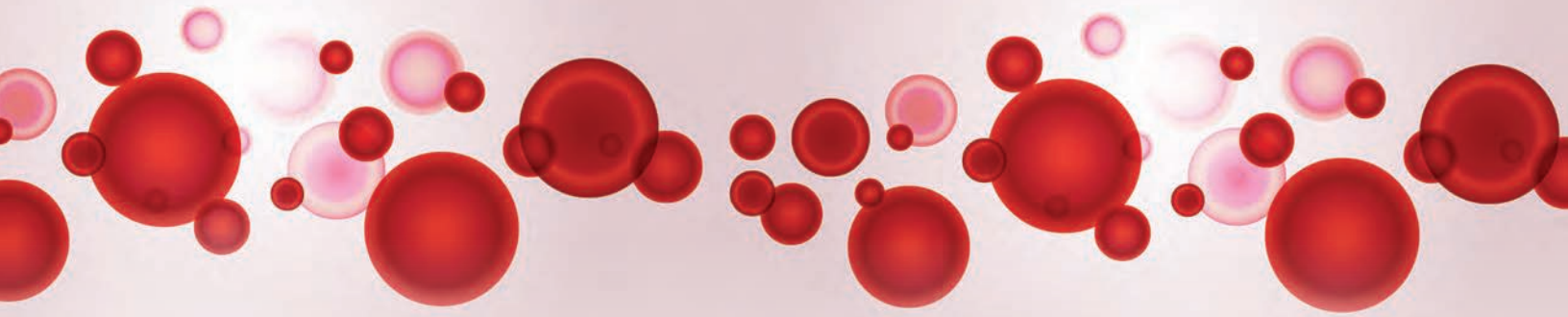
New Approaches for Reversing Oral Factor Xa Inhibitors

EXAMINING THE EVIDENCE



A Midday Symposium and Live Webinar conducted at the 2018 ASHP Midyear Clinical Meeting and Exhibition

Monday, December 3, 2018
11:30 a.m. – 1:00 p.m. PT
Room 252, 200 Level, ACC North
Anaheim Convention Center
Anaheim, California

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AGENDA

11:30 a.m. – 11:35 a.m.

Welcome and Introductions

William E. Dager, Pharm.D., BCPS (AQ-Cardiology), FASHP, FCCM, FCCP, FCSHP, MCCM

11:35 a.m. – 11:50 a.m.

Direct-acting Oral Factor Xa Inhibitors: Current Reversal and Treatment Strategies for DOAC-related Bleeding

William E. Dager, Pharm.D., BCPS (AQ-Cardiology), FASHP, FCCM, FCCP, FCSHP, MCCM

11:50 a.m. – 12:15 p.m.

Overview of Key Clinical Trials: Reviewing the Evidence on Reversal of DOACs

Mark Cipolle, M.D., Ph.D., FACS, FCCM

12:15 p.m. – 12:40 p.m.

Clinical Considerations in Reversal of DOACs: Focus on Wise and Correct Use

Jessica Rimsans, Pharm.D., BCPS

12:40 p.m. – 1:00 p.m.

Faculty Discussion, Frequently Asked Questions

New Approaches for Reversing Oral Factor Xa Inhibitors: Examining the Evidence

William E. Dager, Pharm.D., BCPS (AQ-Cardiology), FASHP, FCCM, FCCP, FCSHP, MCCM, *Activity Chair*

Mark Cipolle, M.D., Ph.D., FACS, FCCM

Jessica Rimsans, Pharm.D., BCPS

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Disclosures

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- In this activity, no persons associated with this activity have disclosed any relevant financial relationships.

Please be advised that this activity is being audio and/or video recorded for archival purposes and, in some cases, for repurposing of the content for enduring materials.

Learning Objectives

- Review currently available agents for reversing direct-acting oral anticoagulants (DOACs).
- Explain the risk factors for bleeding complications with DOACs as well as strategies for minimizing them.
- Review current and emerging data for the treatment of bleeding in patients on DOAC therapy.
- Illustrate using patient cases clinical situations for which reversal of DOAC therapy is warranted, including how it may be implemented.

Current Reversal and Treatment Strategies for Anti-Xa DOAC-Related Bleeding

William E Dager, Pharm.D., BCPS (AQ Cardiology),
FASHP, FCCM, FCCP, FCSHP, MCCM
Pharmacist Specialist – UC Davis Medical Center
Sacramento, California

Oral Anti-Xa Anticoagulants

	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Prodrug	No	No	No	No
Bioavailability	> 80%	> 50%	62%	34%
Time to peak Cp	3 hr (Delayed by food)	3 hr	1.5 hr	3-4 hr
Half-life	5-9 hr (Elderly 11-13hr)	9-14 hr	8-10 hr	19-27 hr
Dosing frequency	Once daily	Twice daily	Once daily	Once daily
Renal excretion	36%	25%	35%	5-7%
Drug interactions	CYP 3A4 or P-gp modifiers	CYP 3A4 or P-gp modifiers	P-gp modifiers	P-gp modifiers

CYP - cytochrome P450; P-gp - P glycoprotein; hr – hours; Cp = peak plasma concentration

Gross PL et al. *Arterioscler Thromb Vasc Biol*. 2008; 28:380-6. Plitt A et al. *J Cardiovasc Pharmacol Ther*. 2014; 19:409-16. Bevyxxa (betrixaban) prescribing information. Portola Pharmaceuticals. 2017 Jun.

What is the situation? Goals of therapy?

