ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Stop That Bleed! Implementing a Reversal Strategy for the Direct Oral Anticoagulants

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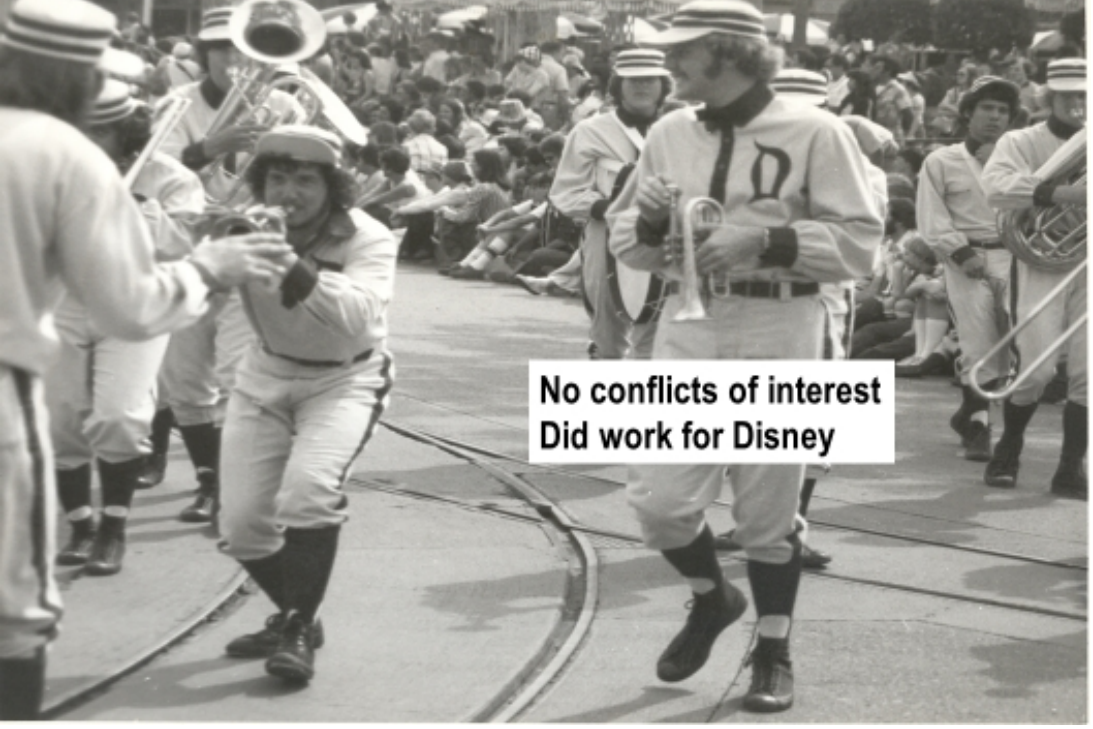
Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.


No conflicts of interest
Did work for Disney

Pre-Test Question

Which of one the following statements is correct?

A. The gastrointestinal tract is the most common site of anticoagulant related bleeding.
B. Intracerebral hemorrhage carries a low 30-day mortality rate ranging from 3.5% to 5.2% with most survivors expected to have full functional recovery.
C. Idarucizumab can be used to reverse rivaroxaban, apixaban, or edoxaban.
D. All of the above are correct.

Pre-Test Question

A 48 YO female taking Rivaroxaban 15mg twice daily (10 AM & 10PM) for DVT arrives unresponsive to your hospital at 12 Noon. Head CT which reveals intraventricular hemorrhage. What is the correct reversal agent and dose?

A. Vitamin K 10 mg subcutaneously
B. Andexanet bolus 400mg, then infusion 480 mg @ 4 mg/min
C. Andexanet bolus 800 mg, then infusion 960 mg @ 8 mg/min
D. Idarucizumab 2.5 grams IV push x 2 doses (total 5 grams)

Pre-Test Question

An 83 y.o. female (70 kg) falls. Her dabigatran, for atrial fibrillation, is reversed prior to hip fracture surgery. She is now post-op day 2. Her dabigatran can safely be restarted:

A. Now
B. In 7 days
C. In 1 month
D. In 3 months

Learning Objectives

- Given a patient case, evaluate current approaches and limitations to therapies used to reverse the effects of direct-acting oral anticoagulants.
- Given examples, describe the process of assessing, choosing, and implementing a reversal plan with follow-up and revisions.
- Develop a strategy for rapid reversal of a direct oral anticoagulant.

Outline

- Rates of bleeding associated with anticoagulant therapy
- Non-specific and specific reversal agents
- Professional guidelines and decision algorithms
- Patient selection
- Key takeaways

How Frequent is Bleeding?

Atrial fibrillation (AF):

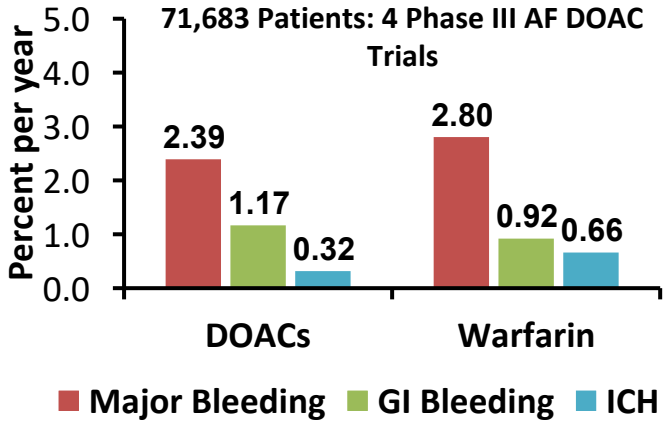
- DOACs reduced intracranial hemorrhage by 52%
- DOACs increased gastrointestinal (GI) bleeding by 25%
- Major bleeding was reduced by 14% but was not statistically different

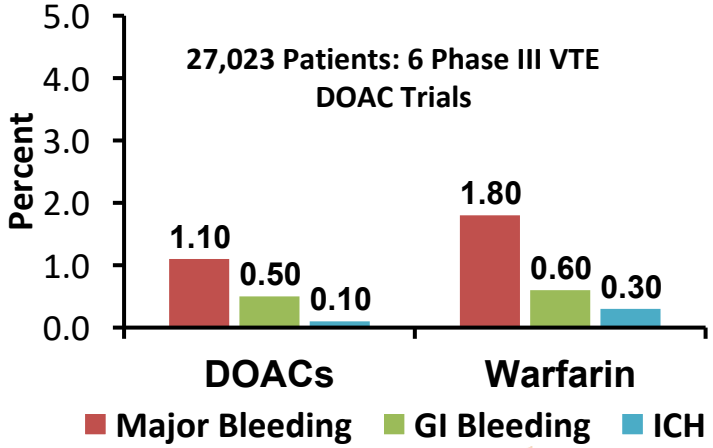
Acute venous thromboembolism (VTE):

- DOACs reduced Intracranial hemorrhage by 63%.
- DOACs reduced GI bleeding by 22% but it was not statistically significant.
- DOACs reduced major bleeding by 39%.

Anticoagulant therapy:

- Incurs a significant risk of bleeding but events are infrequent





Ruff CT, et al. *Lancet*. 2014.
Van Es N, et al. *Blood.* 2014.

Non-Specific Reversal Agents

Only After D/C drug and Supportive Care (fluids / transfusions)

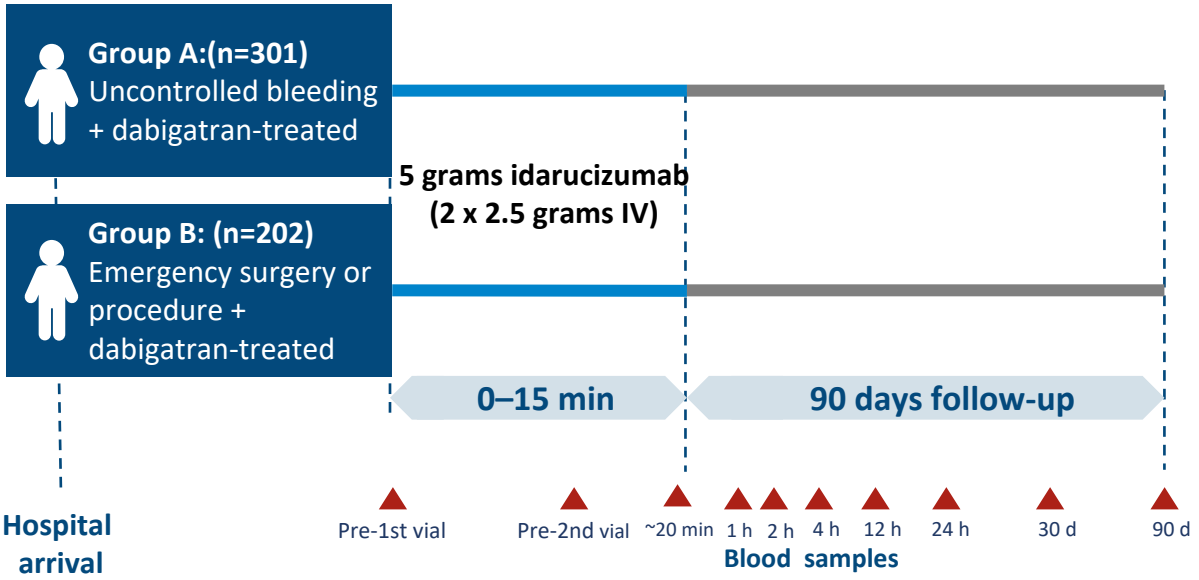
Agent	Clotting Factors Replaced
4 Factor-PCC	Factors II, VII, IX, X
3 Factor-PCC	Factors II, IX, X
aPCC	Factors II, VIIa, IX, X
rFVIIa	FVIIa

