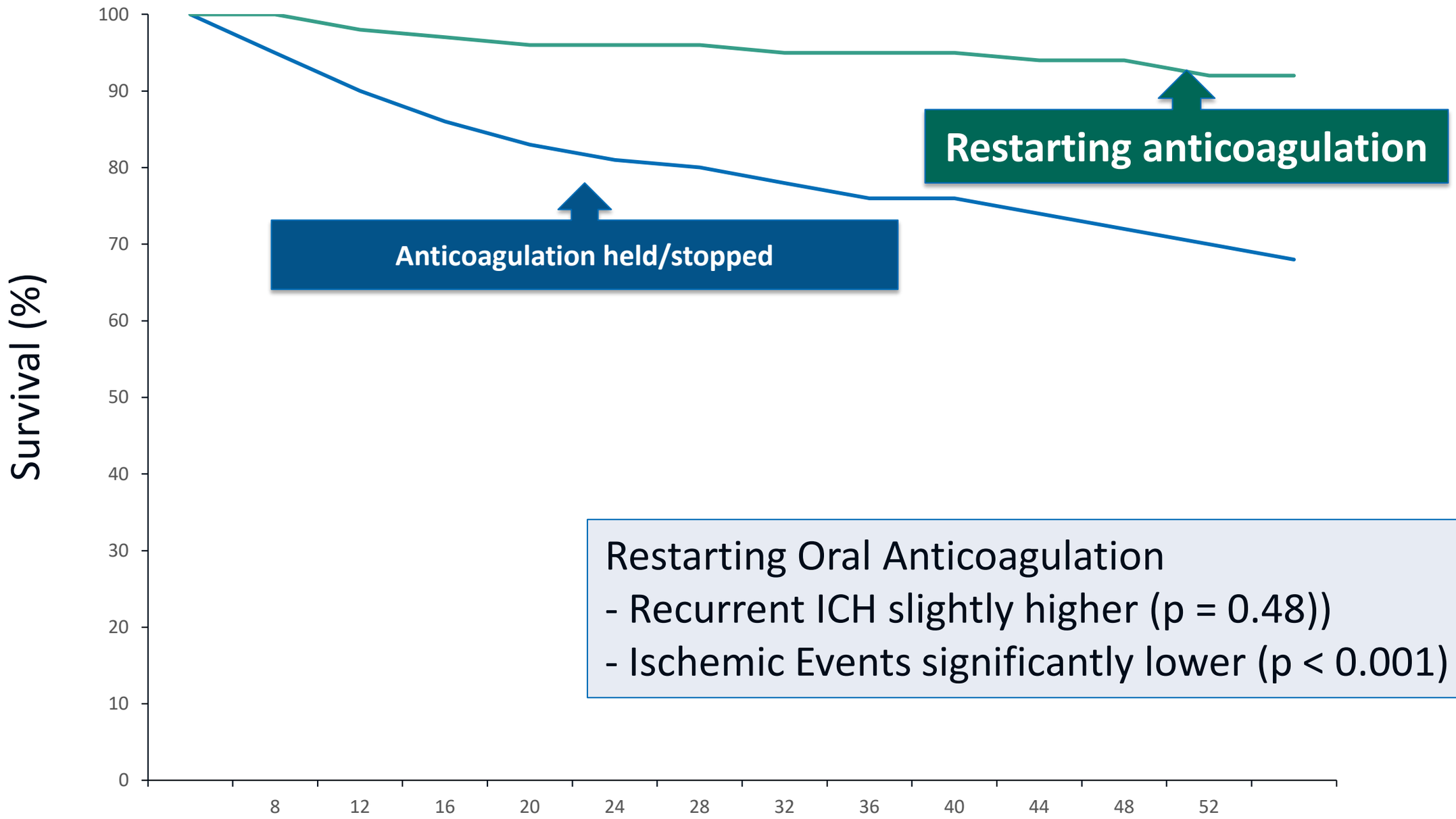
Gastrointestinal Tract Bleeding



Qureshi W et al. *Am J Cardiol*. 2014; 113:662-8.

AF patients post ICH

Survival Rates with or without restarting Oral Anticoagulation



Kuramatsu JB et al. JAMA. 2015; 24; 313:824-36.

Management Considerations

- Establish a standard approach
  - Choose what agents and tests should be used
  - Adaptable to severity of situation
  - Re-assess and adjust therapy
  - Avoid Delays
- Urgency of situation
  - Is there time to use lower doses and titrate to effect?
  - Manage comorbid conditions
- Think of long term consequences
  - VTE risk and need for prophylaxis
  - Re-initiating anticoagulation therapy

Key Takeaways

- **Key Takeaway #1**
  - Antidotes have a important Role in reversing DOAC's.
  - The Pharmacist has a role is determining the necessary dose
  - One size does not fit all situations
- **Key Takeaway #2**
  - Management of Urgent – Life threatening Non-ICH bleeding remains unclear
  - The ability of a antidote alone in this setting remains unestablished
  - A low dose strategy and titration to effect may limit cost and risk for thrombotic complications
- **Key Takeaway #3**
  - Keeping the patient on the Radar and re-initiating anticoagulation remains a key component impacting overall thrombosis and mortality

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The Balancing Act of Managing Bleeding and Thrombosis with Direct Oral Anticoagulants

John Fanikos, RPh, MBA
Brigham and Women's Hospital
Boston, MA

Objectives

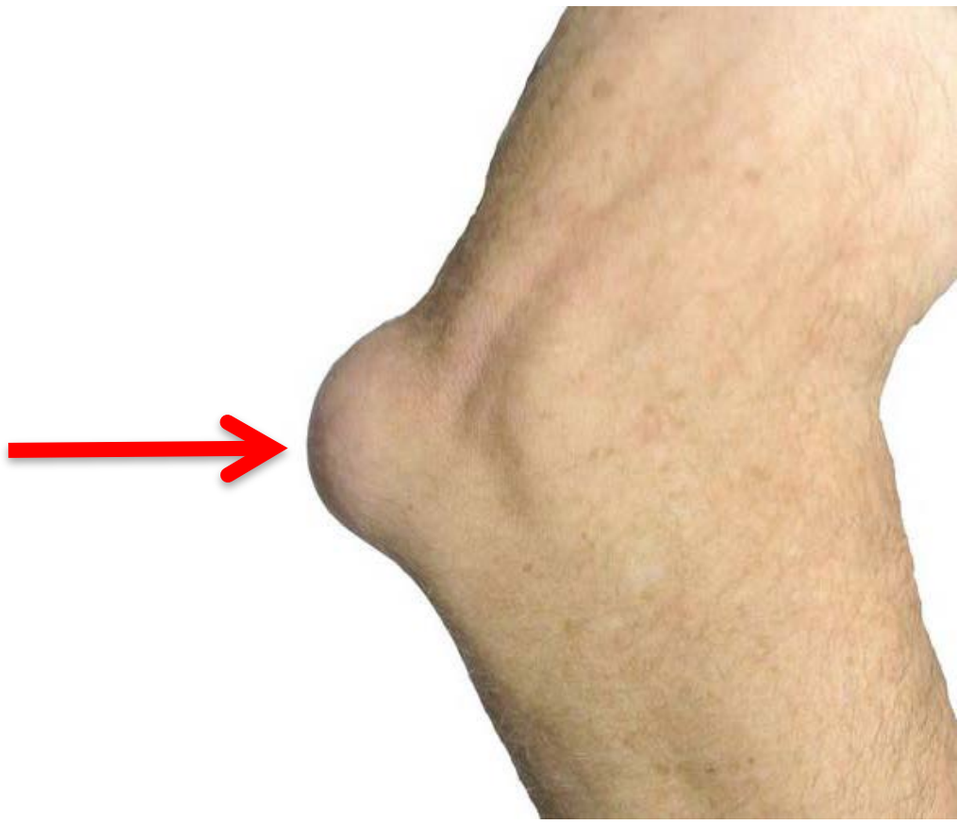
- Identify Pharmacist or Pharmacy Technician action steps needed to ensure access and availability of anticoagulant reversal agents
- Describe support systems that can be implemented for appropriate patient selection and agent administration
- Recognize cost associated with anticoagulant reversal agents and contribution to total costs of treatment

Outline

- Case presentation
- Pharmacy logistics
- Support systems
- Value and cost

Case Study: Presentation

- 83-y-old woman presents to the Emergency Department at 10 AM.
- Resident from assisted living facility.
- Tripped on curb, fell onto face, left elbow, and right knee.
- She denies LOC.
- Her daughter witnessed the fall and found her awake, alert, and oriented x3.
- Patient has not tried to ambulate since her fall.



LOC= loss of consciousness

Case Study: Patient History

Past Medical History

- Atrial fibrillation
- Arthritis
- Dyslipidemia
- Benign essential hypertension
- Diabetes
- Malignant neoplasm of colon
- CVA (cerebral infarction)

Past Surgical History

- 2008: patella fracture surgery
- 2006: sigmoid resection
- 2001: incisional hernia repair

Current Medications

- Amlodipine 10-mg tablet QD
- Atorvastatin 80-mg tablet QD
- Dabigatran etexilate 150 mg BID
  - Last dose 9 AM
- Metoprolol succinate 6.25 mg QD
- Quinapril 10 mg po QD

CVA, cerebrovascular accident

Case Study: Physical Exam

- **Head**: Normocephalic. Abrasions left temple. No hemotympanum.
- **Neurological**: Alert, oriented to person, place, and time.
- **Eyes**: EOMs normal. Pupils equal, round, reactive to light.
- **Neck**: Normal ROM. No cervical midline tenderness.
- **Abdominal**: Soft. Bowel sounds normal. No distension or tenderness.
- **Musculoskeletal**: Abrasion over left patella. Normal ROM. She exhibits tenderness. No edema. No warmth, erythema, or swelling. Tenderness over left olecranon (bony prominence of elbow). Decreased ROM to left elbow on extension and supination, and loss of light touch, sharp v dull sensation distal half of LUE. Good ROM RUE and both lower extremities.

EOM, extraocular movement; ROM, range of motion; LUE, left upper extremity; RUE, right upper extremity

Case Study: Test Results

Laboratory Findings

- Normal electrolytes
- BUN 15
- Cr 1.1 mg/dL
- GLU 131 mg/dL
- aPTT 66 sec

Imaging Results

CT Head w/o Contrast

- No evidence of ICH

X-ray of Elbow

- Displaced fracture of olecranon, distraction ≈2.1 cm. Moderate soft tissue hematoma posterior to distal humerus.

X-ray of Knee

- No fracture seen

aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; Cr, creatinine; CT, computed tomography; GLU, blood glucose

Case Study: Action Plan

- *"This fracture would benefit from operative fixation. OR is available. Surgical team is available."*
- Repeat head CT at 6-h interval

OR, operating room

What agents are available ?

A. Idarucizumab is on Formulary and available.

B. Idarucizumab is non-Formulary, but accessible if needed within a 1-2 hours.

C. Idarucizumab is not available, but 3 factor and 4 factor prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (aPCC) are.

D. Idarucizumab is available but you need to obtain a consult through hematology.

Who distributes blood factors ?

- A Blood Bank distributes all blood factors.
- B The Hemophilia Treatment Center distributes all blood factors.
- C The Pharmacy distributes all blood factors.
- D A collaboration exists with Blood Bank, Pharmacy, and the Hemophilia Treatment Center having a role in both hospitalized and ambulatory patients.

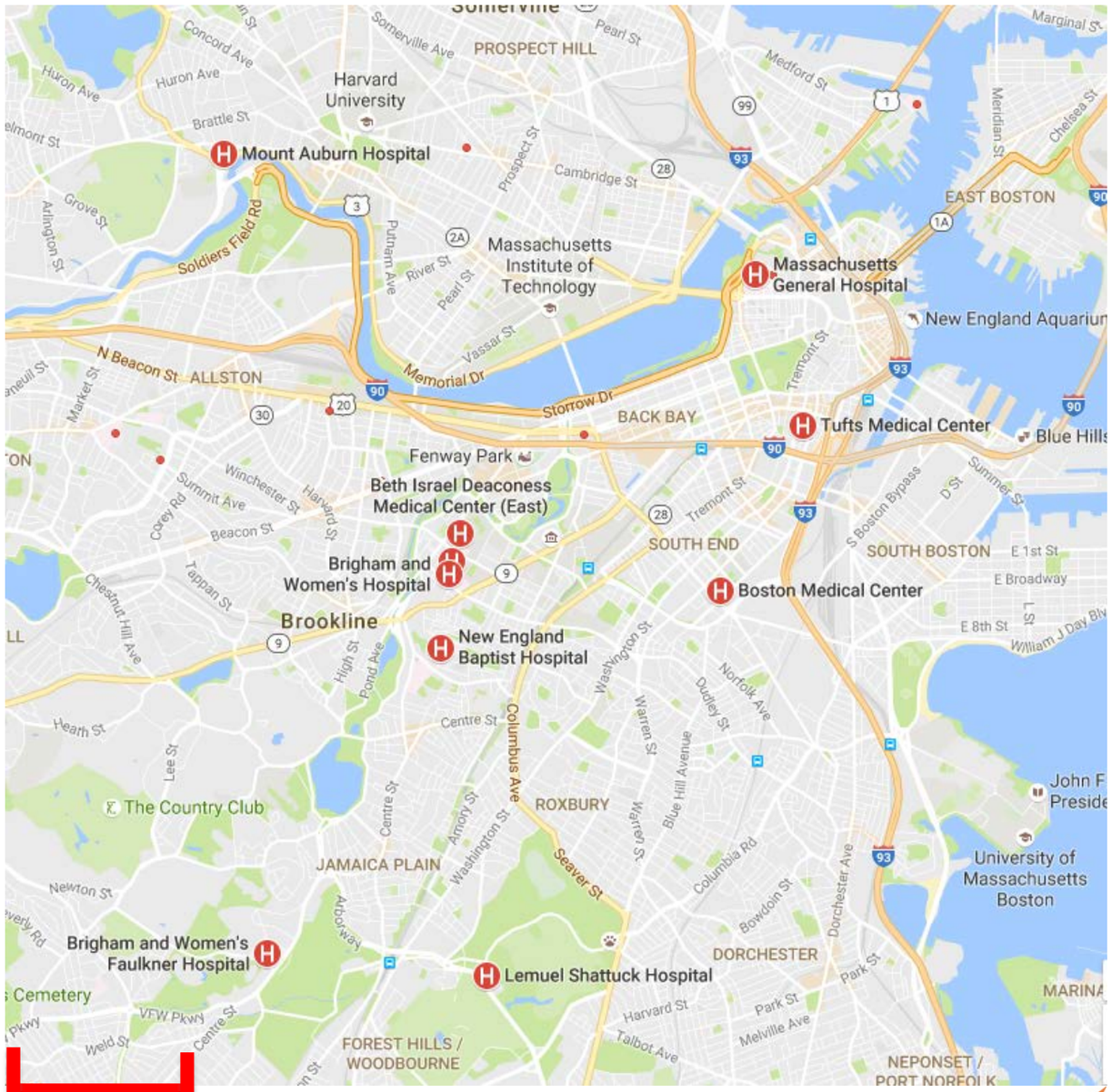
Outline

- Case presentation
- Pharmacy logistics
- Support systems
- Value and cost

Supply Chain Logistics and Collaboration

- 20 hospitals with 20 mile radius
- Wholesale/drug distribution center vs Specialty Pharmacy
- Purchase or consignment or borrow
- Fridge availability, space
- Organizer, Point person
- Models
  - Chemotherapy antidotes, anti-venoms

Greater Boston Area Hospitals



http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsArticle&ID=2196085

Blood factors

Generic name	Brand Name	Source	Indications	Storage	Supply Unit	Administration
Antithrombin concentrate	Atryn®	Recombinant	Prevention of peri-operative and peri-partum thromboembolic events in patients with hereditary antithrombin deficient patients.	Refrigerate at 2-8° C (36-46 ° F)	1750 IU vial range*	IV: Administer a loading dose over 15 minutes followed by a continuous infusion.
Antithrombin concentrate	Thrombate III®	Human Plasma	Patients with hereditary Antithrombin 3 deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism	Room temperature, not to exceed 25° C (77 ° F)	500 IU vial range*	IV: Administer over 10 to 20 minutes as tolerated
Factor I (Fibrinogen) concentrate	RiaSTAP®	Human plasma	Treatment of acute bleeding in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia	Room temperature at 2-25° C (36-77 ° F)	900-1300 mg*	IV: Administer at a rate not to exceed 5 mL/minute
Activated Factor VII	Novoseven RT®	Recombinant	Treatment of bleeding episodes in patients with hemophilia A or B. Prevention of bleeding in surgical interventions or invasive procedures in patients with hemophilia A or B with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia. Prevention of bleeding episodes in patients with congenital Factor VII deficiency. Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital Factor VII deficiency.	Refrigerate or store at 2-25° C (36-77 ° F)	1, 2, 5, 8 mg vials	Hemophilia with inhibitors Bleeding: IV every 2 hours until hemostasis is achieved. Surgery: IV Before surgery and every 2 hours during the procedure. Congenital Factor VII deficiency Bleeding episodes or surgery: IV every 4-6 hours until hemostasis is achieved. Acquired hemophilia bleeding episodes or surgery: IV every 2-3 hours until hemostasis is achieved.