- Urgent
- Semi-Urgent
- Not so Urgent

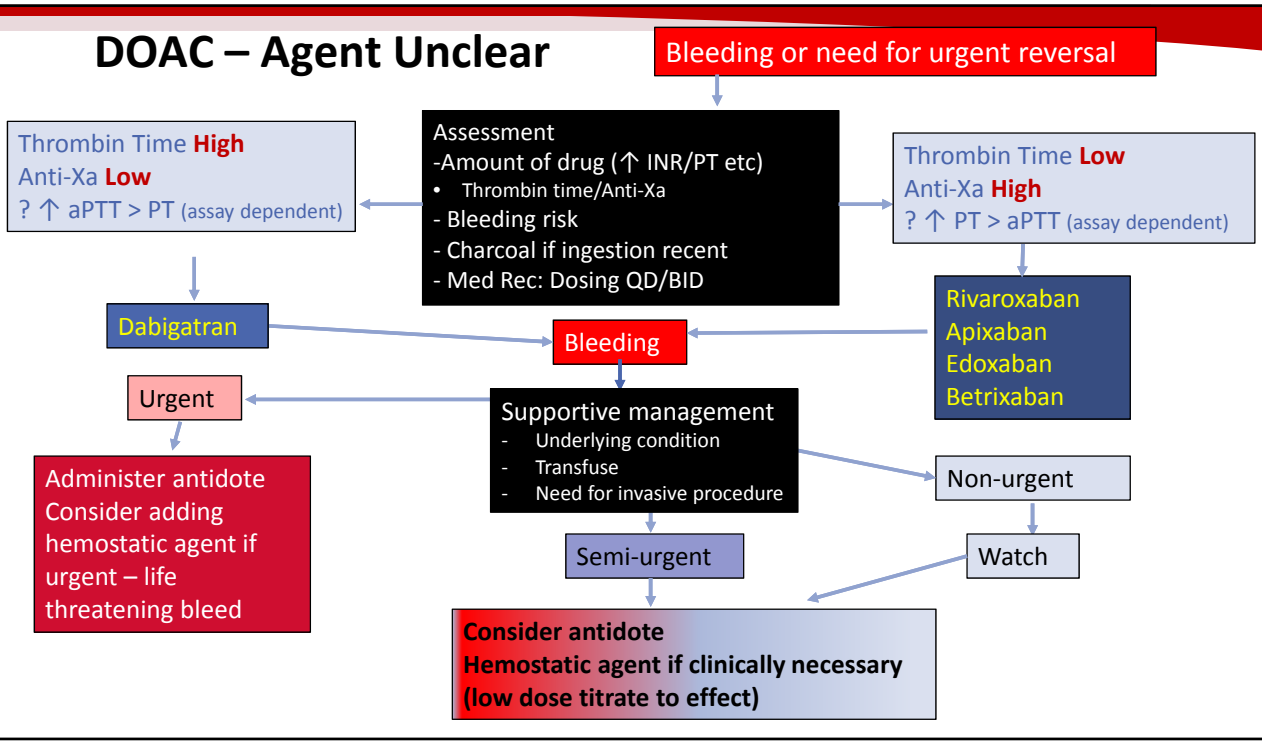
Nutescu E, Dager WE, Kalus JS et al. *Am J Health-Syst Pharm*. 2013; 70:1914-29.

Reversing an Oral Anti-Xa Anticoagulant

- **Assessment**
  - Urgency → patient setting, surgery?
  - Anticoagulant – last dose, how much is involved
    - Assay: Anti-Xa, INR
  - Your role and what agents are available
  - Continuous Process
- **Withhold anticoagulation**
- **Pharmacological intervention**
  - Topical agents
  - Andexanet alfa
  - Prothrombin concentrate concentrate (PCC) (? Titrate to effect)
  - Plasmapheresis ? – Case report (Anti-Xa ↓ 0.8 to 0.3 IU/mL in 2 hours)
- **Replace blood losses**
- **Optimize management of comorbid situations**

Dager W. Anticoagulation Therapy 2nd Ed. 2018. Lam WW et al. *Tex Heart Inst J* 2015; 42:377-80.

DOAC – Agent Unclear



Efficacy Outcomes (n=47)

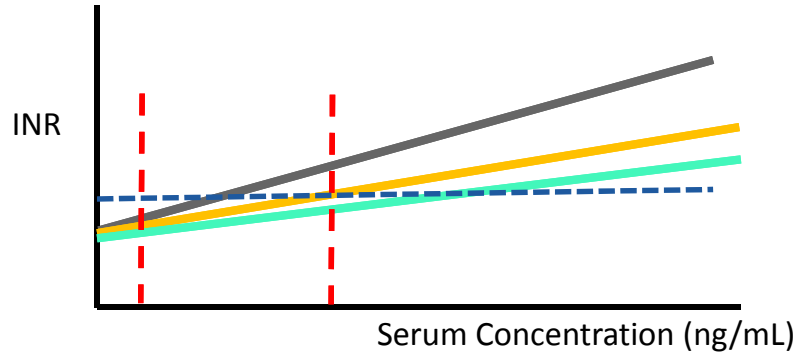
Outcome	Result
Change in anti-Xa activity	~89%
Change in hemostatic efficacy *through 12 hours* ***(Visual 1 and 4 hr; CNS bleed – <20% mass effect by 12 hours)***	79% of patients achieved good or excellent hemostasis post-andexanet alfa • Excellent 66% • Good – 13%

Time from admission to dose administration: 4.8 +/- 1.8 hr

Does this create a negative outcome bias?

Connolly SJ et al. *N Engl J Med*. 2016; 375:1131–41.

Potential INR Response with Higher DOAC Serum Concentrations



Ofek F et al. *Clin Ther*. 2017; 39:1003-10.

	Andexanet alfa
Mechanism	Recombinant truncated human factor Xa variant (decoy) that temporarily shuts down the activity of factor Xa (Does not remove it).
Binding	Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor-activated antithrombin
Target affinity	Affinity for direct factor Xa inhibitors. No effect on dabigatran
Onset	2 min
Half-life	Terminal = 6 hr
Elimination	Not reported
Cost	$25,000 – $50,000 or more (CMS: New technology add-on payment (NTAP) - FY2019 $14,062)