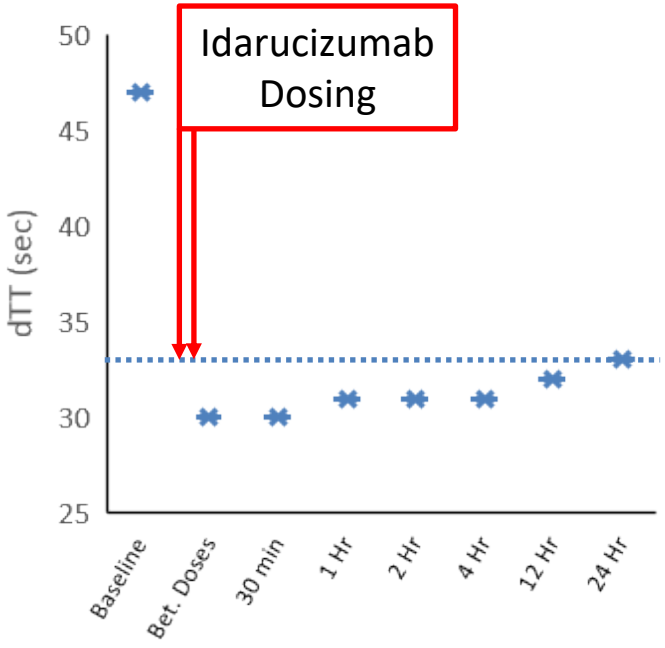
Heidbuchel H, et al. *Europace.*2015.

	Idaracizumab	Andexanet alfa
Alternate names	aDabi-Fab, B1655075	PRT064445
Chemical structure	Humanized monoclonal antibody fragment	Recombinant truncated human factor Xa variant (decoy)
Binding	Noncompetitive binding to dabigatran	Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor-activated antithrombin
Target affinity	=350x greater affinity for dabigatran than factor IIa	Affinity for direct factor Xa inhibitors
Onset	<5 min	2 min
Half-life	Initial: 47 min; Terminal 10.3 h	Terminal = 6 h
Elimination	Kidney (protein catabolism)	Not reported
Anticoagulant(s) reversed	Dabigatran	Direct and Indirect factor Xa inhibitors

Ruff CT, et al. *Circulation*. 2016 ; 134(3):248-261

RE-VERSE AD: Trial Design





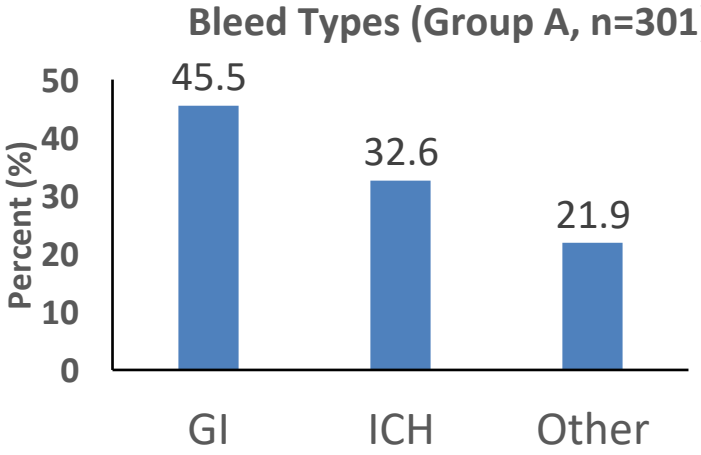
Primary endpoint: Maximum reversal within 4 h based on dTT, ECT

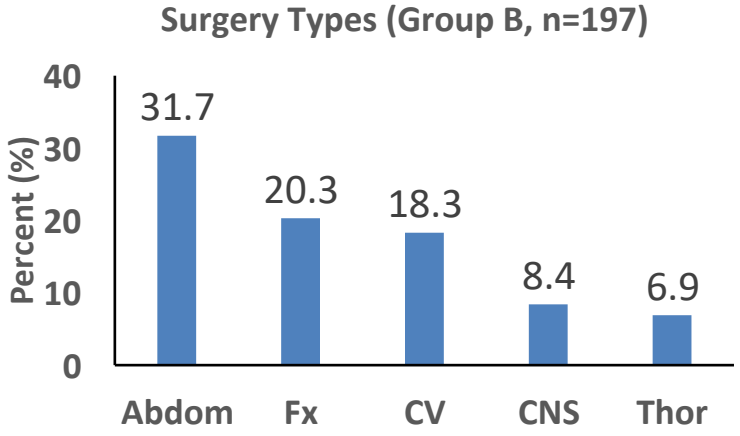
dTT, diluted thrombin time

Adapted from Pollack C, et al. *Thromb Haemost*. 2015.

Patient Demographics

Characteristic	Group A (n=301)	Group B (n=202)
Age (y)*	79 (24–96)	77 (21–96)
Male sex, n (%)	172 (57.1)	102 (50.5)
Creatinine clearance (mL/min)*	50.8 (6.1–216.9)	56.0 (7.9–198.7)
Comorbidities, n (%)		
Congestive Heart Failure	117 (38.9)	65 (32.2)
Prior Stroke	73 (24.3)	36 (17.8)
Dabigatran, n (%)		
Atrial fibrillation indication	288 (95.7)	190 (94.1)
150 mg BID	94 (31.2)	57 (28.2)
110 mg BID	185 (61.5)	126 (62.4)
Patient-reported time since last dose (hrs)	14.6 (1.5, 90.4)	18.0 (2.6, 105.8)
Elevated dTT at baseline, n (%)	244 (81.1)	152 (75.2)





88%=Major and Life-threatening bleeding, 38%=Hemodynamic instability

Pollack CV, et al. *N Engl J Med*. 2017.

Results

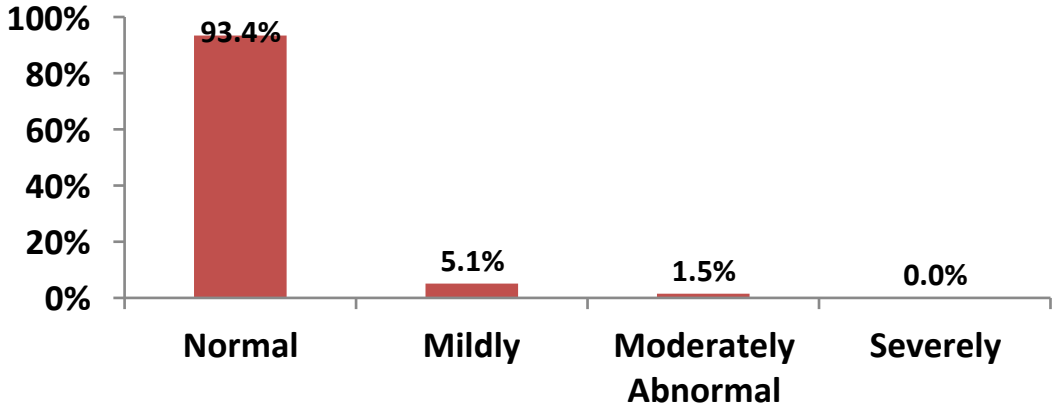
Group A

- dTT normalized within 4 hours in 98.8% (241/244) patients.
- Study did not mandate repeat scanning of ICH events.
- Non-ICH bleeding assessed in 203 patients:
  - Time to Locally Reported Hemostasis (Bleeding Cessation) 2.5 (2.2 – 3.9) hours (median, 95% CI).

Group B

- 197 of 202 (97.5%) patients underwent surgery/procedures
- dTT normalized within 4 hours in 98.7% (150/152).
- Adequacy of hemostasis during surgery determined locally (below)

Peri-Procedural Hemostasis in 197 Patients



Pollack CV, et al. *N Engl J Med*. 2017.