*Potency is stated on labeled vial.

Blood factors (continued)

Generic name	Brand Name	Source	Indications	Storage	Supply Unit	Administration
Anti-inhibitor complex concentrate (Factor VIII inhibitor bypassing activity), Complex of Factors II, VIIa, IX, X.	FEIBA NF®	Human plasma	Patients with VIII inhibitors only for the control of spontaneous bleeding episodes or to cover surgical interventions in hemophilia A and B.	Room temperature, not to exceed 25° C (77 ° F)	500, 1000, 2500 unit vial ranges*	IV: The maximum injection or infusion rate must not exceed 2 units/kg/min
Complex of inactivated Factors IX, II, X, VII	Profilnine SD®	Human plasma	Prevention and control of bleeding in patients with Factor IX deficiency due to Hemophilia B.	Refrigerate at 2-8° C (36-46 ° F)	500, 1000, 1500 IU FIX vial range*	IV: Administer at a rate not to exceed 10 mL/minute
Prothrombin complex concentrate (Factors II, VII, IX, X, Protein C, Protein S)	Kcentra®	Human plasma	Urgent reversal of vitamin K antagonists in patents with acute major bleeding or need for an urgent surgery or invasisve procedure	Room temperature at 2-25° C (36-77 ° F)	500-1000 units* vials	IV: Administer at a rate of 3-210 units/kg/min

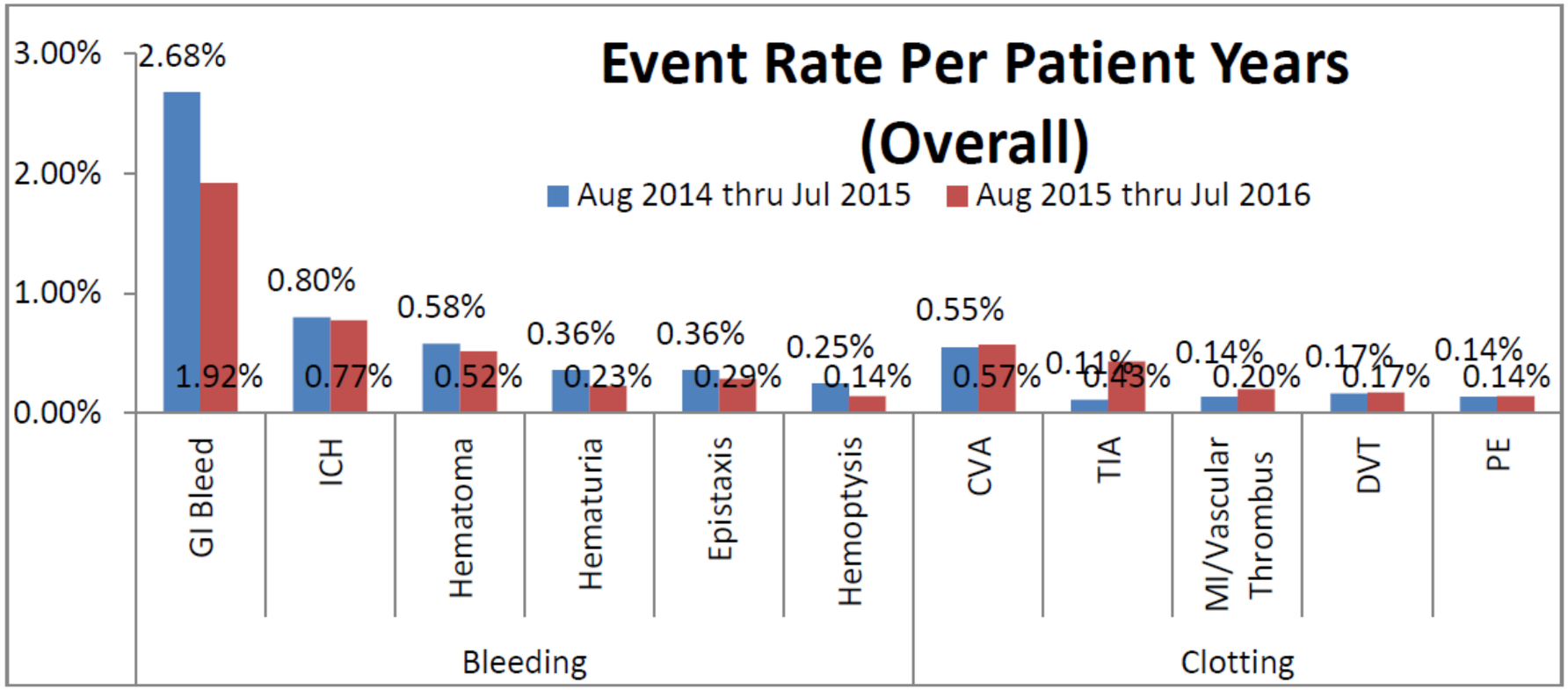
Prescribing information for Atryn (antithrombin, recombinant): Available at: http://atryn.com/pdf/ATryn_PI_0409.pdf. Prescribing information for Thrombate III (antithrombin, human). Available at: http://www.talecris-pi.info/inserts/thrombate.pdf. Prescribing information for Riastap (fibrinogen concentrate, human). Available at: http://riastap.com/professional/prescribing-information.aspx. Prescribing information for Novoseven RT (coagulation factor VIIa, recombinant). Available at: http://www.novo-pi.com/novosevenrt.pdf. Prescribing information for Feiba NF (anti-inhibitor coagulant complex). Available at: http://www.baxter.com/downloads/healthcare_professionals/products/feiba-nf-pi.pdf. Prescribing information for Profilnine (factor IX complex). Available at: http://www.phscorporation.com/pdfs/ProfilninePI.pdf. Prescribing information for KCentra. Available at: http://www.kcentra.com/professional/prescribing-information.aspx. September 1, 2016.

*Potency is stated on labeled vial.

Know your Business

- Velocity of events
- Utilization patterns
- Opportunities for improvement
- Predictors of reversal agent blood product use

BWH AC Related Bleeding & Thrombosis*

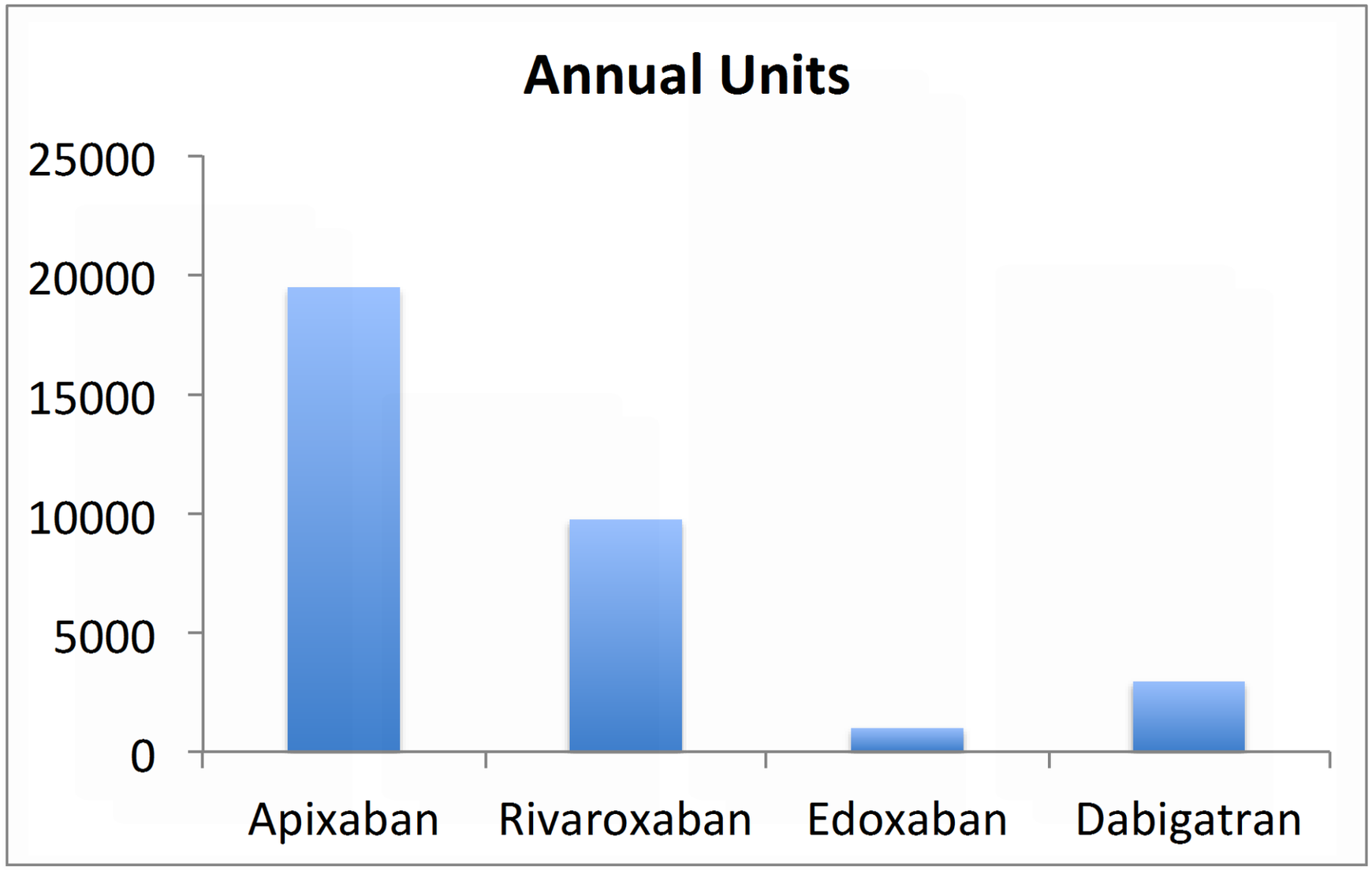


* Brigham and Women's Hospital internal data

Know your Business

- Velocity of events
- Utilization patterns
- Opportunities for improvement
- Predictors of reversal agent blood product use

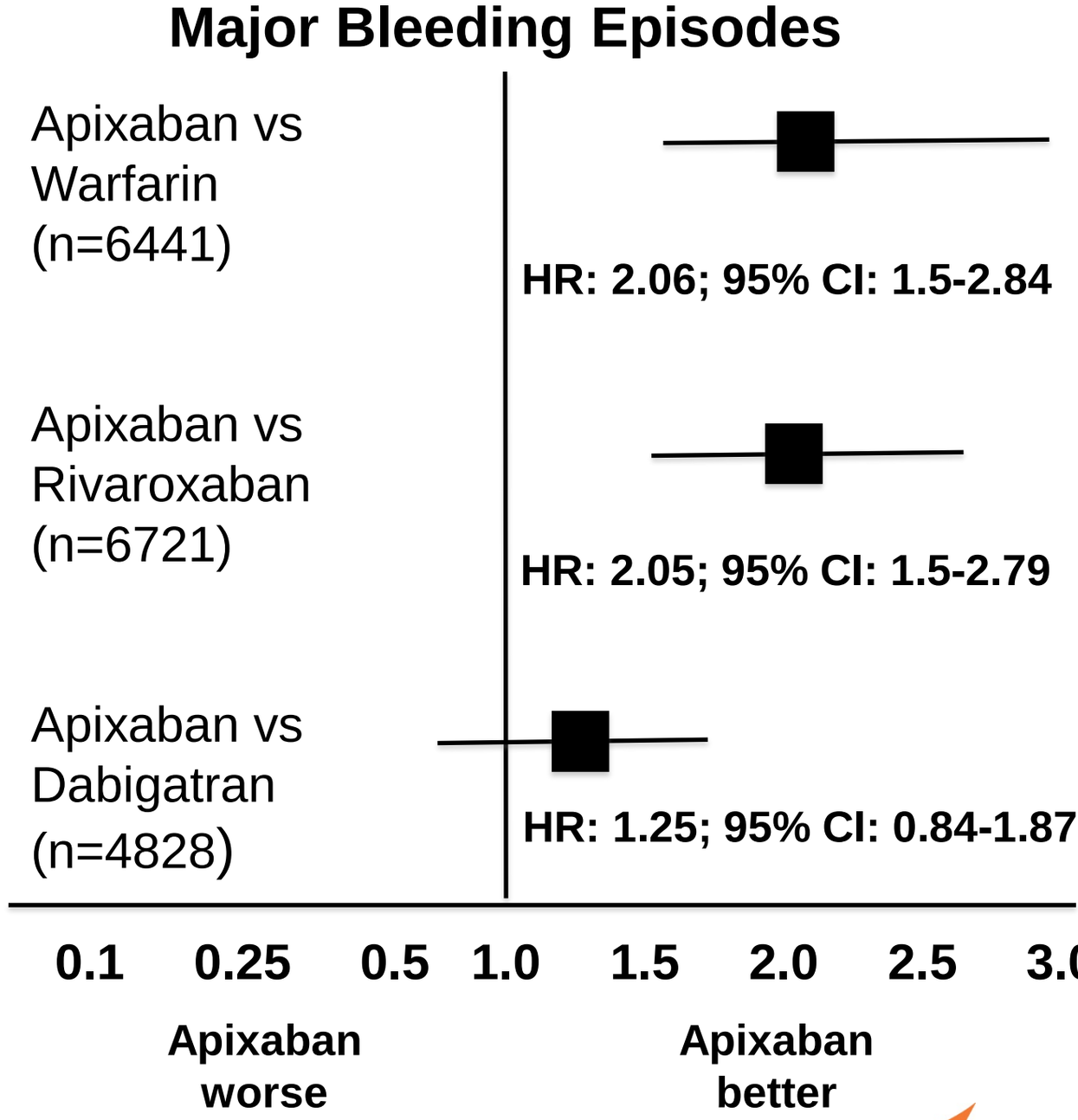
BWH DOAC Annual Utilization*



* Brigham and Women's Hospital internal data

Know Other People's Business

- Retrospective cohort study using Commercial and Medicare supplemental database.
- Propensity score matching to balance age, sex, region, baseline comorbidities, and comedications.
- NVAF patients 18+ years newly prescribed an oral anticoagulant.
- Major bleeding on anticoagulant was defined as first major bleeding requiring hospitalization.