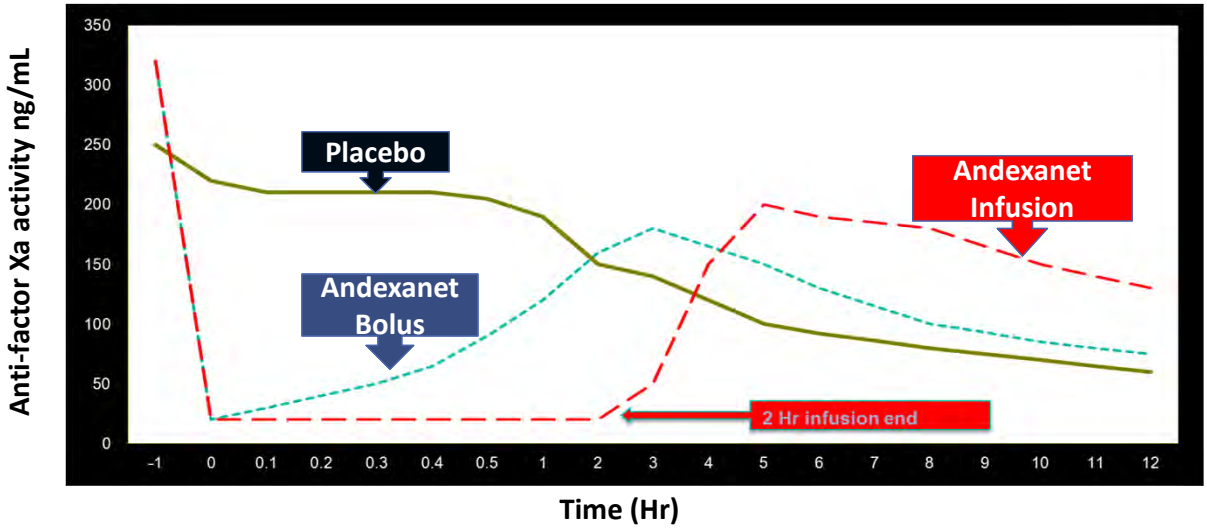
Ruff CT et al. *Circulation*. 2016; 134:248-61.

Safety Outcomes (n=67)

Event	Incidence
30 day thromboembolic events (TE)	18%
Antibodies to factor X, factor Xa, andexanet alfa	No issues
30 day mortality	15%

Connolly SJ et al. *N Engl J Med*. 2016; 375:1131–41.

Andexanet Alfa: Reversing Oral Anti-Xa Agents



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

Use of PCC or aPCC* with Anti-Xa DOAC Bleeding

- **No randomized comparisons to antidotes**
- **Doses variable (8 – 100 units/kg)**
- **Single doses and low doses in GI bleeds have worked**
  - **Onset seems to be rapid**
- **No clear advantage – aPCC* over PCC with anti-factor Xa agents (except heparin allergy)**
- **Thrombosis has been reported - ? If incidence higher**
- **Mortality rates vary**

* = activated prothrombin complex concentrates (aPCC)

Frontera JA et al. *Neurocrit Care*. 2016; 24:6-46.
Majeed A et al. *Blood*. 2017; 130:1706-12.
Shulman S et al. *Thromb Haemost*. 2018; 118:842-51.

PCC or aPCC with Anti-Xa DOAC Bleeding

Study	Mortality	TE
ANEXXA-4 (Safety Population) (n=67)	15%	18%
Majeed et al (n=84) – 4 factor PCC (1500-2000 IU)	32%	6%
Schulman et al (n=66) – 4 factor PCC (2000 IU)	14%	8%
Dager et al (n=48) – activated 4 factor PCC Low Dose – 10 ± 3.6 units/kg Moderate Dose – 24 ± 2.1 units/kg	10%	6%
Santibanez M et al. (n=42 all DOAC with 38 on a Anti-Xa Agent) – 4 factor PCC 25 units/kg (88%)*	Not Reported	7%*

*** 14 day VTE event rate for all 42 patients on a DOAC including 4 receiving Dabigatran**

Connolly SJ et al. *N Engl J Med.* 2016; 375:1131-41.
Majeed A et al. *Blood*. 2017; 130:1706-12. Shulman S et al. *Thromb Haemost*. 2018; 118:842-51.
Dager WE et al. *Thromb Res*. 2019; 173:71-6. Santibanez M et al. *J Crit Care*. 2018; 48:183-90.

Overall Goals

- Stop or control the bleeding
- Stabilize any comorbid conditions and observe
- Identify contributing factors
- Evaluate anticoagulation plan (? Restarting/prophylaxis)
- Make any needed adjustments

Overview of Key Clinical Trials: Reviewing the Evidence for Reversal of DOACs

Mark Cipolle, M.D., Ph.D., FACS, FCCM
Professor of Surgery, Sidney Kimmel School of Medicine
Medical Director Trauma Program
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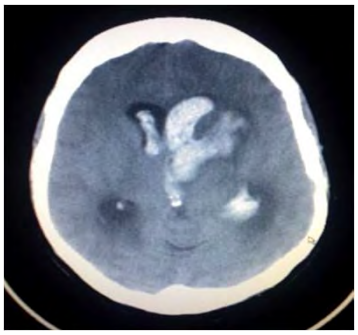
Wilmington, Delaware