Results

Thrombotic events

Events n (%)	Group A (n=301)	Group B (n=202)	Total (n=503)
30 days	14 (4.6)	10 (5.0)	24 (4.8)
90 days	19 (6.3)	15 (7.4)	34 (6.8)

- At 72 hours, 22.9% of Group A and 66.8% of Group B had re-started anticoagulation or antiplatelet therapy
- By 90 days antithrombotic therapy had been re-started in 72.8% of Group A and 90.1% of Group B patients
- Patients restarted on dabigatran:
  28.9% in Group A (median time 16 days)
  61.4% in Group B (median time 6 days)

Mortality

	Group A (n=301)	Group B (n=202)
5 days	6.4%	7.9%
30 Days	13.5%	12.6%
90 days	18.8%	18.9%

- With 5 days of idarucizumab treatment 19 deaths occurred in Group A (6.3%) and 16 deaths had occurred in Group B 7.9%)

RE-VECTO: Idarucizumab surveillance program

Methods:

- Patients ≥18 years of age treated with idarucizumab

Results:

- 359 patients (75%, >70 years of age) at 63 hospitals from 12 countries across Asia Pacific (14%), Europe (42%), and North America (44%).

Indications:

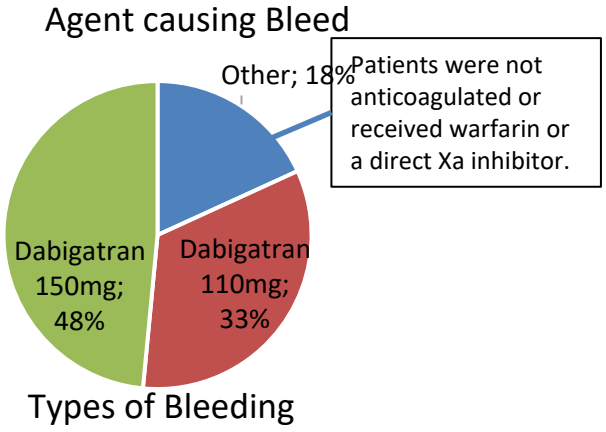
- Bleeding (58%), Emergency surgery/procedure (36%), Planned surgery/procedure (3%).

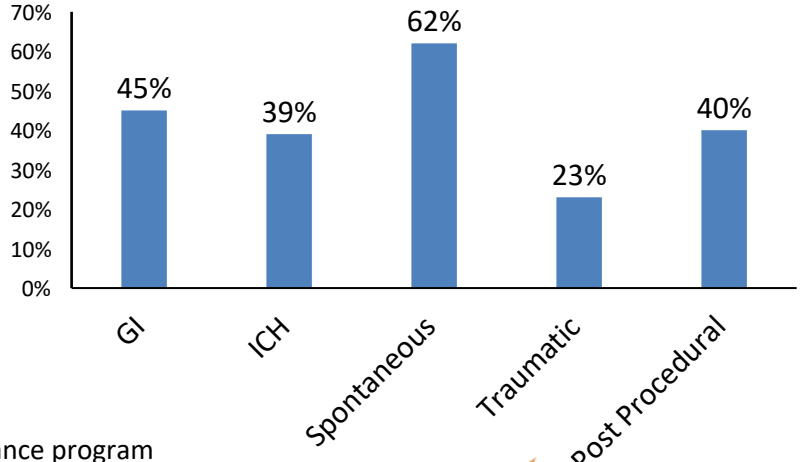
Dosing:

- Patients received 5 g (2 vials, 95%)

Conclusions:

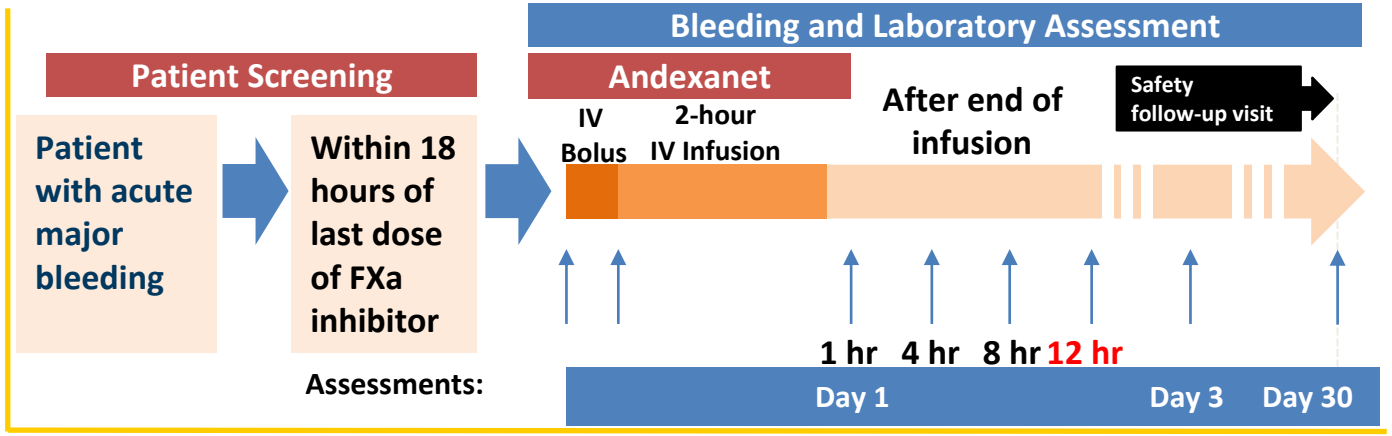
- No new side effects or toxicities reported.
- Off-label use and second-dose use were low.





Abstract, number 48153, titled "RE-VECTO: Idarucizumab drug administration surveillance program results", 2018 ACCP Global Conference on Clinical Pharmacy, Seattle, Washington.

ANNEXA-4 Study Design



Efficacy Outcomes

- Change in anti-fXa activity
- Clinical hemostatic efficacy through 12 hours

Safety Measurements

- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day mortality

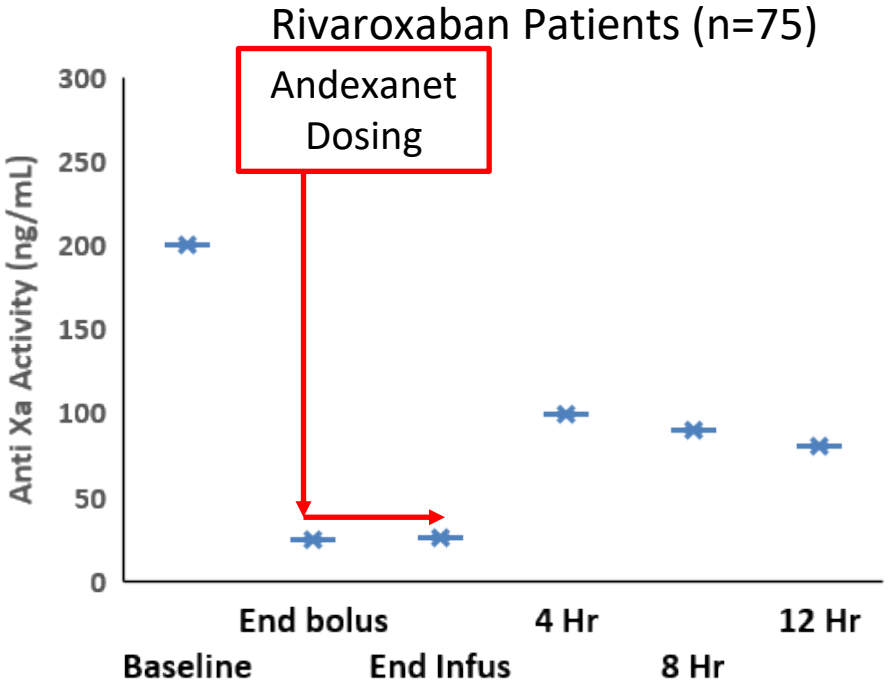
Connolly, S. ANNEXA-4 presented at American College of Cardiology Meeting, Orlando, FL March 17, 2018. Available at: https://www.acc.org/latest-in-cardiology/articles/2018/03/07/15/53/mon-1045am-annexa-4-andexanet-for-reversal-of-anticoagulation-in-factor-xa-acc-2018

ANNEXA-4 Dose Selection

Acute major bleeding ≤ 18 hours of last dose of apixaban, edoxaban, rivaroxaban, or enoxaparin

Andexanet IV bolus + 2 hour infusion

Apixaban or >7 h from last rivaroxaban dose	Enoxaparin, edoxaban or ≤7 h from last rivaroxaban dose
Bolus 400 mg + Infusion 480 mg @ 4 mg/min	**Bolus 800 mg + Infusion 960 mg @ 8 mg/min**