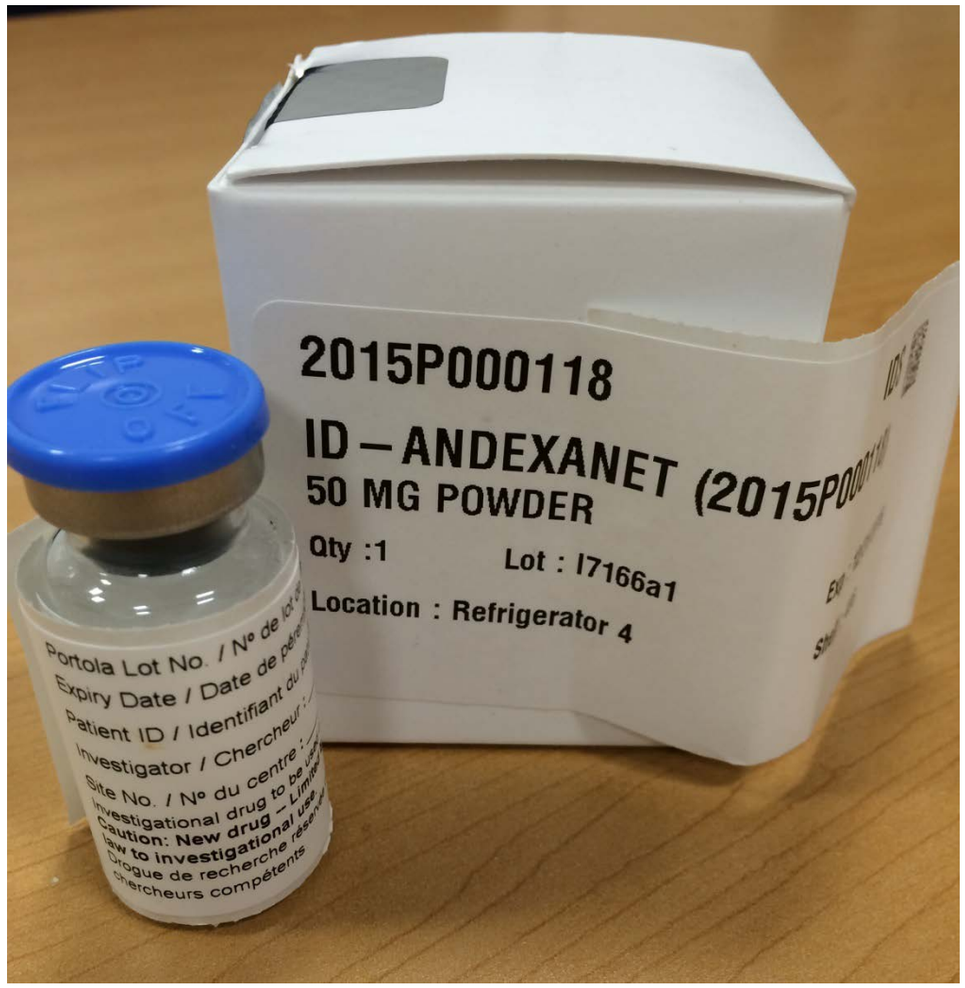
Lip GY. J Am Coll Cardiol. 2016;67(13_S):882-882. doi:10.1016/S0735-1097(16)30883-X.

Portals of Entry, Sites of Injury

- Presentation
  - Emergency Department
  - Electro-physiology laboratory
  - Operating room
- Supply location(s)
  - Central Pharmacy
  - Satellite Pharmacy
  - Automated dispensing cabinets
  - Kits

Preparation and Administration

- Preparation
  - Pharmacy or bedside “immediate use”
- Administration
  - IV push versus Infusion
  - Device drug library
  - Infusion rate



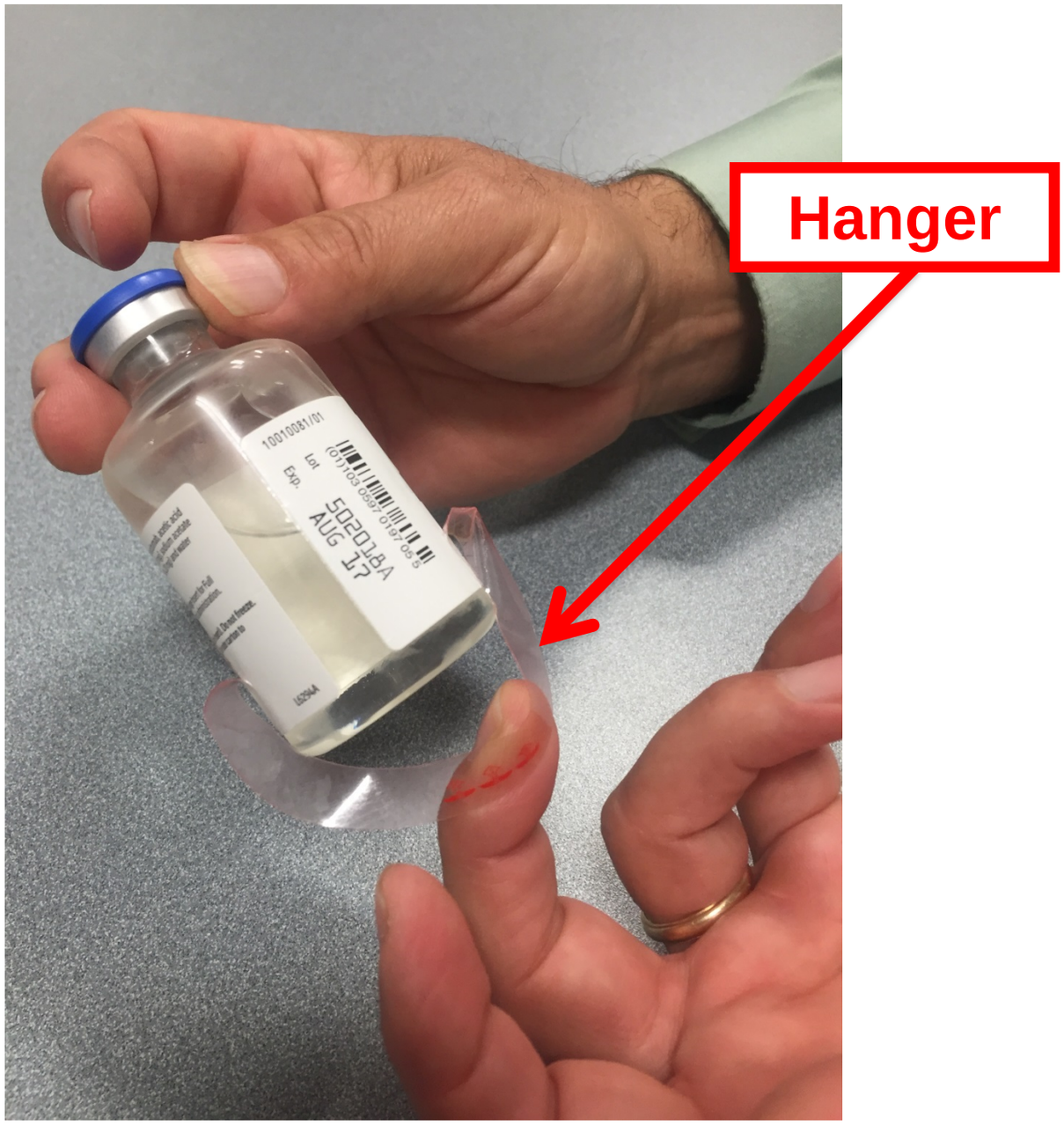
Powder for reconstitution

Preparation and Administration

- Preparation
  - Pharmacy or bedside “immediate use”
- Administration
  - IV push versus Infusion
  - Device drug library
  - Infusion rate

Preparation and Administration

- Preparation
  - Pharmacy or bedside “immediate use”
- Administration
  - IV push versus Infusion
  - Device drug library
  - Infusion rate
  - 600 mL per hour, infuses each vial over 5 minutes.

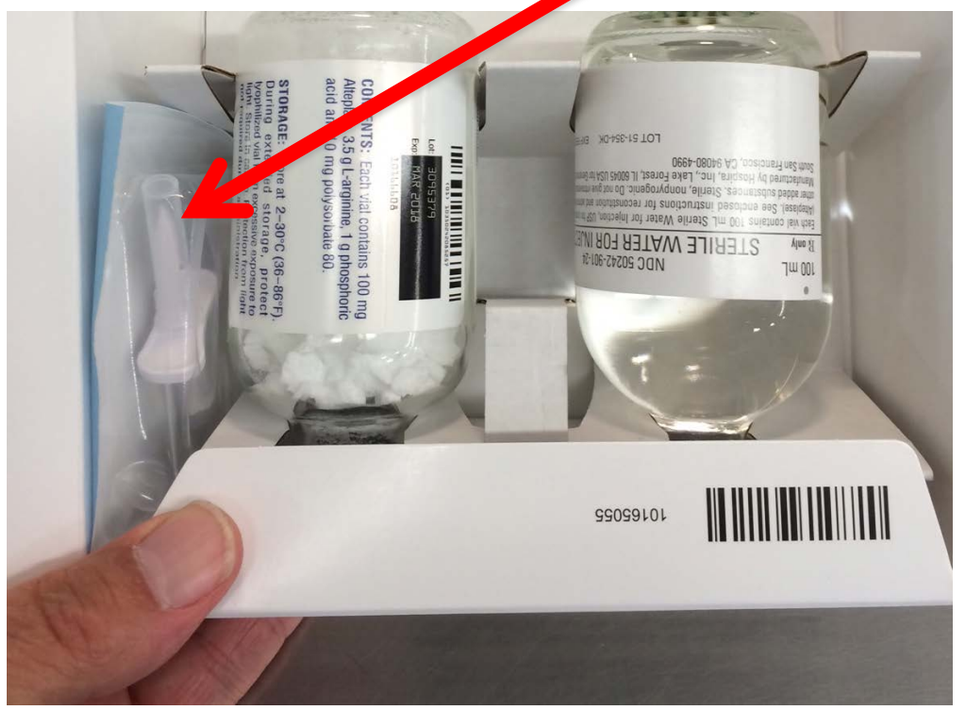


Reconstitution not required

Smythe MA. Am J Health-Syst Pharm. 2016; 73(suppl 2):s27-48

Drug Preparation and Administration

- Preparation
- Pharmacy or bedside “immediate use”
- Administration
- IV push versus Infusion
- Device drug library
- Infusion rate
- 600 mL per hour, infuses each vial over 5 minutes.
- Kits



Reconstitution pin

Smythe MA. Am J Health-Syst Pharm. 2016; 73(suppl 2):s27-48

Outline

- Case presentation
- Pharmacy logistics
- Support systems
- Value and cost

Smythe MA. Am J Health-Syst Pharm. 2016; 73(suppl 2):s27-48

The OR calls and wants to know the correct dose of aPCC to reverse dabigatran ?

A. Look in the package insert for the dosing.

B. Google the International Society for Thrombosis and Thrombolysis (ISTH) and find the most recent guideline authored by Levy, J.

C. Page the hematologist on call and ask him/her for a recommended dose.

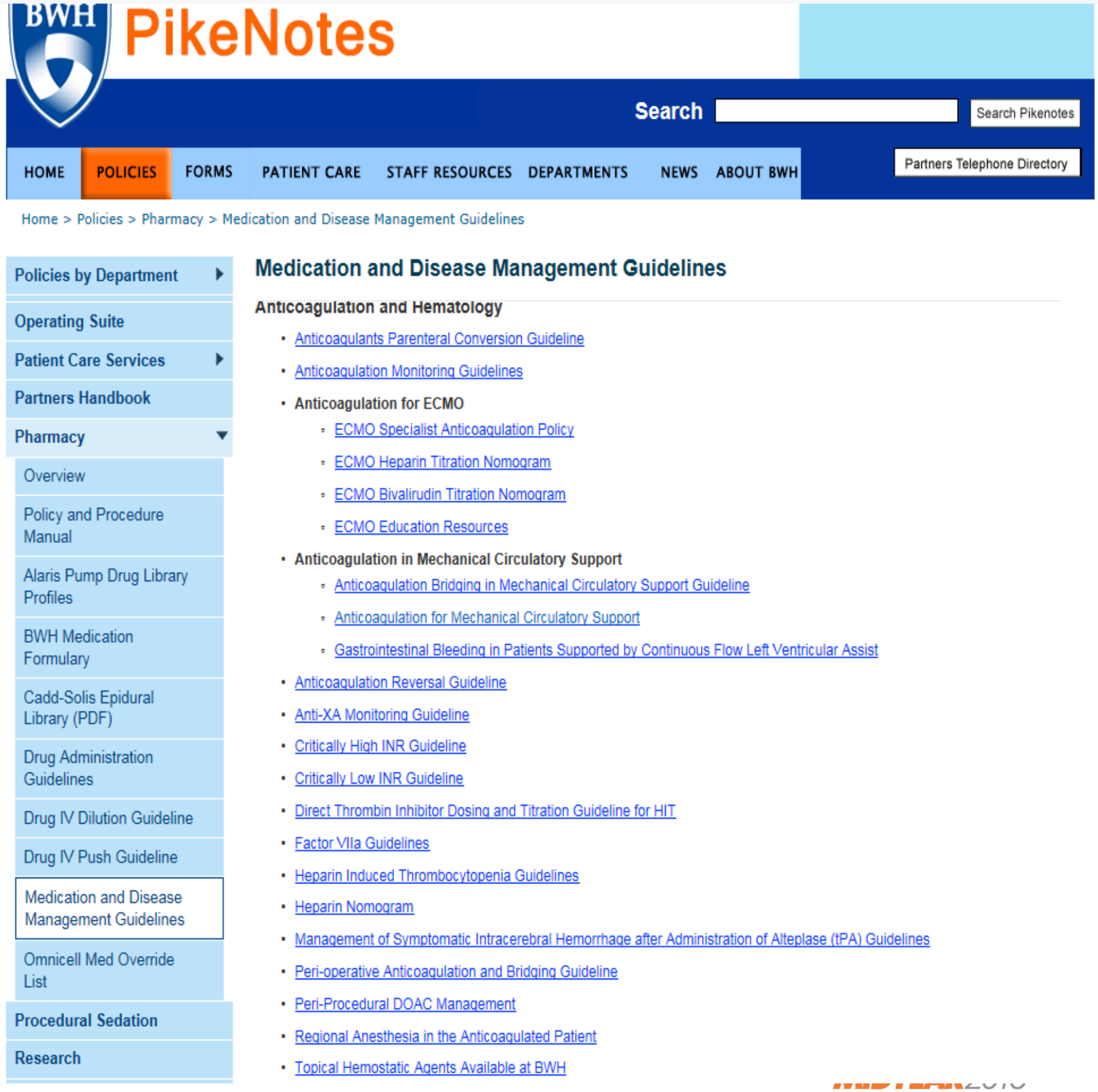
D. Go to the Hospitals' intranet site and print the Hospital guideline and drug administration guide.