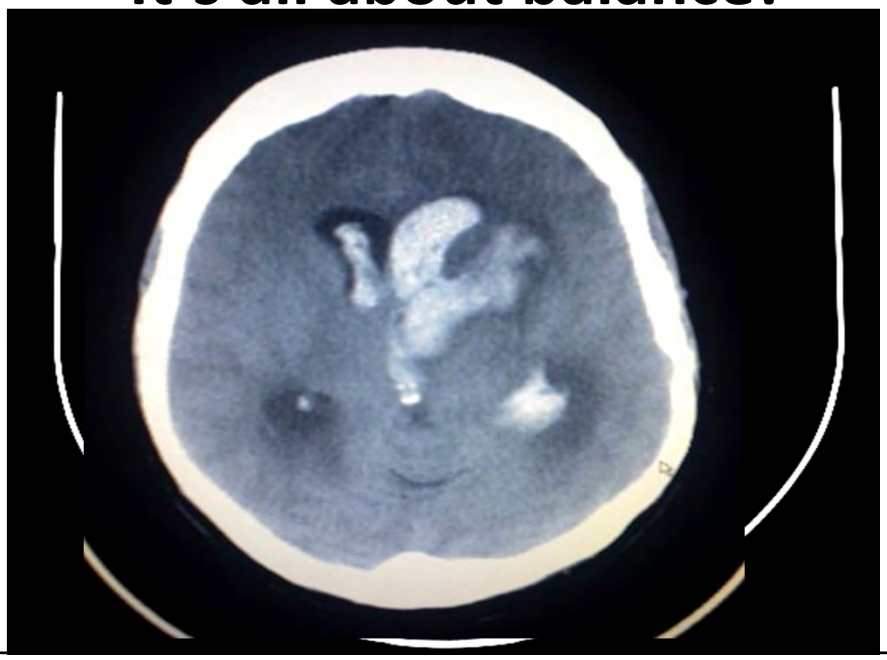


CHRISTIANA CARE HEALTH SYSTEM

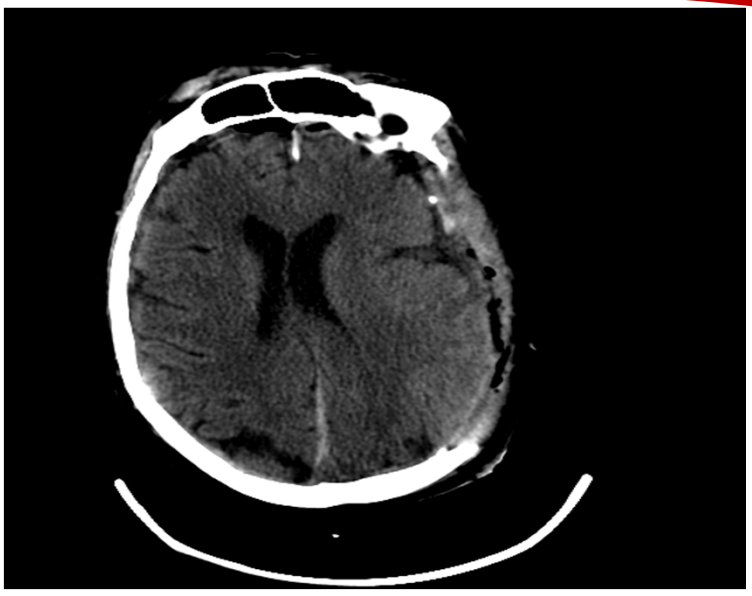
As frontline providers caring for patients on DOACs who are bleeding, our biggest challenges are:

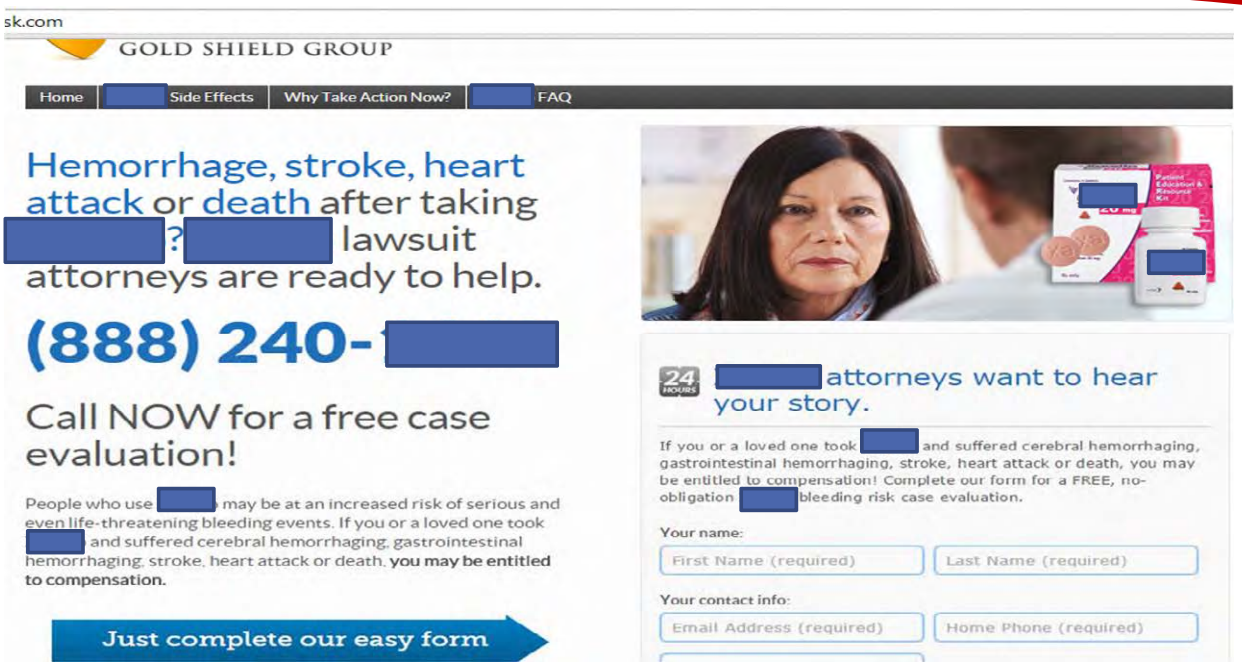
1. deciding who needs urgent reversal
2. knowing when, or if, to resume anticoagulation

It's all about balance!



- 75-year-old man on dabigatran for atrial fibrillation slipped on the ice going to the gym
- PT/INR and aPTT NORMAL
- Thrombin Time (TT) >180
- Urgent craniectomy





Comparison of bleeding rates between DOACs and warfarin: atrial fibrillation

- Randomized trials – DOAC bleeding
  - Major bleeding = 2-3% per year with DOAC
  - Intracranial hemorrhage (ICH) = 0.1 to 0.5% per year with DOAC
- "Real world" N >50,000
  - Dabigatran vs. warfarin
    - Major bleeding: 1.6 vs. 3.5 per 100,000 patient days
    - ICH: 0.8 vs. 2.1 per 100,000 patient days

Southworth MR et al. *N Engl J Med.* 2013; 368:1272-4. Ruff CT et al. *Lancet.* 2014; 383:955-62. Hylek EM et al. *J Am Coll Cardiol.* 2014; 63:2141-7. Piccini JP et al. *Eur Heart J.* 2014; 35:1873-80.