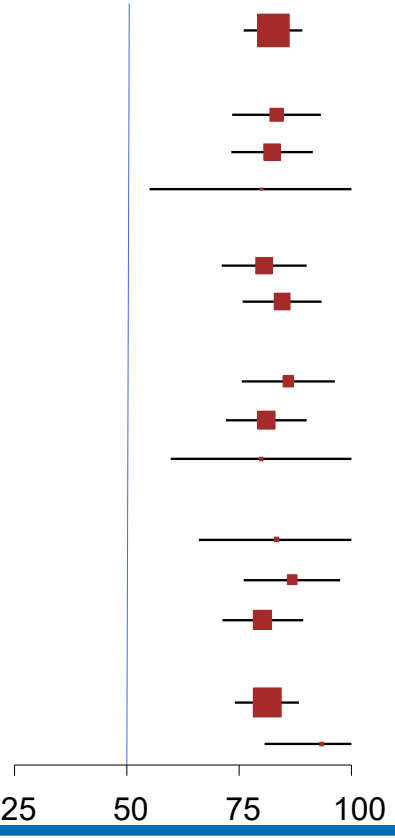
Baseline Characteristics

	Population N=227
Age (yr), mean ± SD	77(±11)
Time from presentation until Andexanet (hrs)	4.7 ± 2.8
Estimated creatinine clearance < 30 mL/min,	21 (9%)
Indication for anticoagulation	
Atrial fibrillation	178 (78%)
Venous Thromboembolic Disease	52 (23%)
Atrial fibrillation and VTE	8 (4%)
Medical History	
Myocardial infarction	32 (14%)
Stroke	47 (21%)
Heart Failure	52 (23%)

	Population N=227
Intracranial Bleeding	**139 (61%)**
Intracerebral site	74 (52%)
Sub-dural site	45 (32%)
Subarachnoid site	23 (16%)
Gastrointestinal Bleeding	**62 (27%)**
Other Bleeding site	**26 (12%)**

Clinical Hemostatic Efficacy

Subgroup	No. of Patients	Excellent or Good (95% CI)
Total Efficacy Patients	132	83 (76- 89)
Drug		
Rivaroxaban	54	83 (73- 93)
Apixaban	68	82 (73- 91)
Enoxaparin	10	80 (55-100)
Sex		
Male	67	81 (71- 90)
Female	65	85 (76- 93)
Site of bleeding		
Gastrointestinal	43	86 (76- 96)
Intracranial	74	81 (72- 90)
Other	15	80 (60-100)
Age		
<65 yr	18	83 (66-100)
65-75 yr	38	87 (76- 98)
>75 yr	76	80 (71- 89)
Andexanet dose		
Low	117	81 (74- 88)
High	15	93 (81-100)

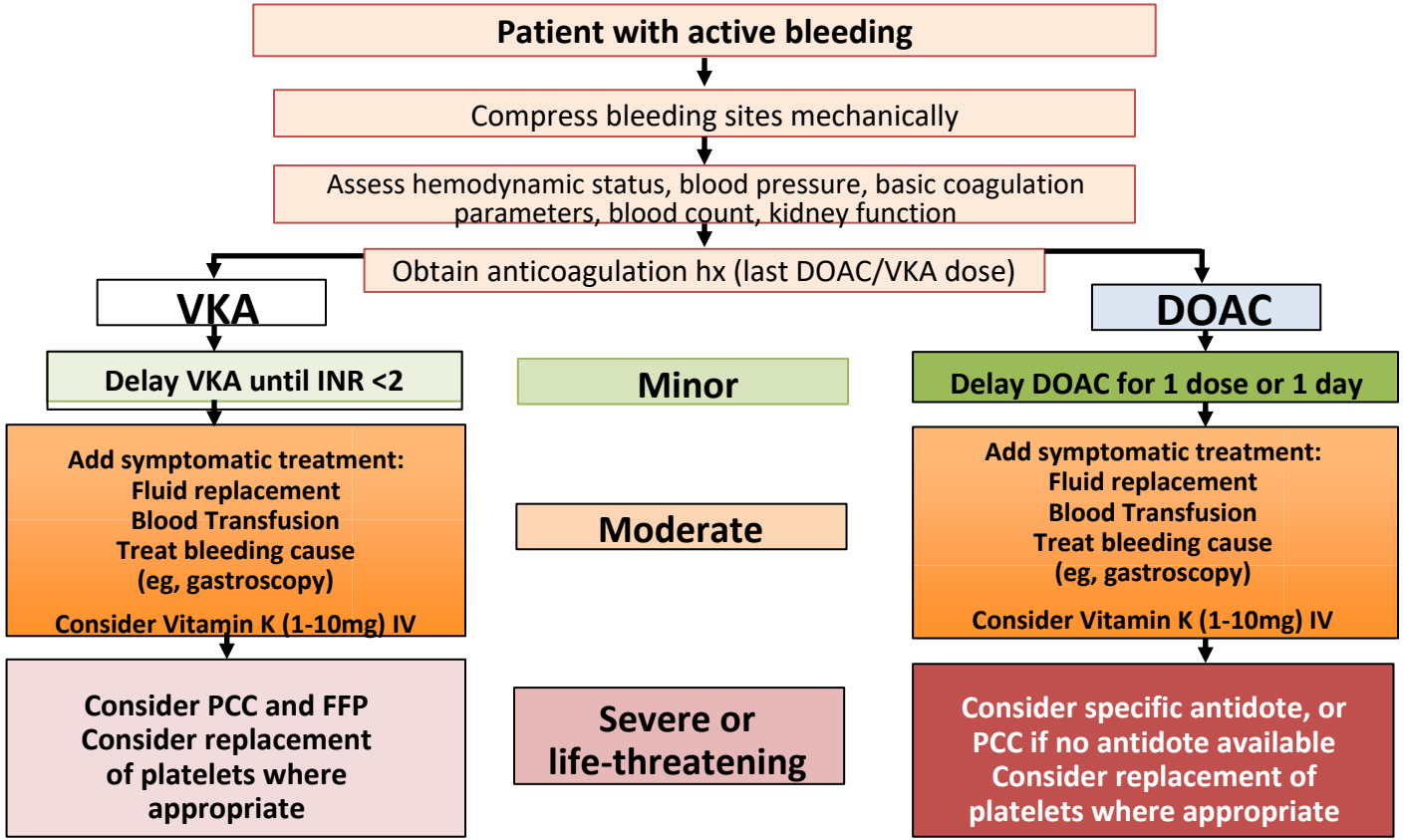


Efficacy and Safety Assessment

Number of Major Bleeds Adjudicated	No. Patients who Achieved Excellent or Good Hemostasis	% of Patients who Achieved Excellent or Good Hemostasis	95% Confidence Interval
132	109	83%	76% - 89%

- Thrombotic events occurred within 3 days of andexanet in 6 (2.6%) patients and by 30 days in 24 (11%)
- Anticoagulation re-started in 129 patients (57%) by 30 days
- Therapeutic anticoagulation was re-started in only 9 patients before a thrombotic event occurred
- 27 deaths occurred by 30 days (12%), of which 11 were cardiovascular

Anticoagulation Bleeding Algorithm



Kirchhof P, et al. *Eur Heart J*. 2016.

VKA = vitamin K antagonist

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Building a DOAC Reversal Management Plan — What Do I Need to Know

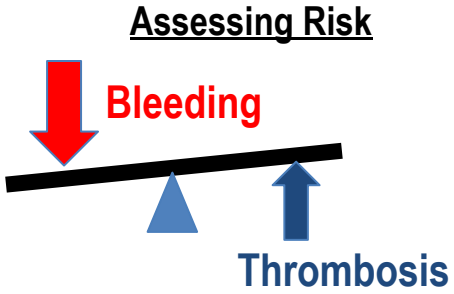
William Dager, Pharm.D., BCPS-AQ Cardiology

A Physician wants to reverse the effects of a DOAC in a patient:

- **Intervention: What is my role?**
- **Assess the situation**
  - Medication History
  - Goals
- **What do I have available to me?**
- **Situation and Setting Dependent**
- **How fast can lab or imaging results be available?**

Assess the Situation and Potential Risks

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



CASE-WB

History of Present Illness:

- 81yo M (112kg) s/p fall from standing at approximately 3 PM today.
- Rivaroxaban 20mg QAM for AF this AM.
- Head strike on a wooden cabinet, denies LOC, laid on the ground for 5 hours
- Taken to an OSH, where CTH showed R SAH and C5-6 jumped facets.
- Transferred for further care.
- He denies headache, nausea, emesis, or lethargy.
- His RUE is subjectively weak.

Physical Examination:

Temperature: 97.2 °F
Heart Rate: 69 [68-69]
Respiratory Rate: 18
BP: 116/56(108-139)/(56-67)
O2 Sat: 96 % [92 %-96 %]
General - NAD. Oriented x 3.