Guidelines

- External Professional organization
- European Society of Cardiology
  - 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS (European Heart Journal doi:10.1093/eurheartj/ehw210).
- AC Forum
  - Management of Venous Thromboembolism: Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment (J Thromb Thrombolysis (2016) 41:206–232).
- National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology
  - Cancer Associated Venous Thromboembolic Disease Available at: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf
- Expert opinion
  - Weitz JW, Pollack CV. Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. Thromb Haemost 2015. http://dx.doi.org/10.1160/TH15-03-0222.
  - Enriquez A, Lip GYH, Baranchuk, A. Anticoagulation reversal in the era of the non-vitamin K oral anticoagulants. Europace 2015. http://dx.doi.org/10.1093/europace/euv030.
  - Huisman MV, Fanikos J. Idarucizumab and Factor Xa Reversal Agents: Role in Hospital Guidelines and Protocols. Am J Med 2016. doi: 10.1016/j.amjmed.2016.06.010.
- Internal crafted
  - UC Davis, University of Washington, University of Kentucky, West Suffolk-NHS

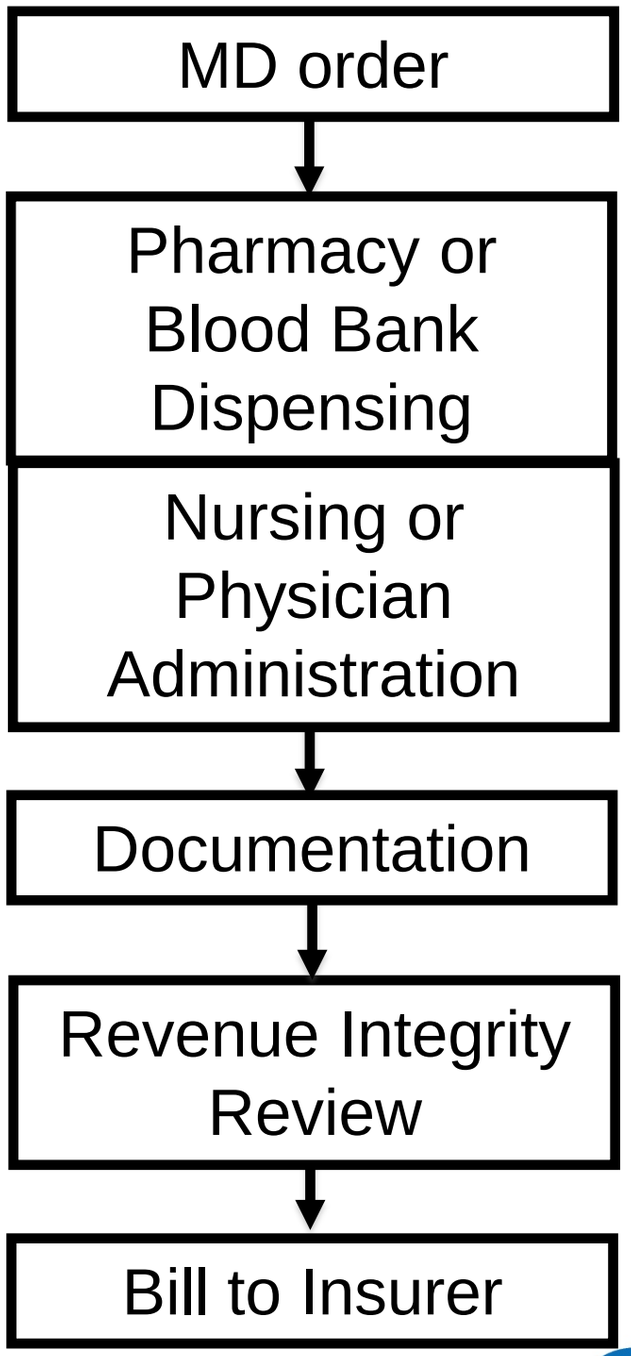
Intranet Access

- Central site for information
- Accessible by handheld devices
- Add “Favorite” list
- Knowledge links via EHR



Electronic Health Records (EHR)

- Get IT resources, access
- Add agents to the medication list
  - J code, billing units
- Add or Preference lists
- Craft enterprise wide order set
  - Task Force or Committee
- Documentation
- Best practice alerts
- Billing Surveillance

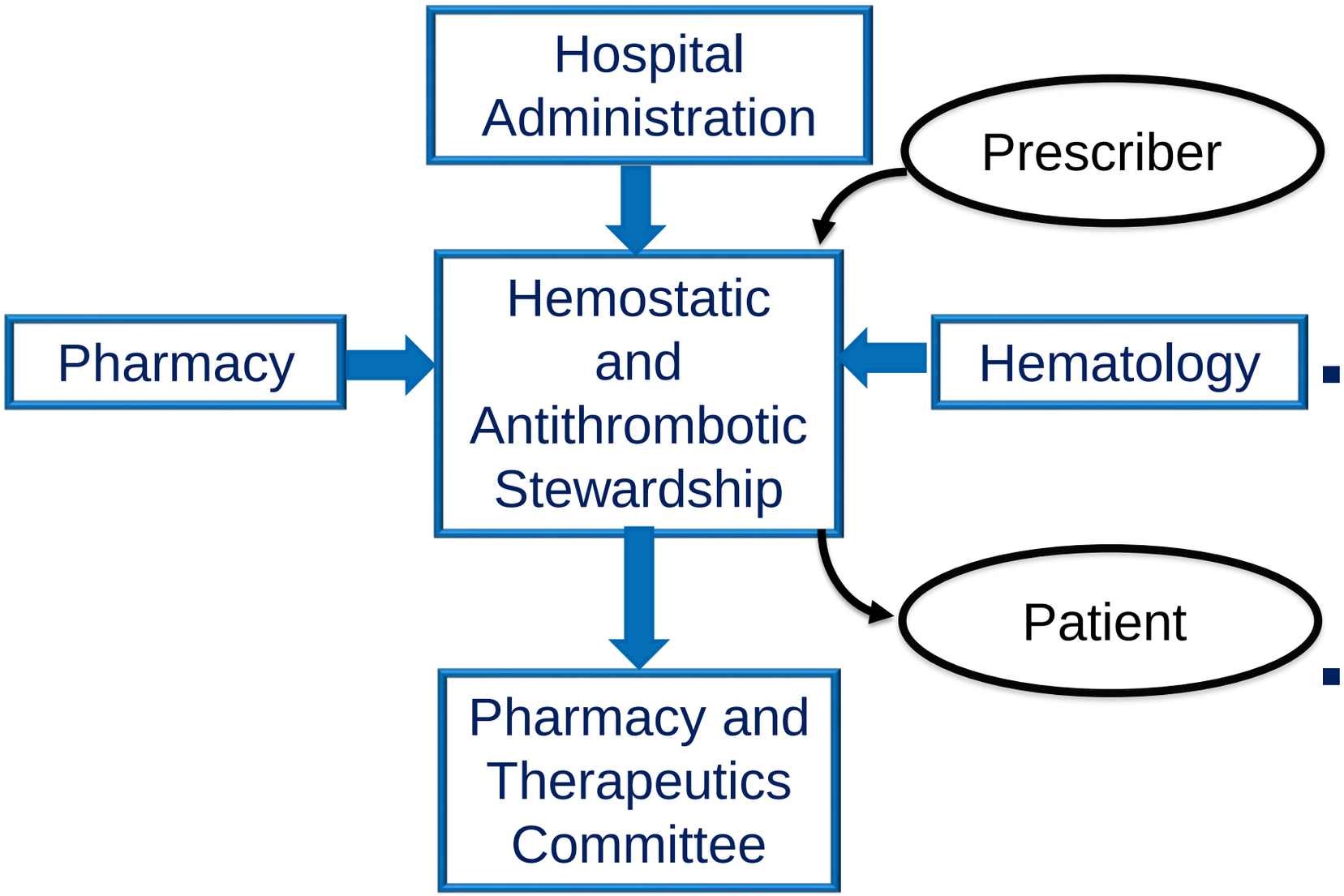


Value-Added Service

- Utilizing local expertise-Gatekeeper
- Rapid Response teams
  - Clinical deterioration
  - PERT
  - Code Aorta
- Structured Teams
  - Anticoagulation Management Service
  - Hemostatic Stewardship programs

Value-Added Service

Stewardship Structure



- **Direct Thrombin Inhibitor Management**
  - Updated Heparin-Induced Thrombocytopenia Guidelines
- **Clotting Factor Management**
  - Ensure appropriate use of agents (i.e. aPCC, PCC, VIIa, etc)
- **Anticoagulation Management of Mechanical Circulatory Support Devices**
  - ECMO, TAH, VAD

Amerine LB. Am J Health-Syst Pharm 2015;72:1579-1584.
BM Ritchie. J Thromb Thrombolysis 2016.42;616-622.
Burnett A. J Thromb Thrombolysis 2016:42:471-78.

Provider Education and Communication

Education

- Engage and utilize local experts
  - Support with data collectors
- Review cases at M&M rounds
- Annual mandatory education requirement
- Web-based CEU programs
- Live-Sponsored CME/ACPE educational programs
- Tool kits
  - Michigan Anticoagulation Quality Improvement Initiative (MAQI^2), SVM

Communication

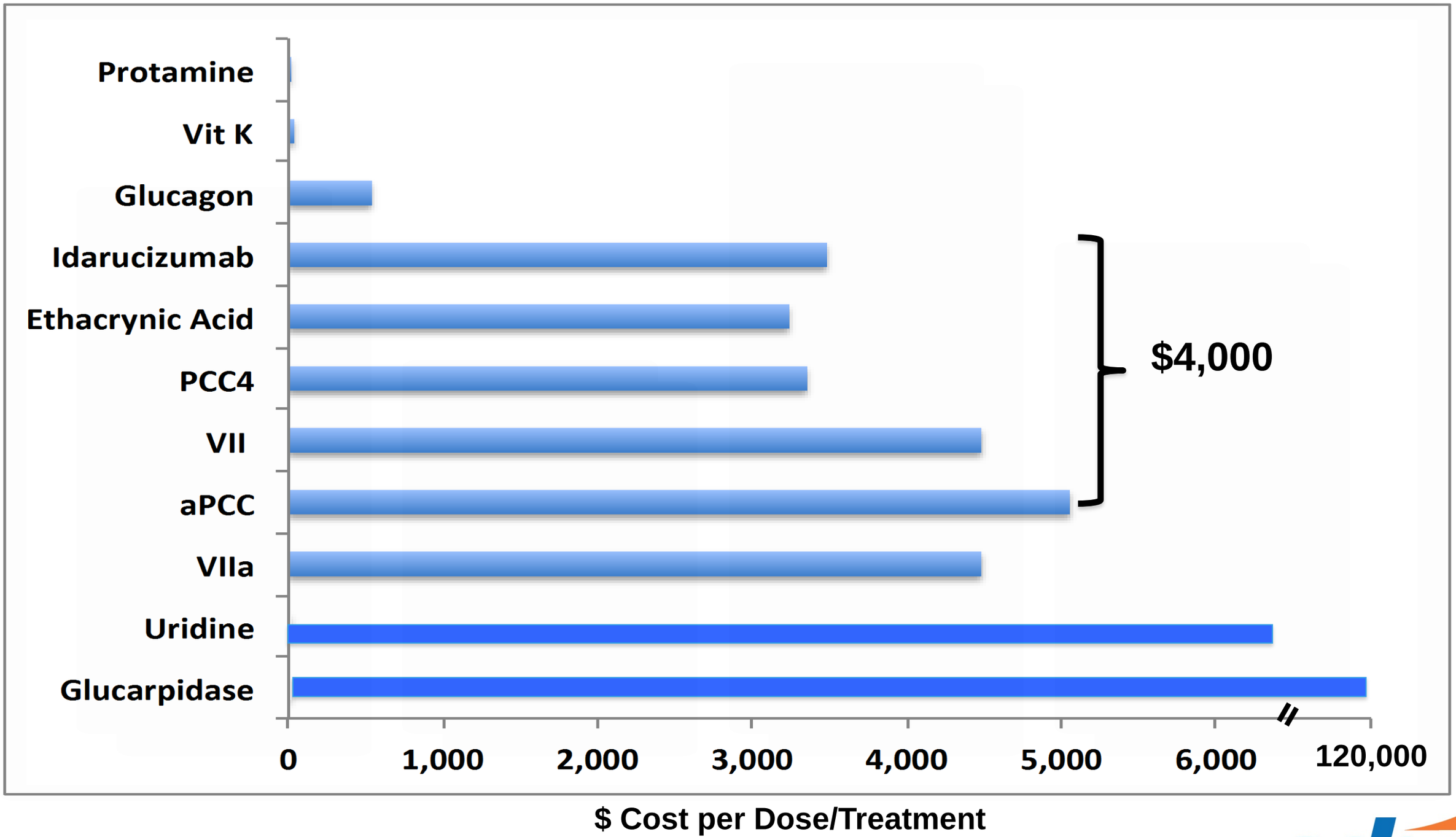
- Document events
  - RE-VECTO Registry
  - SOAR Registry
  - UPSTREAM Registry
- Report events
  - Disseminate successes
- Partnerships are key
  - Align with key stake holders

Outline

- Case presentation
- Pharmacy logistics
- Support systems
- Value and cost

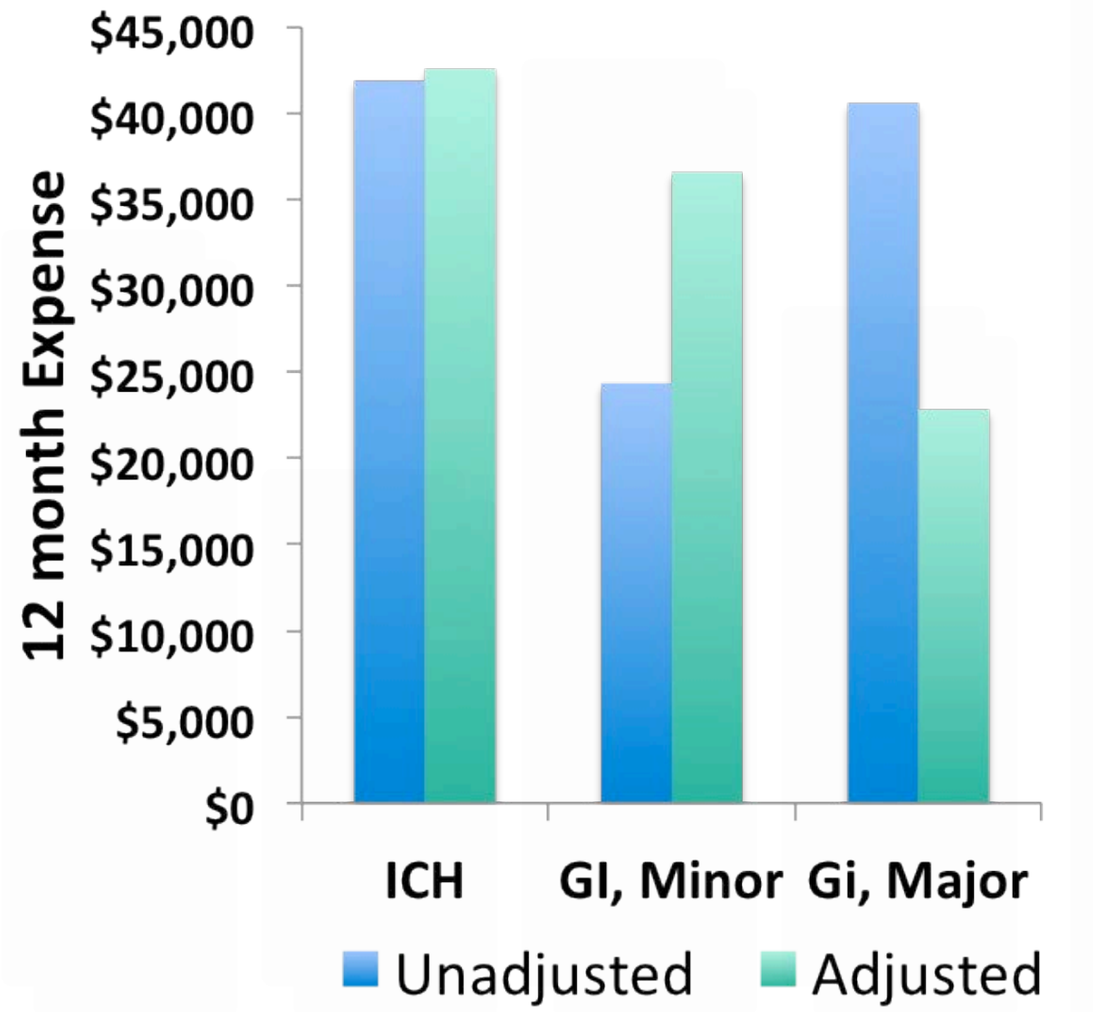
Smythe MA. Am J Health-Syst Pharm. 2016; 73(suppl 2):s27-48