Comparison of bleeding rates between DOACs and warfarin: venous thromboembolism (VTE)

- Meta-analysis of 5 trials
  - N= 24,555
  - Bleeding rates with DOACs
    - Fatal 0.06%
    - Nonfatal ICH 0.09%
    - GI bleed 0.35%
  - **Relative Risk compared with warfarin = 0.5 (0.41-0.88)**

Van der Hulle T et al. *J Thromb Haemost.* 2014; 12:320-8.

Management of Major Bleeding Events in Patients Treated with Dabigatran for Nonvalvular Atrial Fibrillation: A Retrospective Multicenter Review

- 191 cases reviewed
  - 118 (62%) GI bleed
  - 36 (19%) ICH
  - 36 "other locations"
  - Excluded patients enrolled in idarucizumab trial
- 12 (6%) deaths
  - 8 GI bleed
  - 2 ICH
- Red blood cell (RBC) and fresh frozen plasma (FFP) administration was common
- 6% received purified coagulation factors

Milling TJ et al. *Ann Emerg Med*. 2017; 69:531-40.

Efficacy and Harms of DOACs in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of VTE

- Reviewed 19 studies
- DOACs were equivalent or superior to Vitamin K antagonist (VKA) in managing thrombotic risk
- GI bleeding in elderly on dabigatran was higher compared with VKA
- **GI bleeding in non-elderly, ICH, clinically relevant bleeding and fatal bleeding were ALL LOWER in DOACs compared with VKA!**

Sharma M et al. *Circulation*. 2015; 132:194-204.

87-year-old woman on rivaroxaban in MVC

Preinjury Warfarin Worsens Outcome in Elderly Patients Who Fall From Standing

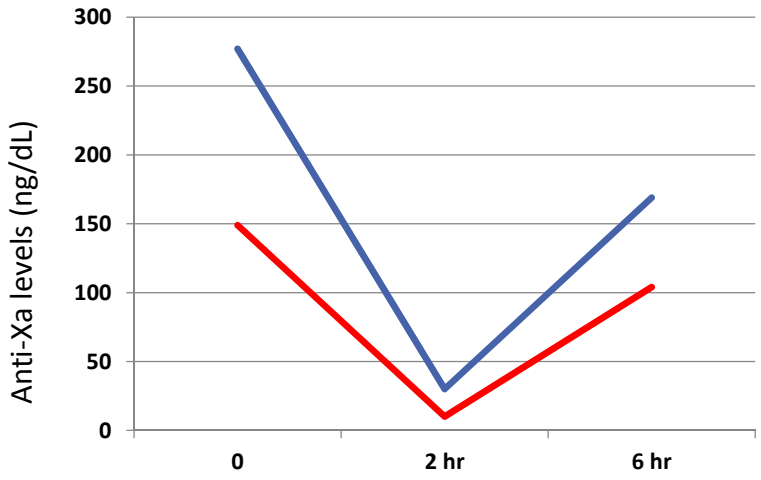
Jerry Lee Howard, II, MD, Mark D. Cipolle, MD, PhD, Sarah A. Horvat, BS, Victoria M. Sabella, RN, BSN, CCRC, James F. Reed, III, PhD, Gerard Fulda, MD, Glen Tinkoff, MD, and Michael D. Pasquale, MD

J Trauma. 2009; 66:1518-24.

Mortality Rate	+warf % (n=537)	-warf % (n=2254)	OR (95% CI)	P value
All	8.6	5.7	1.54 (1.09–2.19)	0.015
Abbreviated Injury Score (AIS) Head <4	2.4	3.9	1.63 (0.55-4.79)	0.377
AIS Head (4 & 5)	23.7	16.0	1.63 (1.03–2.58)	0.035
& GCS (14-15)	13.5	6.4	2.30 (1.12–4.70)	0.019
& GCS (9-13)	38.9	30.2	1.47 (0.48–4.49)	0.496
& GCS (≤ 8)	57.9	65.5	0.72 (0.25–2.09)	0.549

- warf = non-warfarin group; + warf = warfarin group

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors



Results

- **n=67 safety analysis, n = 47 efficacy analysis**
- **Mean age 77**
- **Mean time to bolus 4.8±1.8 hr from presentation**

Connolly SJ et al. *N Engl J Med.* 2016; 375:1131–41.

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

- Hemostatic efficacy excellent or good
  - Rivaroxaban (n=26) 81% (61-93)
  - Apixaban (n=20) 75% (51-91)
  - GI bleed (n=25)84% (64-96)
  - ICH (n=20) 80% (56-94)
- Safety
  - No infusion reactions or antibodies developed
  - Thrombotic events in 12 patients (18%)
  - 6 of 10 deaths cardiovascular causes!!

Connolly SJ et al. *N Engl J Med.* 2016; 375:1131–41.

Update for ANNEXA-4

- Safety analysis n=227
- Efficacy analysis n=137
- Reducing anti-Xa levels and hemostatic efficacy are similar to initial *N Engl J Med* report
- Safety
  - Thrombotic events
    - 6 (2.6%) within 3 days
    - 24 (11%) within 30 days
  - Anticoagulation restarted in 129 (57%) in 30 days and only in 9 patients before thrombotic event
  - 27 (12%) deaths by day 30, 11 cardiovascular

Connolly, SJ. Presentation at American College of Cardiology. March 2018. Orlando, FL.

Management of rivaroxaban- or apixaban-associated major bleeding with PCCs: a cohort study

- 25 centers in Sweden coordinated by Karolinska University Hospital
- Enrolled consecutive patients prospectively needing "prompt" reversal for major bleeding
- Predefined protocol utilizing 1500-2000 units of PCC4, a second dose was given in 3 patients
- Assessment of efficacy performed by 2 independent coagulation specialists using International Society Thrombosis and Hemostasis (ISTH) criteria
- Primary safety endpoint was arterial or venous thromboembolism

Majeed A et al. *Blood*. 2017; 130:1706-12.

Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study

- **Results**
  - Evaluated 39 apixaban and 45 rivaroxaban patients
  - ICH n=59, GI bleed n=13
  - 12.5 hours from last dose to treatment with PCC
  - Hemostatic effectiveness
    - Overall 69%
    - ICH 73%, non-ICH 60%
    - Trauma 73%, atraumatic 67%
  - Safety
    - 32% mortality rate
    - Two strokes with one death attributed to PCC4
    - 4% thrombotic complications

Majeed A et al. *Blood*. 2017; 130:1706-12.