Plan:

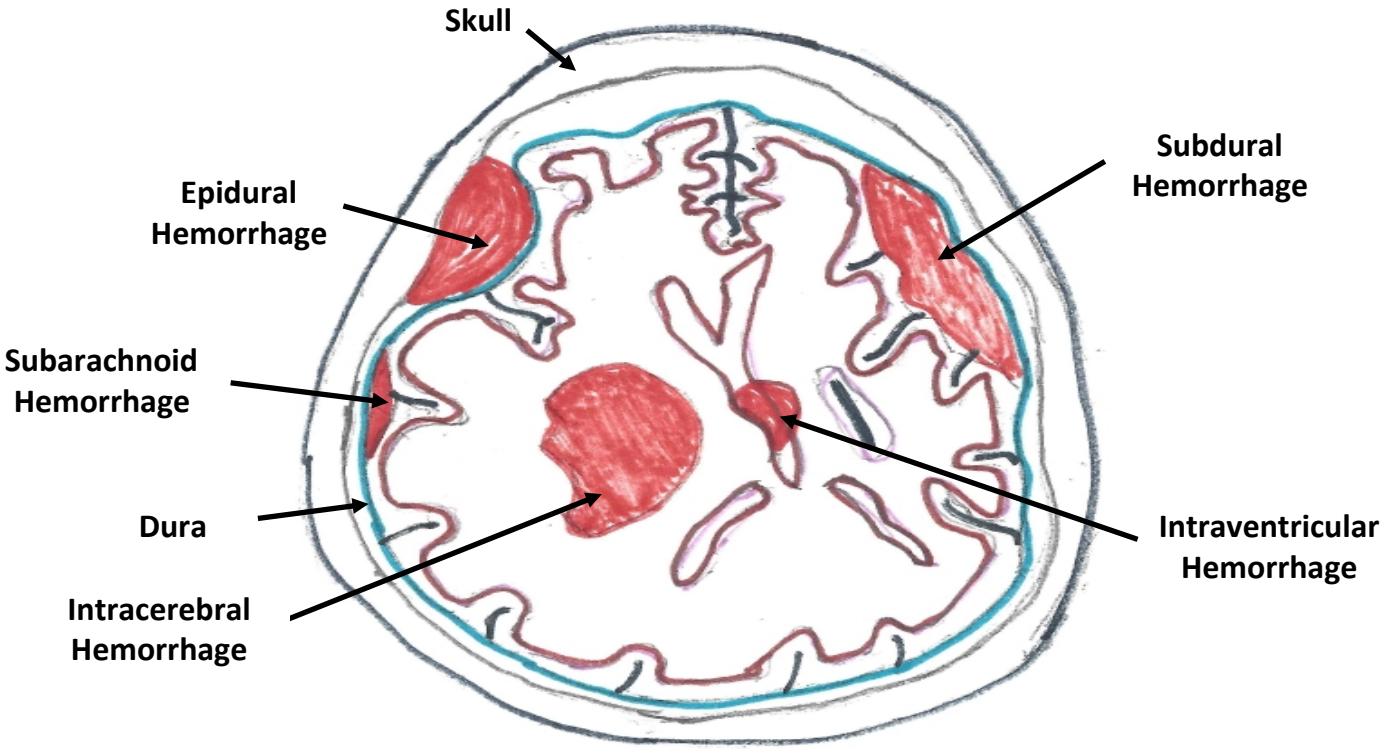
Orthopedic Surgery plans to take him emergently to OR for C5-6 facets for incomplete spinal cord injury.

Audience Response Questions

- Is WB a candidate for anticoagulation reversal?

1. Yes
2. No

ICH: Types


Skull
Epidural Hemorrhage
Subdural Hemorrhage
Subarachnoid Hemorrhage
Dura
Intracerebral Hemorrhage
Intraventricular Hemorrhage

Audience Response Questions

- It is now 11 PM.
- Is laboratory assessment warranted ?

1. Yes
2. No

Laboratory Assessments

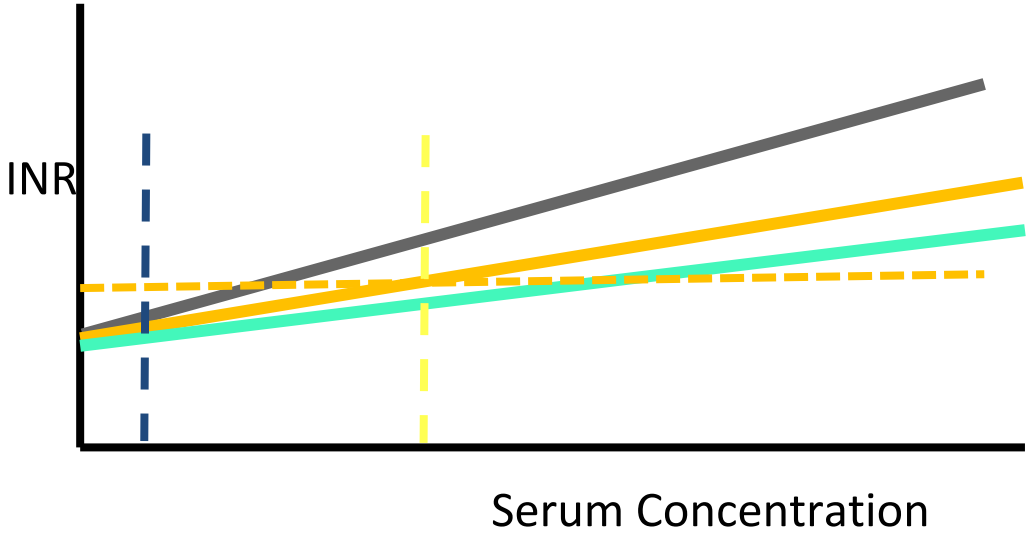
- Timing/Priority
- Reflect the situation
- Correct Assay
  - Anticoagulant Specificity
  - Limitations
  - Bleeding Assessment
- Value ≠ Clinical presentation → Repeat test

Assessing intensity of Oral anticoagulation effects

	Dabigatran	Rivaroxaban/Apixaban/Edoxaban
Drug Present	Thrombin Time	? Chromogenic anti-Factor Xa (Calibrated to the drug versus UFH or LMWH)
Quantative Test	? Dilute thrombin time (dTT) or Chromogenic ECT	Chromogenic anti-factor Xa
Sensitivity: PT vs aPTT (Reagent Dependent)	aPTT > PT (Point-of-Care INR > Central Lab)	PT > aPTT
No/Limited effect	anti-factor Xa activity	ECT, TT

Lindhoff-Last E Ther Drug Monit 2010; Lindahl TL Thromb Haemost 2011; van Ryn Am J Med 2012; van Ryn Thromb Haemost 2010

Potential INR response with higher DOAC serum concentrations




Direct Oral Anticoagulants (DOACs)
Complete Testing Range for Measurement in Plasma, when Needed
Excellent correlation with reference method
XII
XI
PK
HMWK
VIII:C
IXa
TF
VIIa
Va
Xa
Direct Thrombin Inhibitors
Direct Factor Xa Inhibitors
Thrombin
Fibrinogen and Clot


DOAC

Audience Response Questions

Which coagulation test would you recommend?

1. PT
2. INR
3. aPTT
4. Anti-Xa activity
5. All of the above

Lab Tests (12 Midnite)

	Reference Range	Units
SODIUM	136 - 145 mmol/L	140
POTASSIUM	3.4 - 5.0 mmol/L	4.1
CHLORIDE	98 - 107 mmol/L	100
CO2	22 - 31 mmol/L	23
BUN	6 - 23 mg/dL	27 (H)
CREATININE	0.50 - 1.20 mg/dL	1.09
GLUCOSE	70 - 100 mg/dL	199 (H)
ALBUMIN	3.5 - 5.2 g/dL	4.0
CALCIUM	8.8 - 10.7 mg/dL	9.6
ALK Phos	35 - 130 U/L	44
EGFR	>59 mL/min/1.73m2	63
PT	**11.5 - 14.5 sec**	**17.1 (H)**
INR	**0.9 - 1.1**	**1.4 (H)**

	Reference Range	Units
WBC	4.00 - 10.00 K/uL	12.56 (H)
RBC	4.50 - 6.40 M/uL	4.62
HGB	13.5 - 18.0 g/dL	14.0
HCT	40.0 - 54.0 %	40.4
PLT	150 - 450 K/uL	170
MCV	80.0 - 95.0 fL	87.4
MCH	27.0 - 32.0 pg	30.3
MCHC	32.0 - 36.0 g/dL	34.7
RDW	11.5 - 14.5 %	14.6 (H)
MPV	8.4 - 12.0 fl	9.9

Audience Response Questions

- Is laboratory testing warranted after surgery?

1. Yes
2. No

Hospital Course

1 AM

- Coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA) injection 400 mg Intravenous-Once @ 160 mL/hour over 15 minutes.
- Coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA) injection 480 mg Intravenous-Once @ 24 mL/hour over 120 Minutes.

2 AM-Taken to the OR and underwent general endotracheal anesthesia.

- C5-6 laminectomy and C3-T2 fusion
- The patient was extubated and transferred in stable condition to the surgical ICU at 6AM.