Value and Cost*

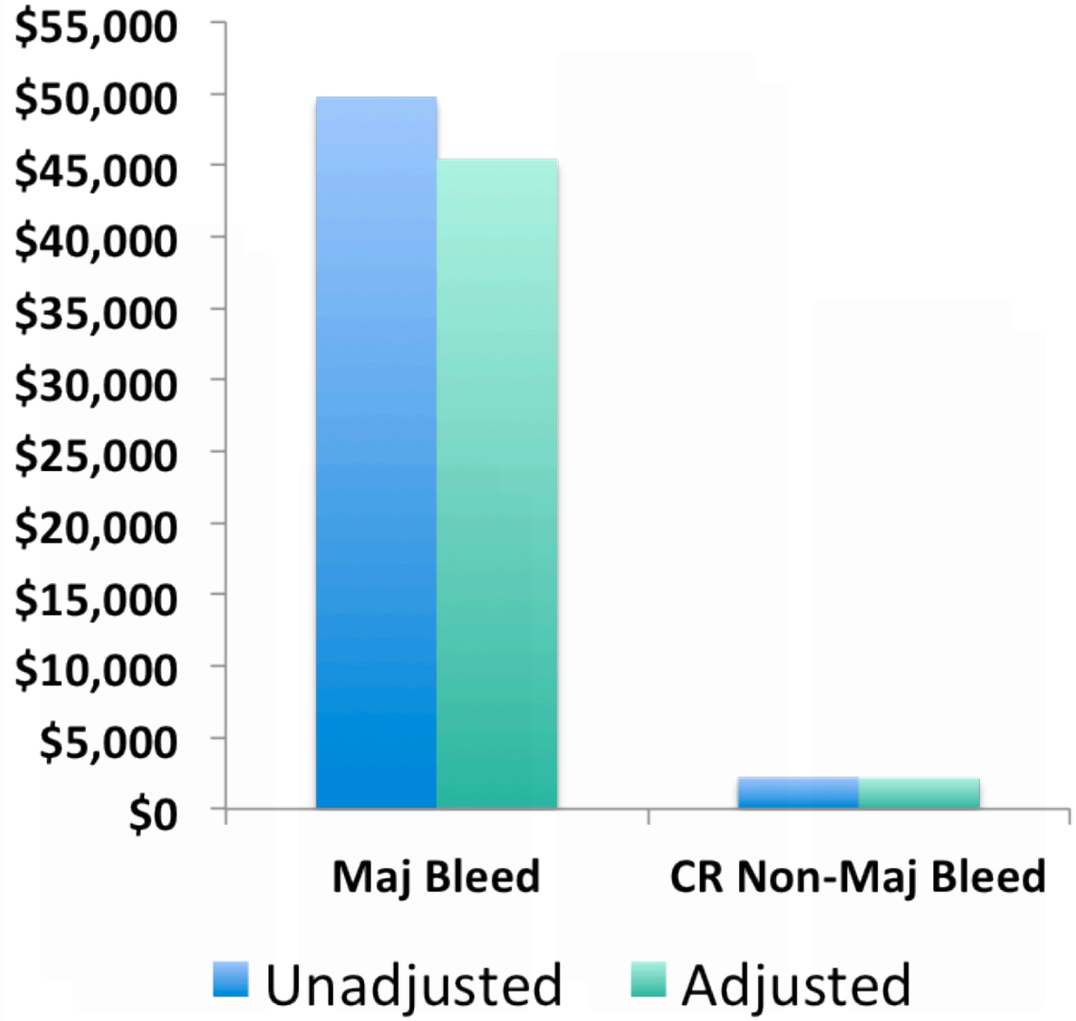


* Wholesale acquisition cost

Value and Cost



- AF patient population (n=48,069)
- Analysis of Medical and pharmacy claims
- All-cause health care costs

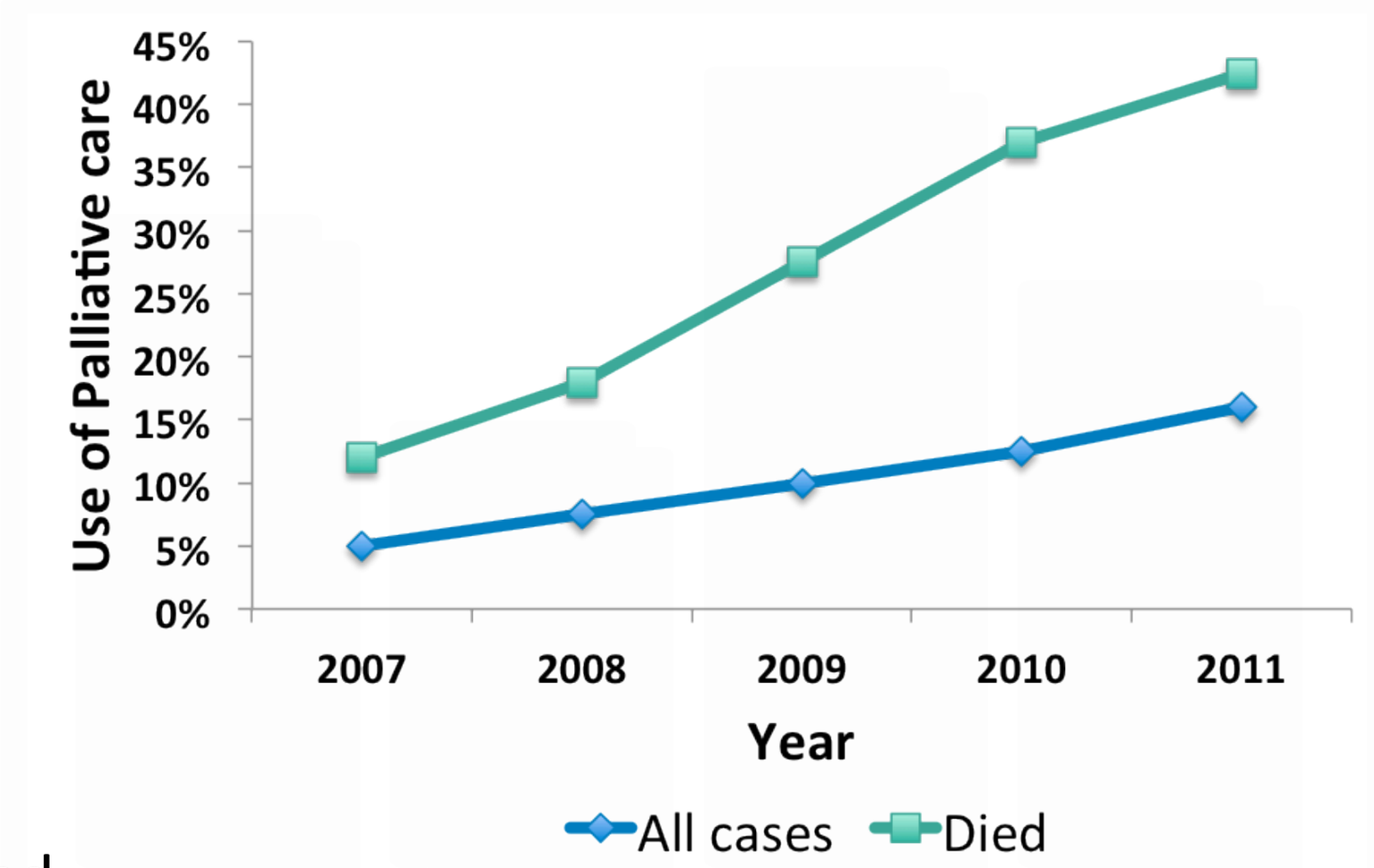


- VTE patient population (n=112,885)
- Commercial and Medicare databases
- Bleed-related health care costs

Ghate SR. J Manag Care Pharm. 2011;17(9):672-84.
Amin A. J Manag Care & Spec Pharmacy 2015; 21(10):965-72.

End of Life

- >5% of all U.S. deaths are stroke related.
  - 73% are ischemic
  - 16% are intracerebral hemorrhage (ICH)
  - 4% are subarachnoid hemorrhage (SAH)
- 50% of deaths occur in hospitals
- >20% of patients hospitalized for stroke are discharged to a skilled nursing facility
- 30% of all patients remain permanently disabled



- Prognostic models vs clinical experience
- Goals of care
- Preference-sensitive decisions

Arnold RM. Stroke. 2014;45:1887-1916.
SB Murthy. Crit Care Med 2016; 44:575–582.

Reversal Agent Check List

Item	Responsible Party	Category
Blood factor procurement	Blood Bank, Pharmacy	Supply Chain
Reversal agent procurement	Pharmacy	
Inventory quantities needed	Blood Bank, Pharmacy	
Storage locations	Pharmacy	Operations
Preparation	Pharmacy, Nursing	
Infusion device “Library” programming	Biomedical, Pharmacy, Nursing	Biomedical
Patient selection	Emergency, Hematology, Cardiology, Pharmacy, Blood Bank	Clinical
Guideline or treatment plan		
Electronic Health Record-Order entry	Prescriber, Pharmacy	Info Systems
Electronic Health Record-Documentation	Pharmacy, Nursing, Revenue Integrity	Finance
Provider education	Emergency, Hematology, Cardiology, Pharmacy, Blood Bank, Nursing	Clinical
Surveillance, effectiveness programs	Pharmacy, Quality	Quality, Safety

Smythe MA. Am J Health-Syst Pharm. 2016; 73(suppl 2):s27-48

Case Study: Conclusion

- Patient is transported to the OR
- OR Pharmacy Satellite obtains Idarucizumab from Central Pharmacy refrigerator
- On call Stewardship pharmacist is paged and reviews case.
- Idarucizumab IV 2.5 g, 2 doses (5 min apart) is administered
- Hospital course
  - Patient brought to OR: locking/nonlocking screws used to compress fracture and plate onto bone. Multiple screws placed, good stability.
  - POD #2: Dabigatran restarted
  - POD #4: Patient discharged, clinic follow-up in 2 wk

POD, postoperative day

Key Takeaways

- Key Takeaway #1
  - Pharmacies will play an important role in anticoagulant reversal agent procurement and dispensing.
- Key Takeaway #2
  - Support systems can be implemented to help identify appropriate patients, ensure safe administration, and accurate documentation.
- Key Takeaway #3
  - Reversal agents are expensive and contribute to overall cost of patient care.

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Balancing Act: Managing Bleeding and Thrombosis with DOACs Pro/Con Debate

Specific Reversal Agents are a Better Option for Reversal than Clotting Factors

Michael P Gulseth, Pharm. D., BCPS, FASHP
Sanford USD Medical Center
Sioux Falls, SD

Objectives

- Describe, in theory, why specific reversal agents are a better option for DOAC reversal than concentrated clotting factors
- Identify the risk of using concentrated clotting factors
- Compare and contrast the specific reversal agents on the market or in development
- Identify challenges in stocking agents in smaller hospitals

Primum non nocere

- "First, do no harm"
  - The patient's wellbeing is the primary concern
  - Reminds us that sometimes, doing nothing can be a better idea than intervening
- In our pharmacy world, this concept should make us think carefully how we use agents that are known to cause harm if used in ways not rigorously tested when better tested alternatives exist
- Despite not actually being in the Hippocratic Oath, it is a concept nearly all healthcare practitioners have heard and is part of our ethics training

http://medical-dictionary.thefreedictionary.com/First,+do+no+harm; accessed 9/28/16

When a concentrated clotting factor is used to reverse DOAC therapy, which of the following is true?