PCC for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study

- 9 Canadian centers
- Apixaban and rivaroxaban
- Most received fixed dose of 2000 units
- Results
  - N=66, ICH 55%, GI bleed 24%, trauma 38%
  - Hemostatic efficacy (Sarode criteria)
    - Overall 65% good, 20% moderate
    - ICH 76%
  - Safety
    - 9 deaths (14%)
    - 5 thomboembolic events (8%)

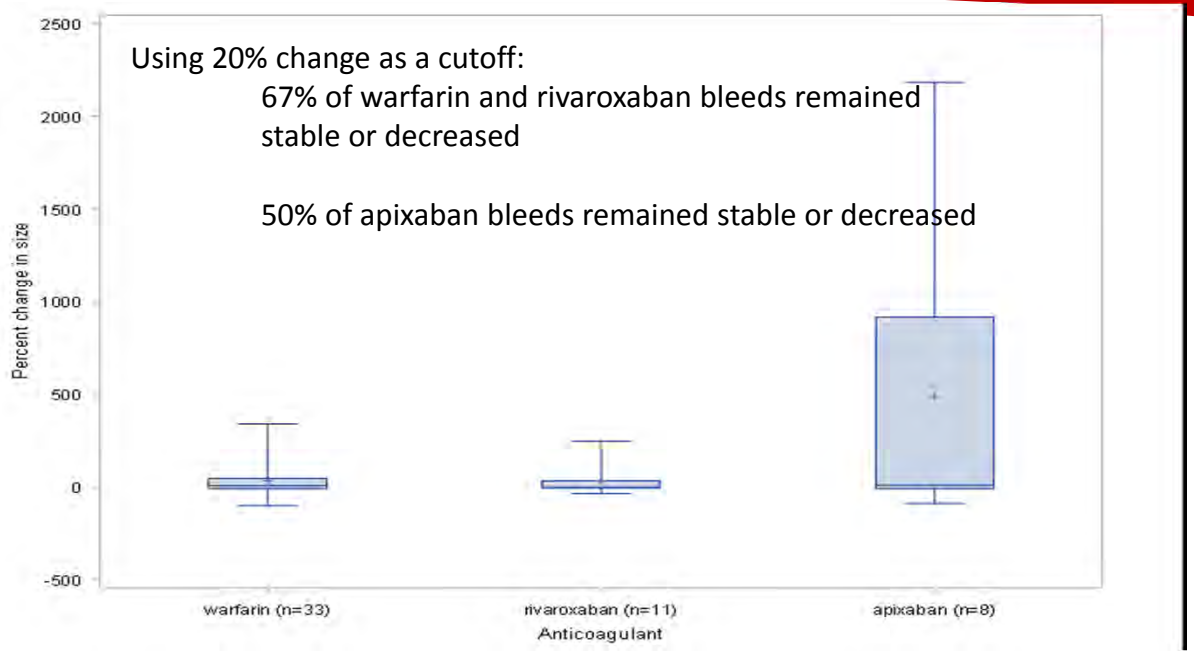
Schulman et al. *Thrombosis Haemostasis.* 2018; 118:842-51.

Andexanet Alfa or PCC4 for Reversal of Bleeding Associated with Xa-inhibitors

Study	ANNEXA-4 (n=67)	Majeed et al (n=84)	Schulman et al (n=66)
Reversal agent	Andexanet alfa	PCC4	PCC4
Age (years)	77.1±10.0	75.0±10.9	76.9±10.4
ICH	42%	70%	55%
Time since last dose (hours)	R 12.8±4.2 A 12.1±4.7	12.5 (9-16)	16.9 (12-21)
Effectiveness for CNS bleeds excellent or good	16 (80%)	43 (73%)	25 (76%)
Thrombotic events	12 (18%)	3 (4%)	5 (8%)
Death	10 (15%)	27 (32%)	9 (14%)

"The similar effectiveness results in our study and in ANNEXA-4 could, if true, be because both methods are effective or, alternatively, because reversal has minimal or no effect on the outcome. The latter could, in turn, be due to too late administration (intracranial hemorrhage—the damage is already done) or that the anticoagulation effect is rapidly vanishing with the short half-life of the Xa inhibitors."

Schulman et al. *Thrombosis Haemostasis.* 2018; 118:842-51.



Some Exclusions in Sarode Bleeding Trial

- Expected survival <3 days
- Expected surgery <1 day
- Acute trauma for which reversal alone would not be expected to control the bleeding
- History of thrombotic event within 3 months
- Sepsis
- Large vessel rupture
- Preexisting fatal disease life expectancy <2 months
- ICH
  - Glasgow Coma Score (GCS) <7
  - ICH >30 mL
  - Subdural hematoma >1 cm or shift >5 mm
  - Infratentorial hemorrhage
  - Epidural hemorrhage
  - Intraventricular hemorrhage

Sarode R et al. *Circulation.* 2013; 128:1234-43.

Exclusions for ANNEXA-4

- ICH volume >60 mL or GCS <7
- Expected survival <1 month
- Expected to undergo surgery in <12 hr
- Major thrombotic event within 2 weeks of hemorrhage
- Received VKA, dabigatran, PCC, blood within 7 days

Connolly SJ et al. *N Engl J Med.* 2016; 375:1131–41.

ICH patients in ANNEXA-4

- 28 (42%) of 67 patients enrolled with an ICH
- Baseline GCS: 14.1 ± 1.7
- Intracerebral hemorrhage:
  - Hematoma volume:
    - ≤10 mL: 8 (57%) of 14
    - 11-60 mL: 6 (43%) of 14
- Subdural hemorrhage:
  - Maximal thickness:
    - ≤10 mm: 8 (73%) of 11

Connolly SJ et al. *N Engl J Med.* 2016; 375:1131–41.