8 AM

- Labs

	Reference Range	Units
PT	11.5 - 14.5 sec	17.1 (H)
INR	0.9 - 1.1	1.4 (H)
APTT	23.8 - 36.6 sec	31.0

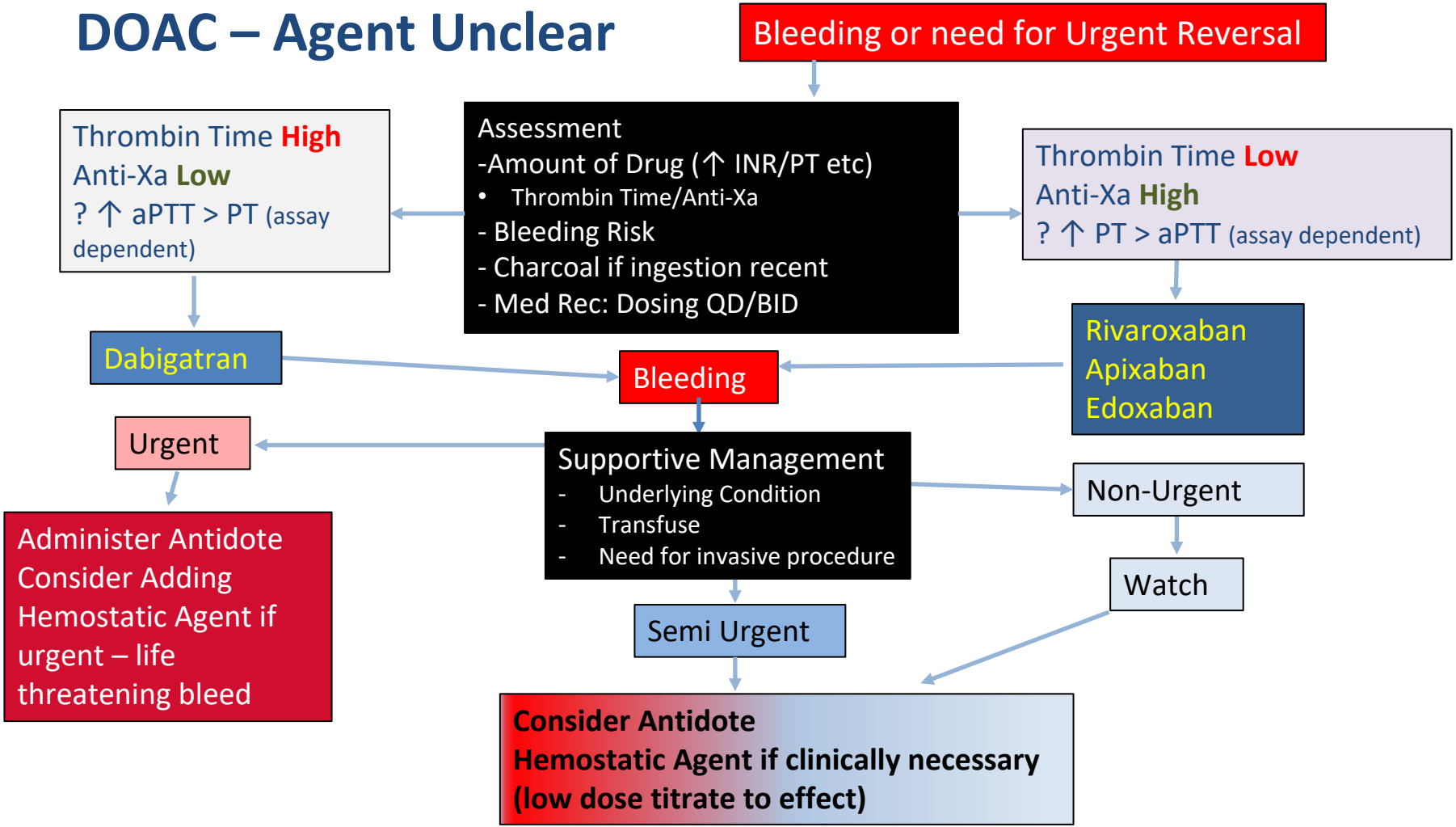
Follow-up

- SICU course was uncomplicated, never requiring intubation.
- Rivaroxban held.
- Enoxaparin 30 mg BID for VTE prophylaxis.

Anticoagulant “Reversal” Strategy

- Depends on:
  - Setting (ED, OR, ICU, Cardiac Cath Lab)
  - Urgency
- Hold Anticoagulation
- Mechanical Intervention (Surgery)
- Pharmacological intervention
  - Topical Agents
  - Neutralize the drug – Need to last the duration necessary
  - Reverse the effects of the drug independently
- Replace losses
- Optimize management of co-morbid situations

DOAC – Agent Unclear



Reversing Newer Oral Anticoagulants: Bleeding Patients

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 5gm • Consider PCC4 (25 units/kg) or low dose factor VIII inhibitor bypassing activity (aPCC)	• Andexanet • 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)	• Andexanet • aPCC 12 - 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

CASE-Unidentified Male

History of Present Illness:

- 67yo M (101 kg) with unknown medical history, transferred from OSH for ICH.
- Last seen at 9 AM on park bench
- Medical bracelet staes “Blood thinner”.
- OSH’s CT showed ICH.
- Given Kcentra 1500 units, Mannitol, Vitamin K 10 mg SC before transfer.
- Patient arrives here minimally responsive hypertensive and not verbally answering questions.

Physical Examination:

Temperature: 99.0 °F
Heart Rate: 69 [68-69]
Respiratory Rate: 30
BP: 158/92(108-139)/(56-67)
O2 Sat: 96 % [92 %-96 %].

Repeat Imaging:

Large left intraparenchymal hemorrhage involving the left MCA territory.
There is associated severe mass effect with subfalcine and uncal herniation with mild coning in the foramen magnum.

Audience Response Questions

- Is the unknown male a candidate for anticoagulation reversal?

1. Yes
2. No

Lab Tests (12 Noon)

	Reference Range	Units
SODIUM	136 - 145 mmol/L	136
POTASSIUM	3.4 - 5.0 mmol/L	4.1
CHLORIDE	98 - 107 mmol/L	93
CO2	22 - 31 mmol/L	31
BUN	6 - 23 mg/dL	13
CREATININE	0.50 - 1.20 mg/dL	1.09
GLUCOSE	70 - 100 mg/dL	**197 (H)**
ALBUMIN	3.5 - 5.2 g/dL	3.5
CALCIUM	8.8 - 10.7 mg/dL	8.6
ALK Phos	35 - 130 U/L	75
EGFR	>59 mL/min/1.73m2	97
PT	11.5 - 14.5 sec	**19.0 (H)**
INR	0.9 - 1.1	**1.6 (H)**
aPTT	23.9-36.6 sec	**38.3 (H)**
Anti-Xa	undetectable	**2.94 (H)**

	Reference Range	Units
WBC	4.00 - 10.00 K/uL	**11.64 (H)**
RBC	4.50 - 6.40 M/uL	4.21*
HGB	13.5 - 18.0 g/dL	11.9
HCT	40.0 - 54.0 %	36.3*
PLT	150 - 450 K/uL	258
MCV	80.0 - 95.0 fL	86.2
MCH	27.0 - 32.0 pg	28.3
MCHC	32.0 - 36.0 g/dL	32.8
RDW	11.5 - 14.5 %	12.7
MPV	8.4 - 12.0 fl	9.1

Hospital Course

3 PM

- In the ED patient has acute worsening of mental status, requiring emergent intubation.
- Arterial line was placed for blood pressure monitoring, boluses of labetalol were given with reduction in blood pressure, and a nicardipine IV started for blood pressure optimization.
- Discussions with Neurology and Hematology ensue.
- Hematology's recommendation to administer andexanet for immediate anticoagulation reversal (last dose greater than 12 hour ago). Order written by Neurology resident.

4 PM

- Coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA) injection 400 mg Intravenous-Once @ 160 mL/hour over 15 minutes.
- Coagulation factor Xa (recombinant), inactivated-zhzo (ANDEXXA) injection 480 mg Intravenous-Once @ 24 mL/hour over 120 Minutes.

9 PM

- Labs

	Reference Range	Units
PT	11.5 - 14.5 sec	15.7 (H)
INR	0.9 - 1.1	1.3 (H)
APTT	23.8 - 36.6 sec	31.3

Follow-up

- Admitted to the MICU.
- Enoxaparin 30 mg BID for VTE prophylaxis.
- Nicardipine for blood pressure control
- Propofol for sedation.