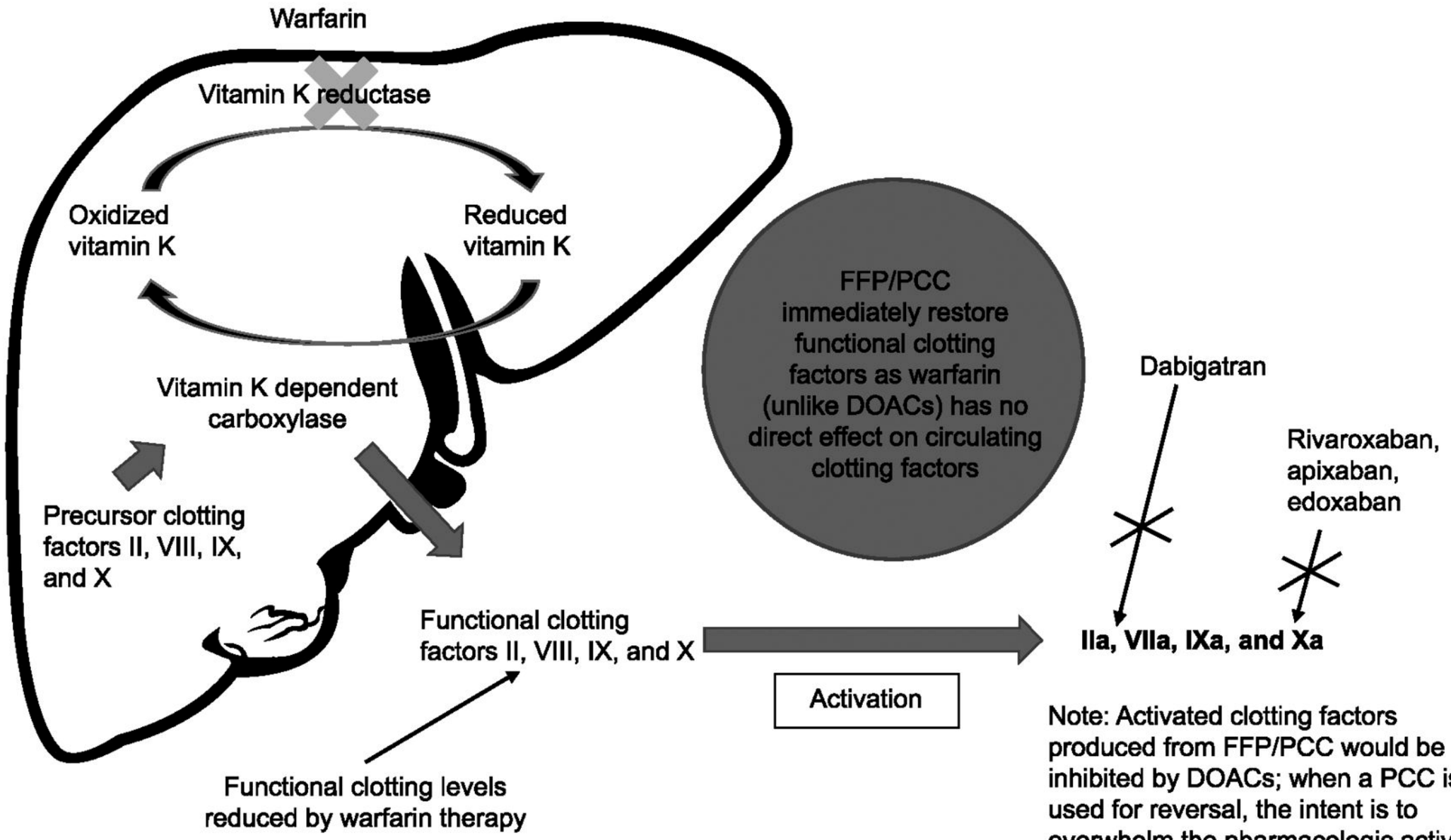
A. The concentrated clotting factor is repleting clotting factors to physiologic levels to restore normal coagulation function

B. Concentrated clotting factors directly bind to the DOAC and inactivate the DOAC permanently

C. Concentrated clotting factors promote DOAC removal from the plasma

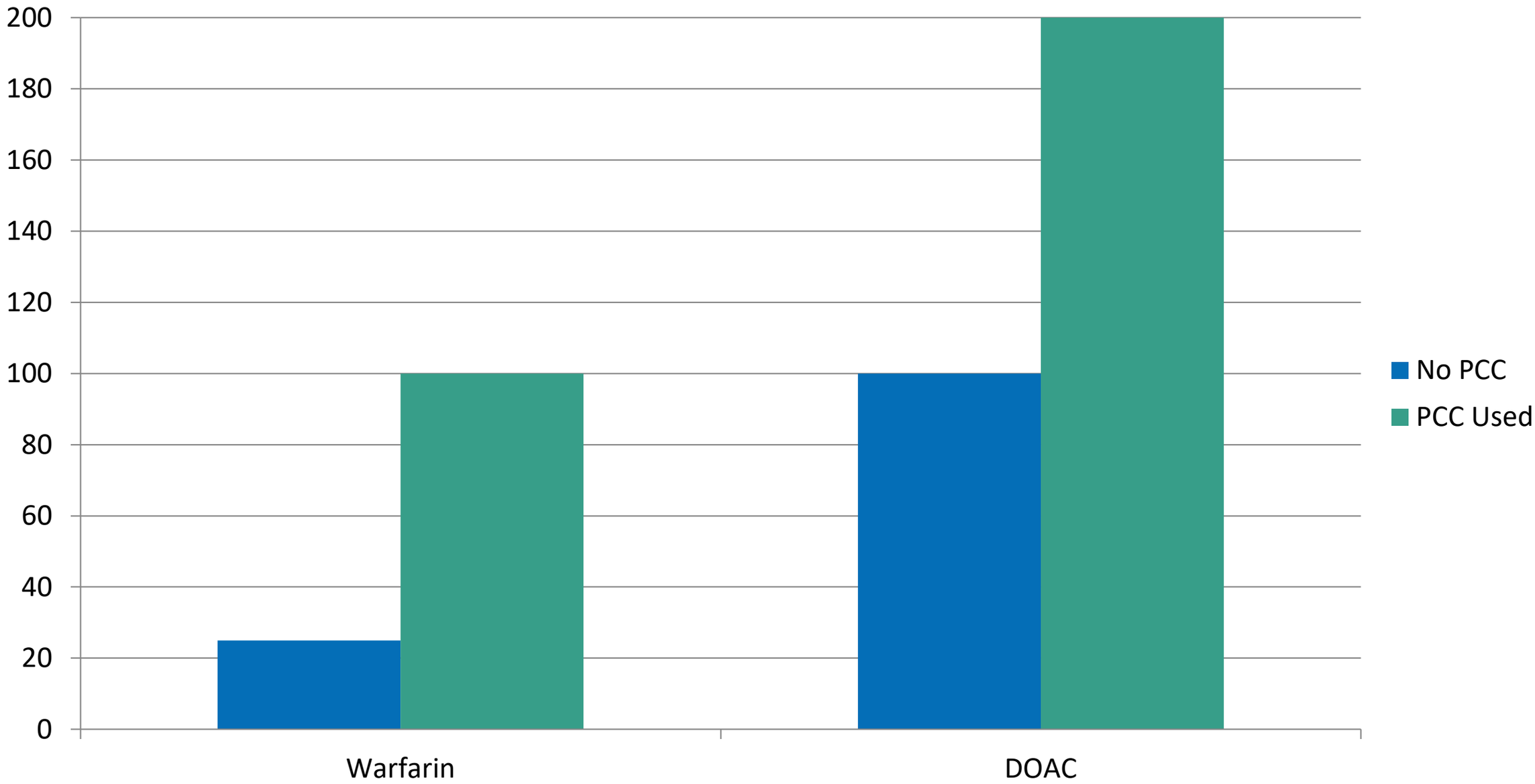
D. Concentrated clotting factors have to be given in a dose large enough to “overwhelm” the pharmacological activity of the DOAC

Theory of reversal



Gulseth MP. Overview of direct oral anticoagulant therapy reversal. *AJHP* May 15, 2016 vol. 73 no. 10 Supplement 2 S5-S13

Theory of reversal



Why I worry……recombinant factor VIIa

- Phase 2:
  - Randomized trial in intracerebral hemorrhage not on warfarin
  - Patients given within 3 hours of onset:
    - o Placebo (96 patients)
    - o 40 mcg rVIIa/kg (108 patients)
    - o 80 mcg rVIIa/kg (92 patients)
    - o 160 mcg rVIIa/kg (103 patients)
  - rVIIa reduced hematoma volume compared to placebo and there was less death/severe disability in the rVIIa patients
  - More thromboembolism in the rVIIa patients, mainly MI and CVA (not statistically significant like the above findings)

Mayer SA, et. al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; 352: 777-85.

Why I worry……recombinant factor VIIa

- Phase 3:
  - Randomized trial in intracerebral hemorrhage not on warfarin
  - Eligible if + CT scan within 3 hours of onset; given:
    - o Placebo (268 patients)
    - o 20 mcg rVIIa/kg (276 patients)
    - o 80 mcg rVIIa/kg (297 patients)
  - Only the 80 mcg/kg group had a significant reduction in hematoma growth over placebo (11% increase vs. 26% increase, $p<0.001$)
  - No differences between groups in outcomes (mortality, modified Rankin score)
  - Arterial thromboembolism was more common in the 80 mcg/kg group than placebo (9% vs. 4% $p=0.04$)

Mayer SA, et. al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; 358: 2127-37.

Factor product thromboembolism reports

- Activated prothrombin complex concentrate (APPC, FEIBA®) had a reported rate of 4-8 events per 10,000 infusions when used for thrombophilia
  - Most common in those at risk for thrombosis
- One the same studies found an incidence rate of 25 events per 10,000 infusions for recombinant VIIa (rVIIa)
- In 2006, it was reported from 03/99 to 12/04 that 185 possible thromboembolisms due to rVIIa had been reported to the FDA; about a third of the reports were off label use
  - In 36 of 50 deaths, the probable cause of death was thrombosis

Ehrlich HJ, et. al. Safety of factor VIII inhibitor bypass activity (FEIBA®):10-year compilation of thrombotic adverse events. *Haemophilia* 2002; 8: 83-90.
Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *J Thromb Haemost* 2004; 2: 1700-08.
O'Connell KA, et. al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; 295: 293-298.

Factor product thromboembolism reports

- Safety of rVIIa was analyzed in a combined analysis of 35 randomized clinical trials to determine frequency of thromboembolic events
- No difference from placebo for venous thromboembolism
- Higher rates of arterial thromboembolism versus placebo
  - 5.5% vs 3.2%, p=0.003
    - 2.9% vs 1.1% for coronary events, p=0.002
  - If ≥ 65 yo, 9% vs 3.8%, p=0.003
  - If ≥ 75 yo, 10.8% vs 4.1%, p=0.02
  - Dose likely matters

Levi M, et. al. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med* 2010; 363: 1791-800.

What is in aPCC/PCC?

Vitamin K-dependent factors	4F-PCC Nonactivated	Plasma	4F-aPCC activated (factor VIIa)	3F-PCC	rFVIIa
II	✓	✓	✓	✓	
VII	✓	✓	✓ Activated	Low levels	✓ Activated
IX	✓	✓	✓	✓	
X	✓	✓	✓	✓	
Protein C	✓	✓			
Protein S	✓	✓			

Profilnine SD [package insert]. Los Angeles, CA: Grifols Biologicals Inc; January 2013.
NovoSeven RT [package insert]. Princeton, NJ. Novo Nordisk Inc.; August 2010.
FEIBA NF [package insert]. Westlake Village, CA. Baxter Healthcare Corporation; February 2011.
Kcentra [package insert]. Kankakee, IL . CSL Behring; 2013

Which of the following concentrated clotting factor agents has a boxed warning of thrombosis risk in its PI?

A rVIIa

B 4 factor PCC

C aPCC

D All of the above

Are PCCs/aPCC safer than rVIIa?

- Short answer is I don't think we can say for sure
- rVIIa package label:
  - Boxed warning regarding risk of thrombosis
- aPCC
  - Boxed warning: "Thrombotic and thromboembolic events have been reported during postmarketing surveillance following infusion of FEIBA VH or FEIBA NF, particularly following the administration of high doses and/or in patients with thrombotic risk factors"
- 4 factor PCC
  - Boxed warning: Warns of risk of thrombosis in those at risk since warfarin patients are inherently at risk

Profilnine SD [package insert]. Los Angeles, CA: Grifols Biologicals Inc; January 2013.
NovoSeven RT [package insert]. Princeton, NJ. Novo Nordisk Inc.; August 2010.
FEIBA NF [package insert]. Westlake Village, CA. Baxter Healthcare Corporation; February 2011.
Kcentra [package insert]. Kankakee, IL . CSL Behring; 2013

Specific Reversal Agents for NOACs: Approved and in Development

Antidote	Target	Mechanism of Action	Status
Idarucizumab[1,2] (BI 655075)	Dabigatran	Humanized Fab: specifically binds dabigatran (binding affinity ≈350 x higher than binding of dabigatran to thrombin) NO reversal for FXa inhibitors or LMWH/fondaparinux	Approved by US FDA October 16, 2015 for use in patients on dabigatran during emergency situations when there is a need to reverse dabigatran's blood-thinning effects[3]
Andexanet alfa[1,3] (PRT064445)	FXa inhibitors	Recombinant FXa analogue that binds to direct FXa inhibitors and antithrombin, so provides reversal for rivaroxaban, apixaban, edoxaban, LMWH, fondaparinux NO reversal for dabigatran	Phase 2 completed for rivaroxaban, apixaban, enoxaparin; ongoing for edoxaban Phase 3 completed for apixaban, rivaroxaban; started or planned for edoxaban
Ciraparantag[1] (PER977)	Universal	Synthetic small molecule that binds to NOACs, heparins and fondaparinux	Phase 1 completed for edoxaban

Fxa, factor Xa

1. Weitz JI et al. *Thromb Haemost*. 2015 Jul 9;114(5). [Epub ahead of print]. 2. Pollack CV Jr et al. *N Engl J Med*. 2015;373(6):511-520. 3. FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm. Accessed 10/16/15. 3. Siegal DM et al. *N Engl J Med*. 2015 Nov 11; doi: 10.1056/NEJMoa1510991. [Epub ahead of print].

Idarucizumab: A Specific Reversal Agent for Dabigatran

- Humanized Fab fragment
- Binding affinity **≈350 × higher** than dabigatran to thrombin
- IV administration, immediate onset of action
- Short half-life
- No procoagulant or anticoagulant effects expected

1. Schiele F et al. *Blood*. 2013;121(18):3554-3562. 2. Stangier J et al. ISTH 2015; OR320.

Idarucizumab for Dabigatran Reversal

- Prospective cohort study to determine safety of 5 g IV idarucizumab, its capacity to reverse anticoagulant effects of dabigatran
  - Group A (n=51): Serious bleeding
  - Group B (n=39): Required urgent procedure
- Median maximum percentage reversal 100% (95% CI, 100–100)[a]
- Normalized test results in 88% to 98%, effect evident within minutes
- In group A (N=35 evaluable pts) hemostasis restored at median of 11.4 h
- In group B (N=36) pts who underwent a procedure
  - 33 pts: normal intraoperative hemostasis reported
  - 2 pts: mildly abnormal hemostasis
  - 1 pt: moderately abnormal hemostasis
- One thrombotic event within 72 h after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated

[a]Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ECT at baseline

Pollack CV Jr et al. *N Engl J Med*. 2015;373(6):511-520.

Key Takeaways

- Key Takeaway #1
  - We don’t know the full risks of raising coagulation factors to concentrations well over physiologic levels; clotting factor use in this population is fundamentally different than warfarin patients or hemophiliacs
- Key Takeaway #2
  - We have tried raising clotting factor levels to over physiologic levels before without success (ICH and rVIIa)
- Key Takeaway #3
  - Specific reversal agents that are approved have/will have more rigorous data to support safe and efficacious use

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DOAC-Specific Antidote ***PLUS*** PCC

A. Josh Roberts, Pharm.D., BCPS-AQ Cardiology

What are Our Goals?