Resumption of anticoagulation

Restarting Anticoagulation Treatment After Intracranial Hemorrhage in Patients with Atrial Fibrillation and the Impact of Recurrent Stroke, Mortality, and Bleeding

- Three Danish nationwide registries 1997-2013
- 1752 patients with 1 year follow-up
- VKA 65%, VKA + antiplatelet 33%, DOAC 2%
- Primary outcome: ischemic stroke/systemic embolism (SE)/all cause mortality
- Compared three groups
  - Resumed oral anticoagulation (OAC)
  - Resumed antiplatelet therapy
  - No resumption of anticoagulation or antiplatelet therapy

Nielsen PB et al. *Circulation*. 2015; 132:517-25.

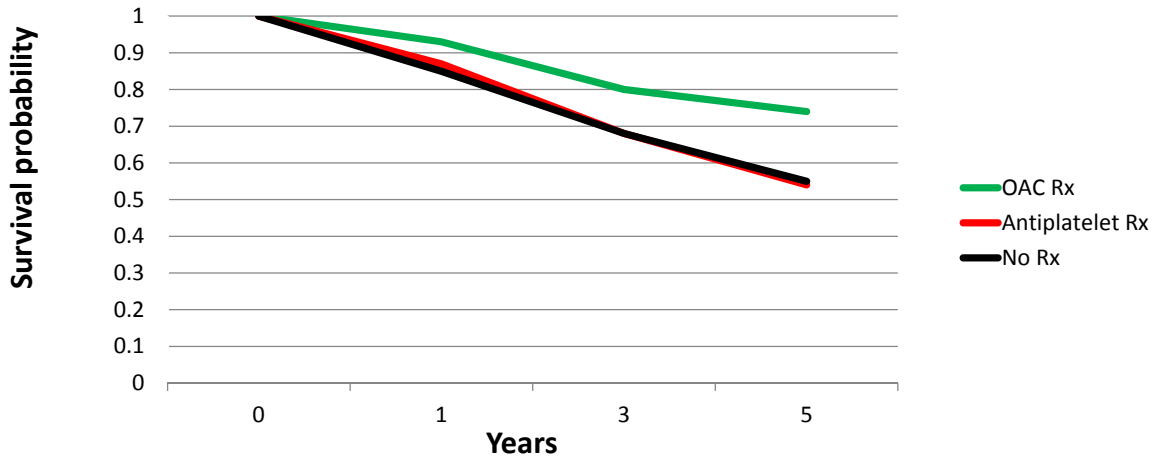
Restarting Anticoagulation Treatment After Intracranial Hemorrhage in Patients with Atrial Fibrillation and the Impact of Recurrent Stroke, Mortality, and Bleeding

Outcome	No treatment	OAC treatment	Antiplatelet Rx
Ischemic stroke/systemic embolism and all cause mortality event rate	27.3% (23.6-31.6)	13.6% (10.1-18.3)	25.7% (20.7-31.9)
Recurrent ICH event rate	8.6% (6.6-11.2)	8.0% (5.4-11.8)	5.3% (3.3-8.4)

OAC=oral anticoagulation

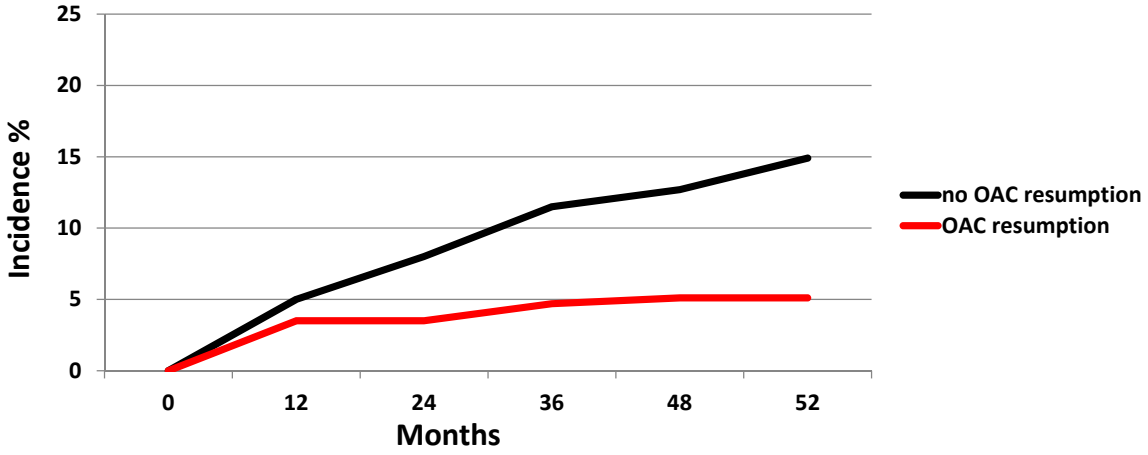
Nielsen PB et al. *Circulation*. 2015; 132:517-25.

Restarting Anticoagulation Treatment After Intracranial Hemorrhage in Patients with Atrial Fibrillation and the Impact of Recurrent Stroke, Mortality, and Bleeding



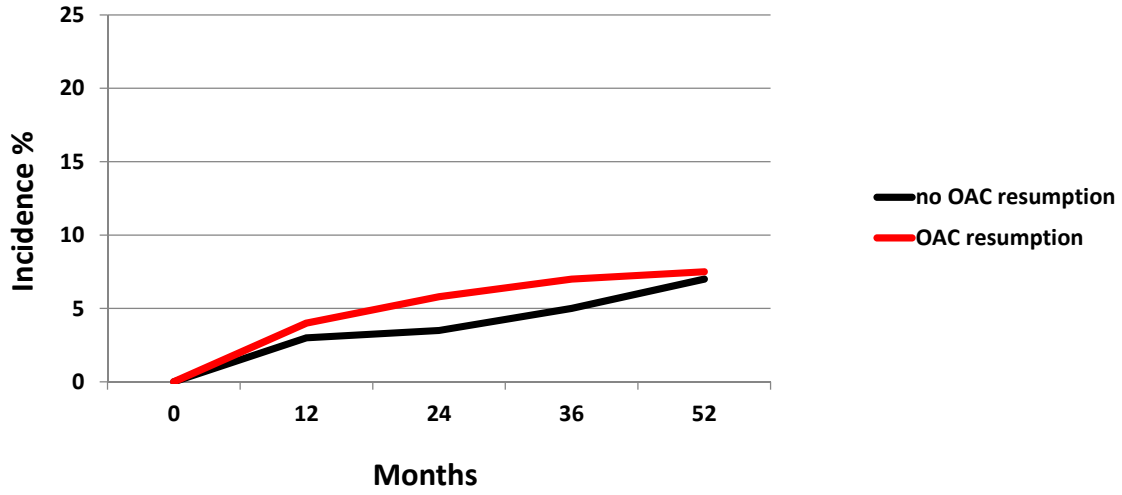
Nielsen PB et al. *Circulation*. 2015; 132:517-25.