Idarcuizumab – Dabigatran Reversal

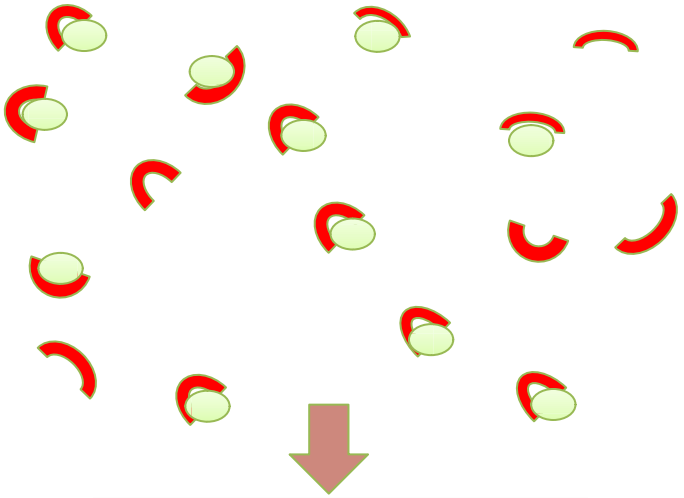
Humanized Fab fragment specific to dabigatran

- **Affinity: Dabigatran 350 times > Thrombin**
- **No evidence of prothrombotic effect**
- **Rapid onset and dose dependent effect**
  - **Sustained > 24 hours with dose > 2 gm**
  - **2.5gm Vial – 2 vials = 5gm dose**
- **aPTT, TT and ECT normalized**

Van Ryn J Circulation 2012;126; Schele F et al. Blood 2013;121:3554-62; Clinical Trials.gov

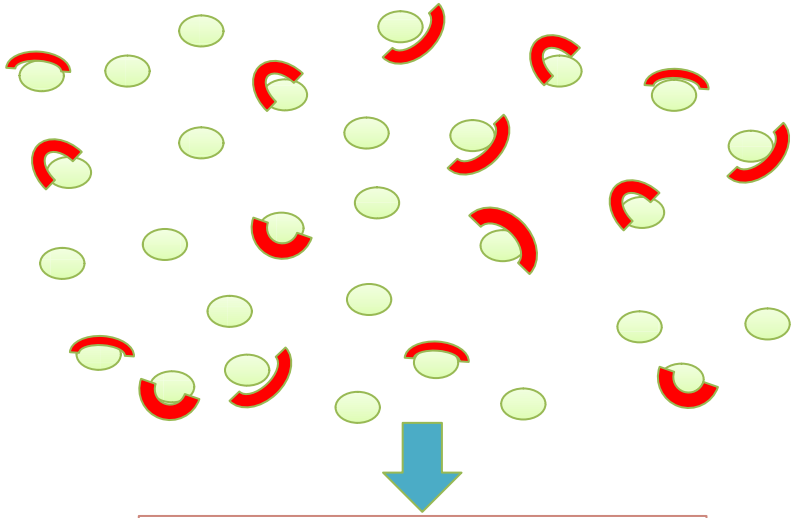
Antibody Maximal Effect

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

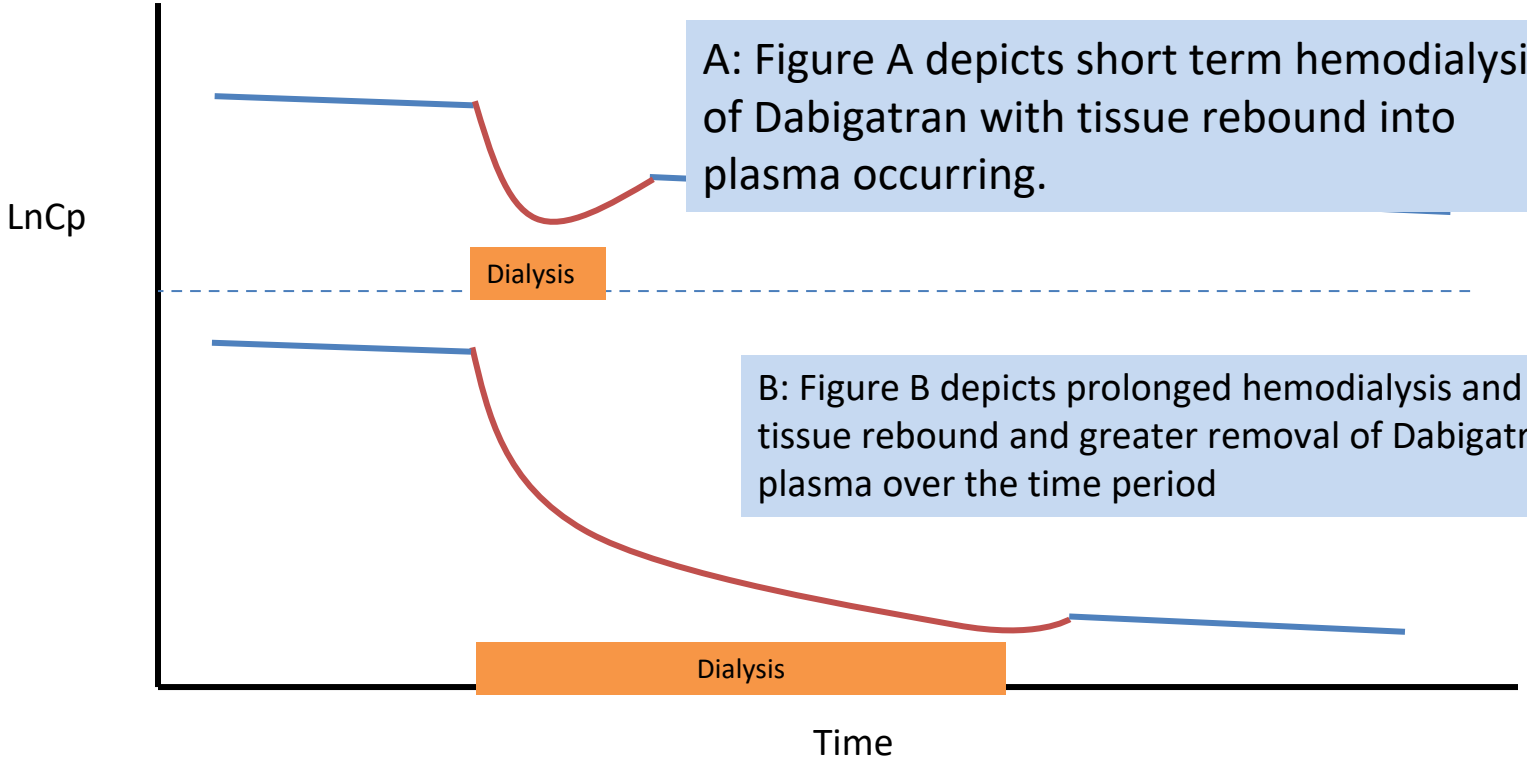
Idarucizumab and excessive Dabigatran levels

2 cases – high dabigatran levels (1480ng/ml and 2260 ng/ml)

- Both had AKI (Scr increased baseline to 1.98 and 2.08)
- INR values were > 13
- 5gm Idarucizumab reversed ~ 700 - 800ng/ml Dabigatran
- FEIBA ~20 units/kg given both cases
- One pt had CRRT initiated – unclear if CRRT removed the bound up Dabigatran as their was no means to measure this.

Ref: Steele AP, Lee JA, Dager WE: Clin Tox 2018;56:216-18

Hemodialysis of Dabigatran



A: Figure A depicts short term hemodialysis of Dabigatran with tissue rebound into plasma occurring.

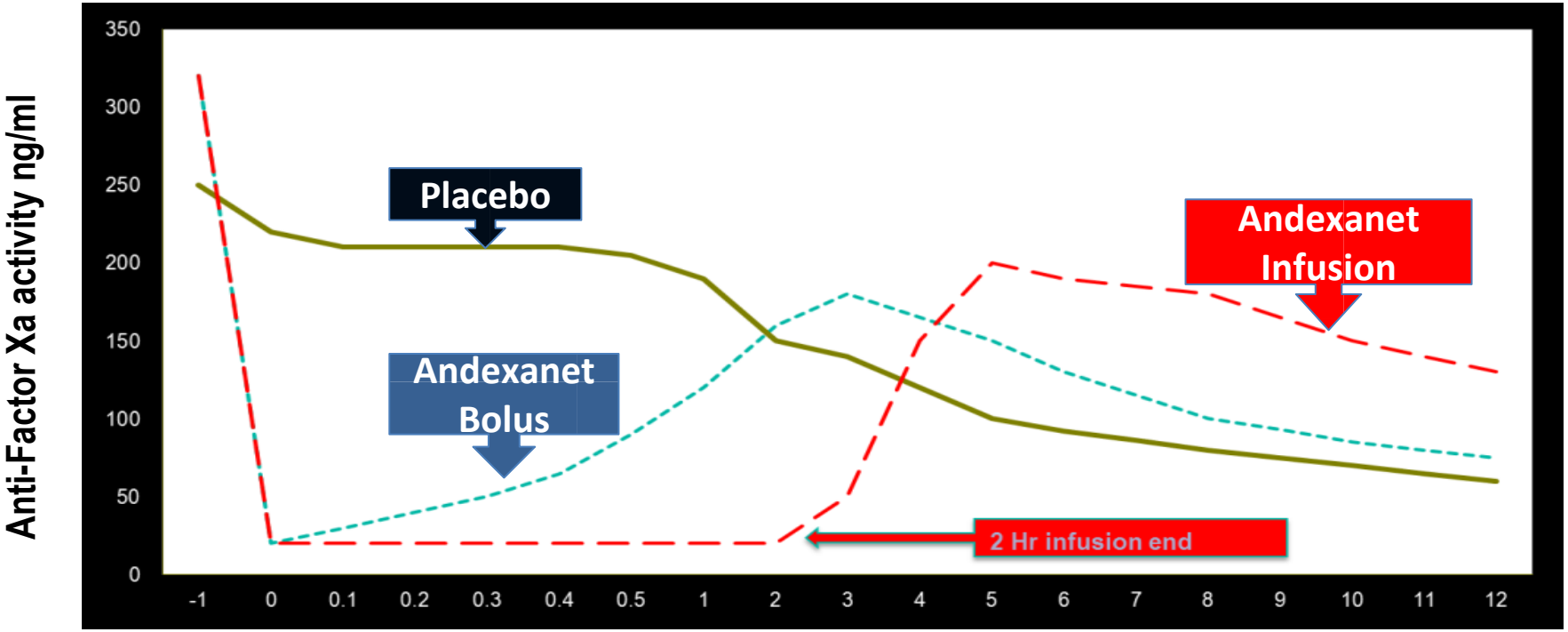
B: Figure B depicts prolonged hemodialysis and reduced tissue rebound and greater removal of Dabigatran from the plasma over the time period