- Urgent / Emergent Anticoagulant Removal

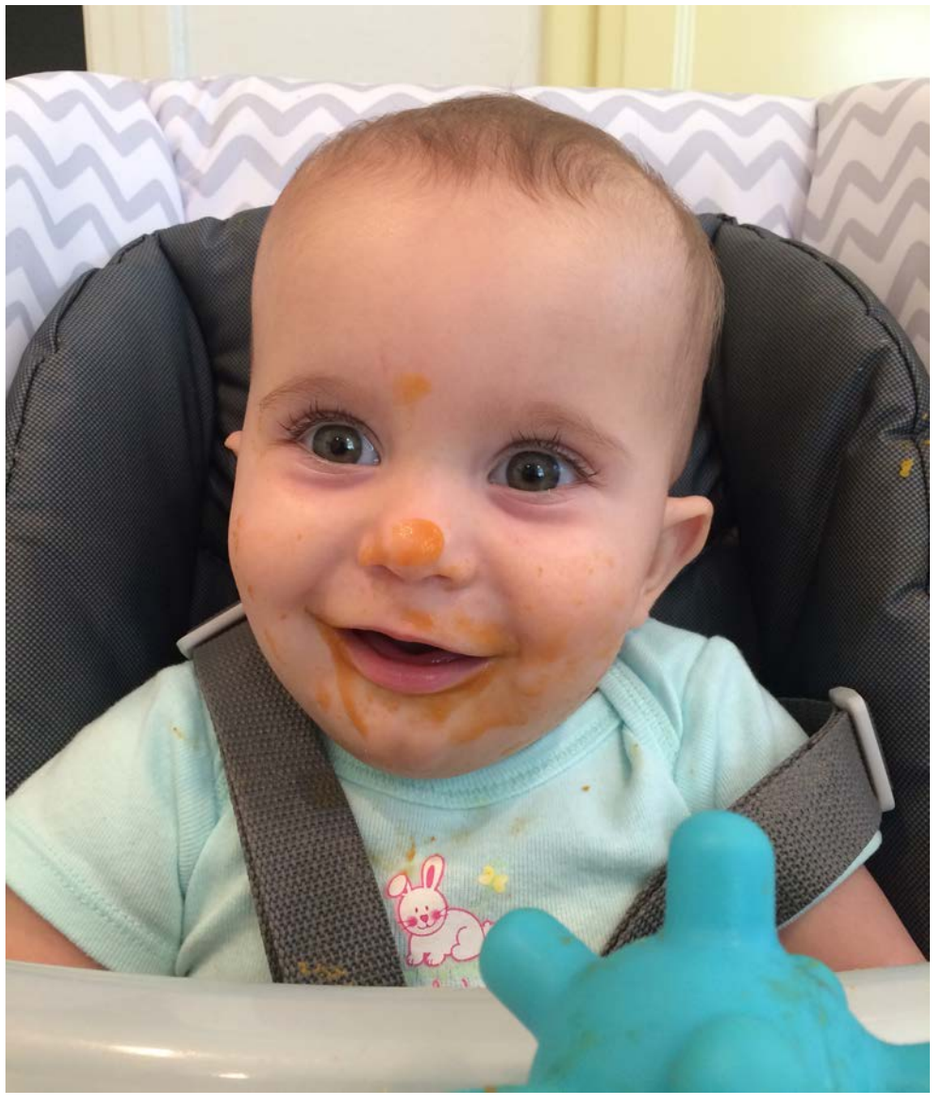
- Emergent, sustained hemostasis!

- Patient stabilization
  - Discharge ALIVE !!!

http://www.nasa.gov/centers/goddard/images/content/95339main_ghana_rain_m.jpg
CREDIT: Distinguished Professor, Dr. James W. Jones, University of Florida

Antidote + PCCs

- Guideline recommendations for antidote + PCC
  - NONE
- “Real Life” Experience
  - Infancy
  - Messy



Watch and Wait ???

- **When the storm is raging and the water is rising, it's not a good time to sit-back, wait, and see what happens.**

http://www.floodsafety.noaa.gov/during.shtml (photo credit: USGS)

Let’s do the “if this were friend or my Grandma” test?

- Let’s call our patient / friend “Mike”
- “Mike” has a lot to live for…
- Let’s give “Mike” every chance to discharge home on his own two feet

Major Bleeding & Fatality in Phase-3 Trials: Clinically Acceptable?

- Time to Antidote = Hours

- Significant Mortality Rates with <u>single agent</u> treatment
  - Dabigatran + PCC/aPCC: 18.6%
  - Idarucizumab + dabigatran *(active bleed group)*: 17.6%
  - Andexanet Alfa + Anti-FXa Inhibitors: 15%

Trinh-Duc A, et al. Thromb Res. 2016 Aug 24;146:43-45.
Connolly SJ, et al. N Engl J Med. 2016 Sep 22;375(12):1131-41.

Exsanguinating Bleed - DO WE HAVE THE TIME??

Pla C.
Bo
Nov 2016

RIP
"Auntie"
Dote
Dec 2016

R.X. D-
Lay
797 Clean

Bench *vs* Bedside

- Time to clinical hemostasis post antidote **>10hrs**
  - Some bleeds hard to assess (ICH, RPB)
    - *All the more reason for addition of PCC*

- DOAC-specific antidotes are coag-inert, only bind drug
  - Normalization lab parameters ≠ hemostasis
    - other drivers of anticoagulation & hemostasis
    - Antidotes do NOT directly promote thrombosis

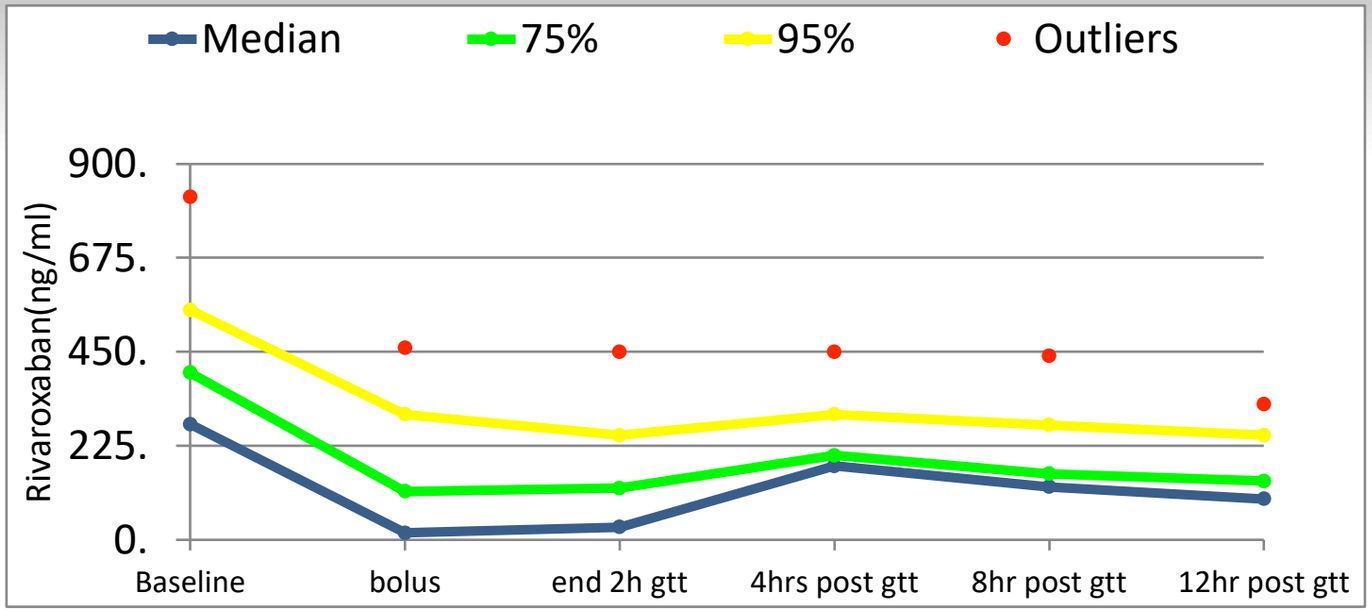
Connolly SJ, et al. N Engl J Med. 2016 Sep 22;375(12):1131-41.
Pollack CV Jr, et al. N Engl J Med. 2015 Aug 6;373(6):511-20

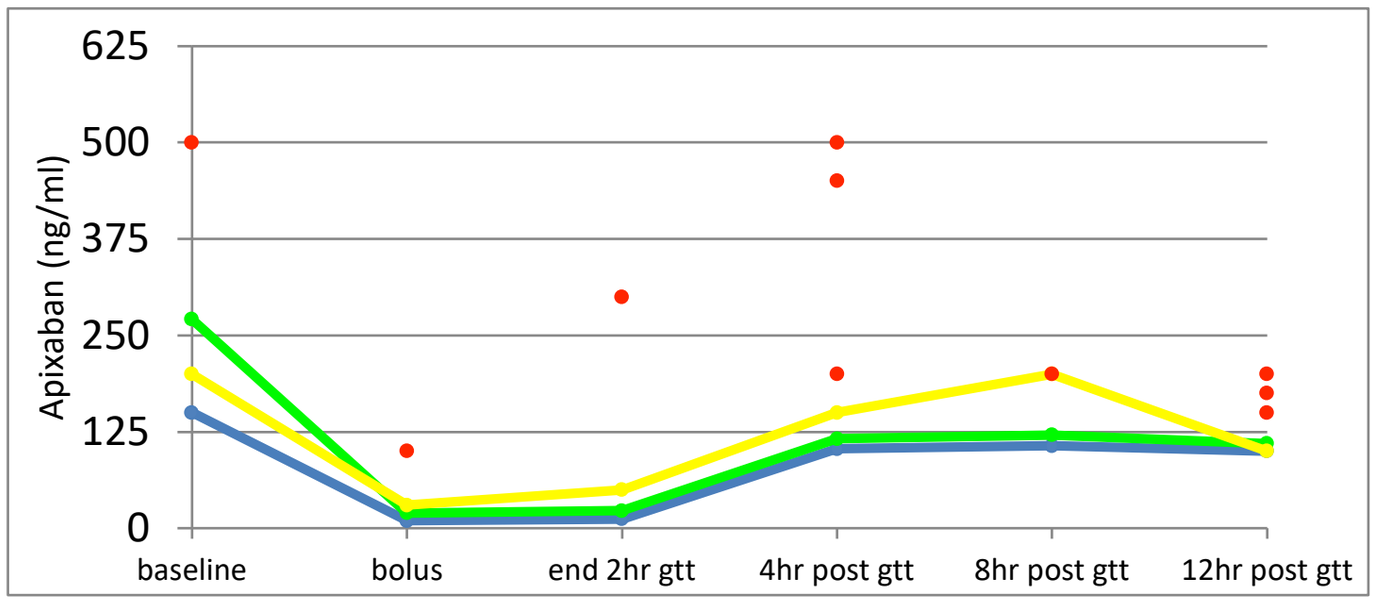
Bedside Clinicians in Clinical Trials

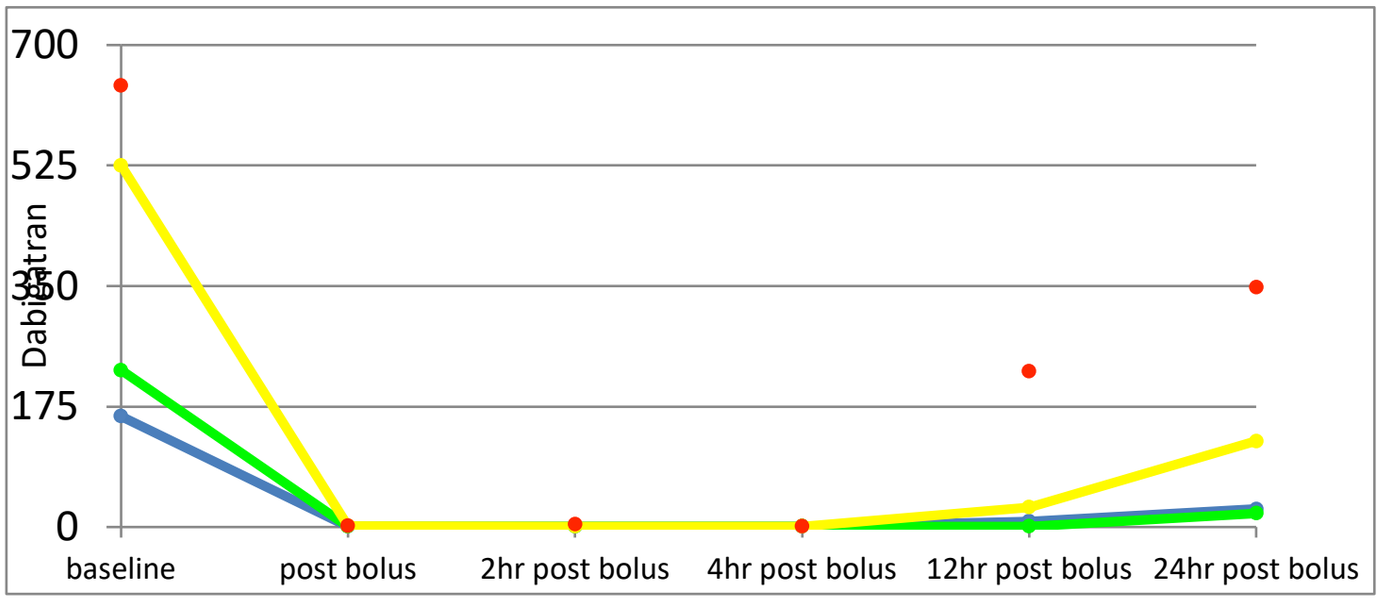
- Idarucizumab
- Bleeding: PRE-antidote aPCC (n=2) >> *nothing post*
- Procedure: PRE-antidote aPCC (n=1), post-aPCC (n=1)

- Andexanet Alfa
- Post administration: 8% received plasma, TXA, or platelets

Does One Size Reverse All?







- Supra-therapeutic DOAC levels
  - Greater redistribution?
  - Overwhelm standard antidote doses?

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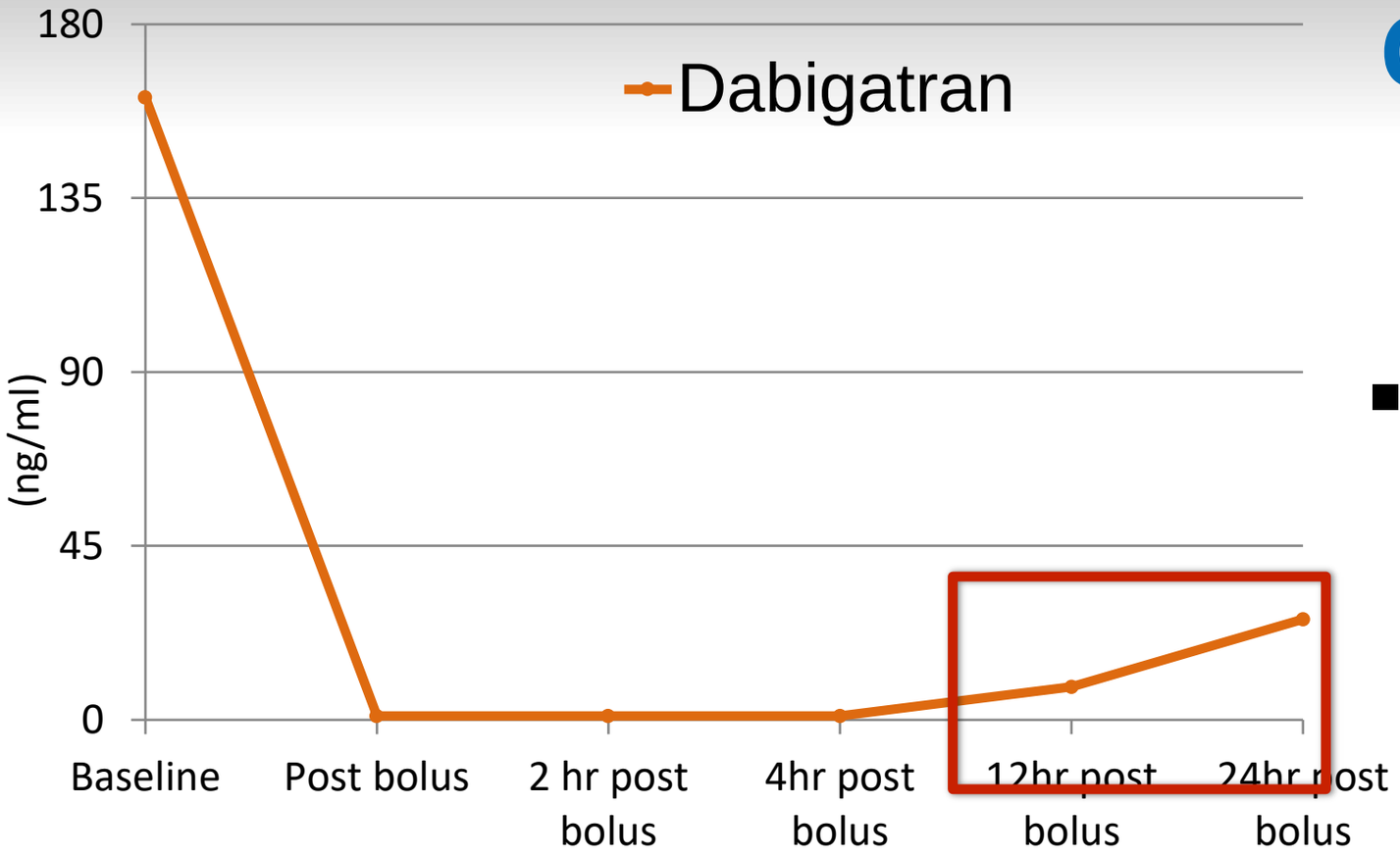
Is giving the antidote enough?