Reversing oral anti-Xa Anticoagulants

Plasmapheresis	**Limited information, with apixaban being removed.**
Antidote	**Andexanet Alfa**
Concentrated clotting factors	**The agent and dose to reverse the effects of oral anti-Xa agents: Not established.** • **Minor bleeding: monitor and recheck laboratory results.** • **Major bleeding: PCC or aPCC.** • **Unclear if any differences between nonactivated and activated PCC.** • **Less urgent bleeding → treatment can begin with a low-dose (8-12 U/kg IV strategy).** • **Semi-urgent bleeding: PCC/aPCC up to 25 U/kg IV. If time allows, treatment can begin with a lower dose approach, with additional doses based on clinical assessment.** • **Emergent life-threatening bleed: PCC/aPCC 25-50 IV U/kg.**

Dose	Initial IV Bolus	Follow-On IV Infusion
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minute
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

Andexanet: Reversing Oral Anti-Xa agents



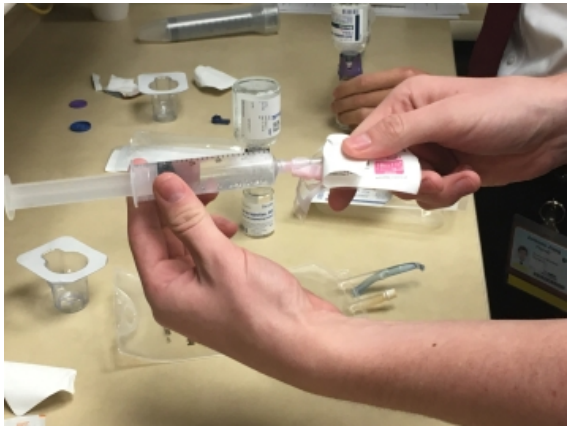
Siegal DM et al. *N Engl J Med*. 2015; 373: 2413-24.

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
- Rapid availability to patient; adaptable order sets
- Ability to measure/assess when the antidote can be stopped
- Prolonged infusion until bleeding stops as anticoagulant effects may be sustained for days
- Neutralization of other anticoagulants that may be necessary for a emergent therapy (e.g. ECLS or cardiopulmonary bypass)
- Availability, especially if the cost is high; Storage

Use of PCC or aPCC with DOACS: Bleeding

- No randomized comparisons to Antidote's
- 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.
- Any advantage with aPCC over PCC with Anti-Factor Xa agents unclear
- Thrombosis has been reported - ? If indcience higher
- Mortality Rates Vary
- Neurocritical Care Society Guidelines: Rec 50 units/kg PCC or aPCC in ICH
  - Dabigatran: If no Idarucizumab given
  - Some success in case reports



Study	Mortality	VTE
ANEXXA-4 (Safety Population) (n=67)	15%	18%
Majeed et al (n=84) – 4 Factor PCC	32%	6%
Schulman et al (n=66) – 4 Factor PCC	14%	8%

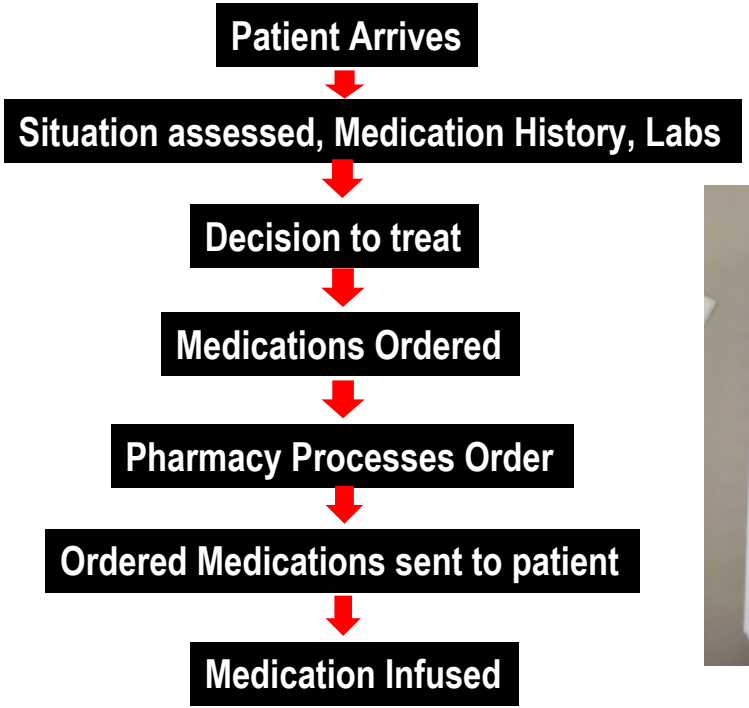
Frontera JA Et al Neurocrit Care 2015; Majeed A, Blood 2017; Shulman S Thromb Haemost 2018; Connelly SJ N Engl J Med 2016; 375:1131–41.

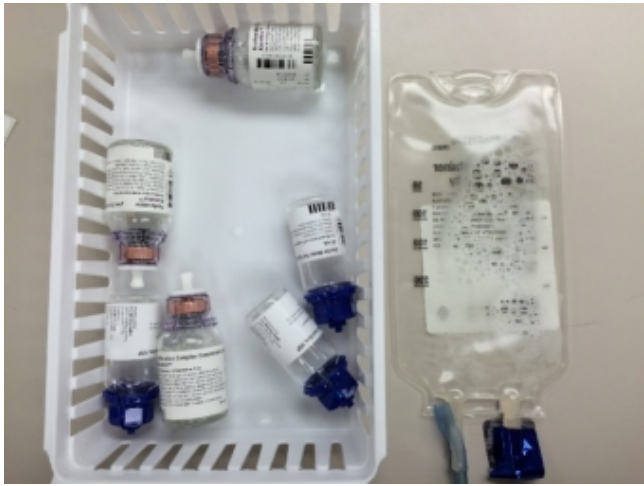
Key Considerations

- Being in the know: Assessing Urgency once on your radar
  - Bleeding Severity
  - Other management modalities
  - Who are the players
  - What is my role – and seeing it through
- Operating Room
- Labs ordered (baseline and follow-up assessments)
- Seeing it through – (Bedside assessments)
- Duration of reversal effect understood
  - Therapy in place
  - Avoid interruption with short acting agents

Getting Drug to the patient

- Labs
- Orders
- Antidote
- PCC/aPCC
- Dialysis
- Blood
- Surgery





Restarting Anticoagulation

Assessment of Thrombosis vs Bleeding
↑ Thrombosis Risk: Surgery, PCC, Acutely Ill
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.

Be Prepared

- Pre thought out process in place --- Avoid Delays
- Order set(s) developed
- Key services on board (Medical, Lab, Nursing)
- Who is involved in each step

  Initial Presentation → Process Completed
- Key services on board (Medical, Lab, Nursing)

- Follow up for long term considerations
  - VTE Prophylaxis
  - Re-establishing Anticoagulation

KEY TAKEAWAYS

1) **KEY TAKEAWAY**
   Reversal agents for direct acting oral anticoagulants are available for use.

2) **KEY TAKEAWAY**
   Careful patient assessment and goals of treatment are key

3) **KEY TAKEAWAY**
   Reversal agents have unique characteristics and may require support with blood products or dialysis