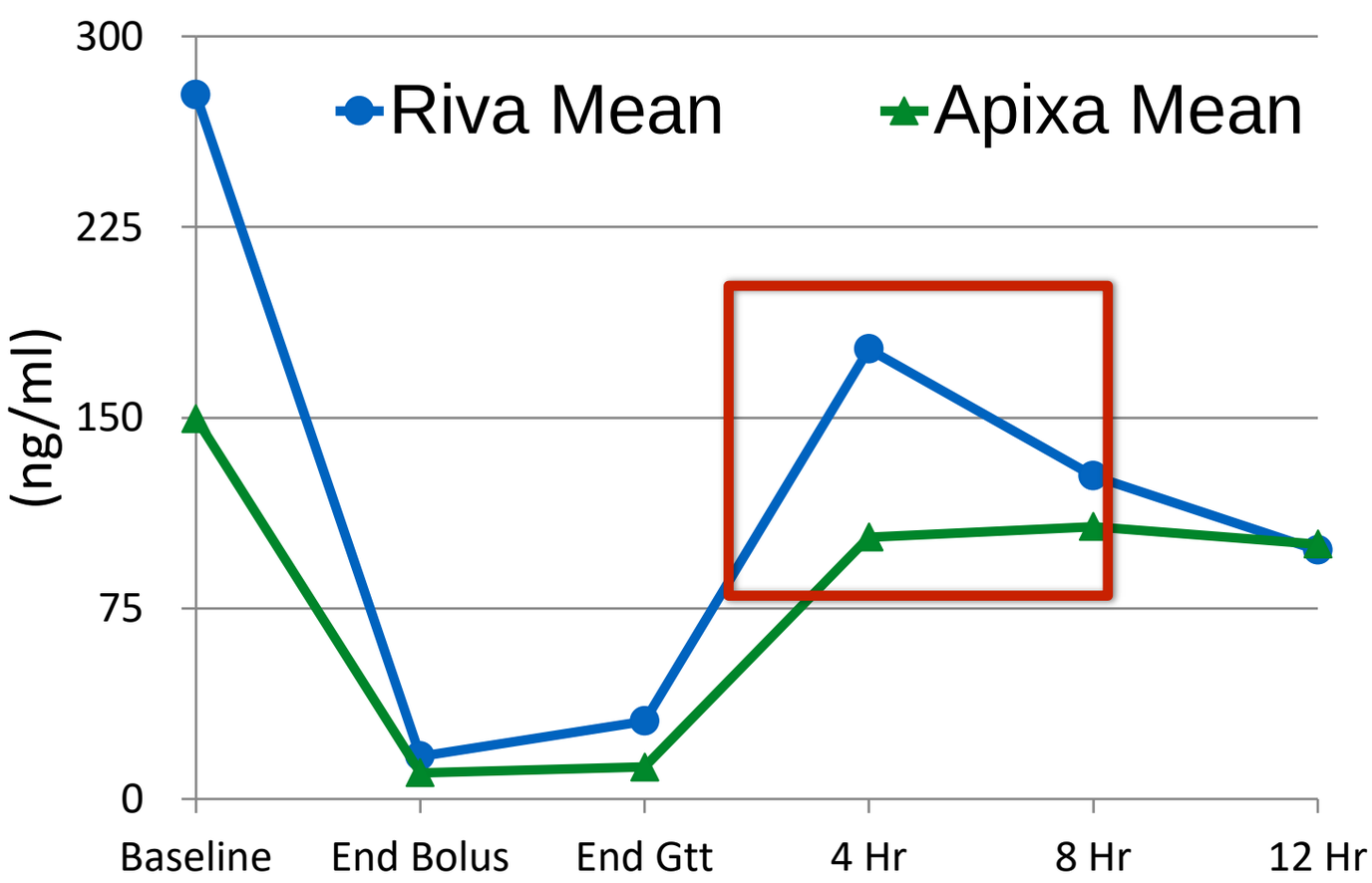
- 65M with GIB on Dabigatran >> idarucizumab 5gm
  - Corrected Thrombin Time
  - EGD 3hrs later = actively hemorrhaging vessel
    - Unable to control hemorrhage
  - **Administered aPCC** + PRBCs
  - Discharged home

Alhashem H, et al. Am J Emerg Med. 2016 Jun 30. pii: S0735-6757(16)30353-9.

Complete, Sustained Reversal



- Short lived reversal
- Post infusion rebound
- Drug redistributes



- Can tenuous, critically ill patient tolerate “re-anticoagulation?”

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Clinical Effects of Anticoagulant Redistribution

- 79F with GI perforation on Dabigatran + clopidogrel >> idarucizumab 5gm
  - Hemorrhage Cessation + normalization thromboelastomeric parameters
  - 11hrs later rebound hemorrhage + rebound dabigatran (290ng/ml)
  - Considered REPEAT (did not admin) idarucizumab 5gm
  - Deceased

Thorborg C, et al. Br J Anaesth. 2016 Sep;117(3):407-9.

PCC May *Add To* The Reversal Effect

- PCC's correct coagulation parameters ex-vivo in animal models
  - solely aPCC 30-50 units/kg normalizes parameters
- PCC may reduce additional blood products
- Low dose (9-14 units/kg) aPCC clinical stabilized major GIB and non-ICH bleeds

Grottke O,et al. Crit Care. 2014;18(suppl 1):P118.
Schultz N, et al. ISTH 2015;13(suppl 2): OR317
Castellucci LA., et al. ISTH 2015;13(suppl 2): PO320
Dager WE., et al. ISTH 2015;13(suppl 2):PO359
Dager WE., et al. SCCM 2017; in press

http://www.floodsafety.noaa.gov/ (photo credit: FEMA)

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Rebuttal:
Specific Reversal Agents are a Better Option for Reversal than Clotting Factors

Michael P Gulseth, Pharm. D., BCPS, FASHP
Sanford USD Medical Center
Sioux Falls, SD

Current literature opinions

- Deborah M. Siegal, MD, McMaster University, 2015
  - “Given the lack of established efficacy of DOAC treated patients with bleeding complications, these agents should be administered with caution due to their thrombogenic potential.”
- TIMI study group, Brigham and Women’s Hospital, 2016
  - “In a patient with serious bleeding, however, specific reversal agents (if available) should be used instead of general hemostatic agents because of the nonspecific agents are less effective in reversing coagulation abnormalities, have not been shown to improve outcomes, and are potentially prothrombotic.”

Siegal, DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents. *J Thromb Thrombolysis* 2015; 39: 395-402.
Ruff, CT, et. al. Management of bleeding with non-vitamin K antagonist oral anticoagulants in the era of specific reversal agents. *Circulation* 2016; 134: 248-261.

Current literature opinions

- Anticoagulation Education Task Force White Paper, 2016
  - Algorithm for management of bleeding or surgery specifically says “Idarucizumab is the preferred treatment to reverse dabigatran.”
- Statement from the Neurocritical Care Society and the Society of Critical Care Medicine, 2016
  - Recommends use of idarucizumab to reverse intracranial hemorrhage associated with dabigatran
  - Recommends PCC and aPCC only be used in intracranial hemorrhage associated with dabigatran if “Idarucizumab is not available.”

Angeno, W, et. al Managing reversal of direct oral anticoagulants in emergency situations. *Thrombosis and Haemostasis* 2016; 116: epub ahead of print.
Frontera, JA, et. al. Guidelines for reversal of antithrombotics in intracranial hemorrhage. *Neurocrit Care* 2016; 24: 6-46.

The difference from UC Davis to the typical SD hospital

Cost of reversal

- PCC3 (Profilnine®)
  - $1.14/unit
  - 500 units=$570
  - 25 units/kg dose, 80 kg patient=$2280
- PCC4 (Kcentra®)
  - $1.51/unit
  - 500 units=$755
  - 25 units/kg dose, 80 kg patient=$3020
- aPCC (Feiba®)
  - $1.76/unit
  - 500 units=$880
  - 25 units/kg dose, 80 kg patient=$3520
- Idarucizumab (Praxbind®)
  - $1741.25/2.5 gram vial
  - $3482.50/dose
  - BUT, some hidden advantages

Idarucizumab perks

- Idarucizumab, after purchase, can be returned:
  - Products with less than 3 months remaining shelf life but not more than 6 months beyond expiration date
  - Product must be in original container bearing its original label and legible lot number and expiration date
  - Full and partial containers are accepted
- Idarucizumab qualifies for new technology add on payments from Medicare until September 30, 2017
  - Additional reimbursement of up to $1,750 when idarucizumab exceeds the Medicare Severity Diagnosis-Related Groups (MS-DRG) payment amount

Personal communication. Boehringer Ingelheim. Data on file.
https://www.praxbind.com/reimbursement accessed 10/5/2016

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Rebuttal:

There is a Role for PCC!

A. Josh Roberts, Pharm.D., BCPS-AQ Cardiology

What is there to be scared of ??

- Bleeding ?
- Clotting ?
- Cost ?
- We can affect all these things

Front-line Experience

- Concede to ‘watch and wait’ approach of antidote strategy in the relatively stable patient with mild-to-moderate bleed

- Mike – “Have you been to the ER and managed a massive bleeding event in a DOAC-anticoagulated patient?”

- Severe, **Massive bleeding event >> Time is everything**
  - Clinical Trials - administration of antidote >4hr
  - If you miss the “wave”, you may lose the patient
    - Massive bleeding >> no time to “sit and wait” 10-12hrs for ‘clinical hemostasis’

Fatal Bleeding Events

- Antidote ALONE
  - Time to clinical hemostasis post antidote **>10hrs**
    - Idarucizumab: 5 fatal bleeds
      - acute bleed group: 9 deaths
    - Andexanet Alfa: 7 deaths

- aPCC
  - Some fatalities within case series

- Antidote + PCC
  - ??? – none identified thus far

Connolly S, et al. N Engl J Med. 2016;375(12):1131-41.
Pollack CV Jr, et al. N Engl J Med. 2015;373(6):511-20.

Effectiveness of a Low Dose Strategy

- Low dose non-ICH (n = 19)
- **Mean Dose: ~10 units/kg**
  - N=9 had 500 units
  - N=8 had 1000 units
  - N=2 had 1500 unit
- **Hospital Mortality: None**
- 30-day Thromboembolism (n=2; 10%)
  - n=1: 9 day post tx
    - Heparin SQ prophylaxis started 8 days post aPCC
  - n=1: 30 days post aPCC
    - Receiving apixaban 5mg BID

Dager W, et al. SCCM 46th Critical Care Congress. Honolulu, Hawaii; January 21-25, 2017. Pending Publication

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DOAC Interruption & Thromboembolism Risk

- >20-fold Increase risk of Thromboembolism
  - Median 14 days (1-37days)

- Idarucizumab: 10%
- Andexanet Alfa: 18%
- low dose aPCC: 10%
- antidote + PCC: ??

Photo Courtesy of A. Josh Roberts, Pharm.D.

Vene N, et al. PLoS One. 2016 Jun 9;11(6):e0156943

Tips for Potentially Avoiding Thromboembolism

- Restarting anticoagulation 7days post-GIB
- Majority of thrombotic events occur >7 days post anticoagulant cessation / reversal
- Infrequent events <7days
  - idarucizumab n=1
  - andexanet alfa n=6

Qureshi W, et al. Am J Cardiol. 2014;113(4):662-8.
Connolly S, et al. N Engl J Med. 2016;375(12):1131-41.
Pollack CV Jr, et al. N Engl J Med. 2015;373(6):511-20.

Cost-effective Therapy: Don’t think in the silo

Consider all products in treating the patient

<u>Pharmacy</u>

- Idarucizumab: $3482
  - 2.5g vial = $1741
- Andexanet Alfa: $???
- PCC-4: $1.51 / unit
- aPCC: $1.76 / unit
  - 500 unit = $880
  - 1000 unit = $1760

<u>Blood Bank</u>

- PRBC: $200
- FFP (~300ml): $100
- Platelets: $500
- Cryoprecipitate: $300

Cost of Treating Our 80kg Patient

Idarucizumab 5gm = $3482

Idarucizumab + aPCC 25 units/kg

- Idarucizumab 5gm + aPCC 2000 unit = $7002

Idarucizumab + Low Dose, Titration

- Idarucizumab 5gm + aPCC 500 unit = $4362

Low-dose aPCC

- **aPCC 500 unit = $880**
- **aPCC 1000 unit = $1760**

Low-dose aPCC vs Antidote

- **Cost avoidance favors aPCC = $1722 - $2602**

✓ *25% - 50% PRICE over Antidote alone*

Will Andexanet alfa & Ciraparantag be cost competitive or prohibitive??

Finally…

- Let’s give our massive bleeding patients the best chance to discharge home alive

- No head-to-head comparisons between PCC and antidotes
  - Is there equivalence in terms of clinically efficacy???
  - Antidote with labeled indication though cost-prohibitive?
    - What’s the threshold to switch from one to the other?

- What’s the cost of a life?

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Panel Discussion

William Dager
John Fanikos
Michael Gulseth
Aaron Roberts

Post Debate Analysis
For “Major” Non-ICH Bleed

A Antidote alone

B 4 factor PCC/aPCC + Antidote if Urgent

C 4 Factor PCC/aPCC alone

D A, B or C depending on the Urgency of the situation and Cost if Antidote is very expensive

Case

- **AJ is a 65 year old, 80kg male with a history of unprovoked DVT 1 year ago who was managed on warfarin for 3 months. 2 months ago, he was diagnosed with atrial fibrillation and requested to be on a different oral agent as warfarin was very hard to keep controlled with a lot of lab testing and dosing adjustments done. He takes the agent twice daily, but does not remember what the name is and is very confused. He is now being admitted with bright red blood in his stools that has been going on for several hours and very weak.**
- **PHH: CAD (NSTEMI), GERD, DVT, HTN, AF and CKD IV**
- **Labs: Scr 3.5, Hgb 5.2, INR 2.6**

For AJ – what is your next management step

A Thrombin Time

B Anti-Xa activity

C Bedside assessment of the current bleeding

D All of the above

For AJ – what anticoagulation reversal approach would you initiate

A rFVIIa

B 4 factor PCC/aPCC – 50 units/kg

C Idarucizumab or Andexanet

D Low dose PCC/aPCC – 8-12 units/kg and watch

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Questions?
Panel Discussion

William Dager
John Fanikos
Michael Gulseth
Aaron Roberts