Ischemic Events: OAC stopped for ICH
19 German Centers



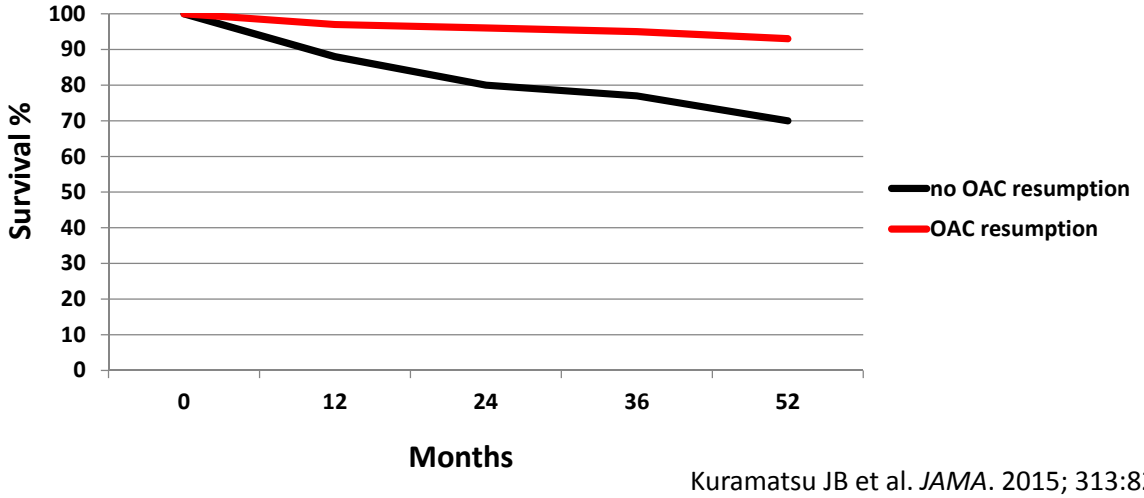
Kuramatsu JB et al. *JAMA*. 2015; 313:824-36.

Hemorrhage Events: OAC stopped for ICH
19 German Centers



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

Survival Rate: OAC stopped for ICH
19 German Centers



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

Christiana Care Health System AC and AT Resumption

Trauma	Full anticoagulation should be resumed after bleeding stopped based on thrombotic risk: High risk- within 4 days[5] Moderate risk- within 1-2 weeks Low risk – Consider within 2-4 weeks	Withhold dual antiplatelet therapy (DAPT) for 24 hours to assess bleed For all patients on aspirin indications listed in Table 1, we recommend resuming aspirin (81mg) 24 hours after bleeding stops For patients with a DES <12 mo, BMS <3 mo, or intracranial stent <12 mo–restart second agent within 1-2 weeks
Intracranial or intraspinal hemorrhage : Traumatic and Spontaneous	Trauma: Re-evaluate reason for anticoagulation: Antithrombotics vs Antiplatelets Anticoagulation should be resumed after bleeding stopped based on thrombotic risk: High risk- resume 7-10 days after bleeding event Moderate risk- resume within 2-3 weeks Low risk – resume within 3-4 weeks Spontaneous: -Identify/Secure underlying lesion: aneurysm/AVM *Neurologic consultations prior to re-initiation of full anticoagulation	Trauma: Withhold dual antiplatelet therapy (DAPT) for 24 hours to assess bleed For all patients on aspirin indications listed in Table 1, we recommend resuming aspirin (81mg) Small bleeds: within 48 hours if neuro exam and CT stable or improved for small bleeds Large bleeds: Hold aspirin for 5 days For patients with a DES <12 mo, BMS <3 mo, or intracranial stent <12 mo–restart second agent within 1-2 weeks Spontaneous: Identify/Secure underlying lesion: aneurysm/AVM For patients with a DES <12 mo, BMS <3

Clinical Considerations in Reversal of DOACs: Focus on Wise and Correct Use

Jessica Rimsans, Pharm.D., BCPS
Clinical Pharmacy Specialist
Hemostatic Antithrombotic Stewardship
Brigham and Women's Hospital
Boston, Massachusetts

What is the American College of Cardiology recommended dose of PCC4 or aPCC for life threatening ICH associated with factor Xa inhibitors ?

a. 12.5 units/kg
b. 30 units/kg
c. 25 units/kg
d. 50 units/kg
e. 100 units/kg

What is the recommended dose of andexanet alfa for a patient presenting with ICH whose last dose of apixaban 5 mg was 10 hours ago?

a. Bolus 400 mg
b. Bolus 200 mg then a 2 hour infusion of 480 mg
c. Bolus 800 mg then a 2 hour infusion of 960 mg
d. Bolus 400 mg then a 2 hour infusion of 480 mg
e. Bolus 480 mg then a 2 hour infusion of 400 mg

Patient Case: PP

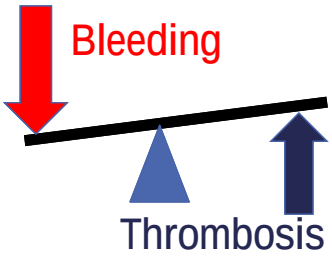
- PP is an 81 YOM with a history of CAD, s/p DES implant 2009, AF, hypertension, s/p right occipital ventriculoperitoneal shunt placed in 2008.
- On rivaroxaban 20 mg QD (last dose 9 pm night prior to admission) and ASA.
- CT scan was performed which demonstrated a large right basal ganglia hemorrhage with IVH and hydrocephalus.
- **At OSH**: INR 2.3 and patient was given PCC4 50 units/kg + vitamin K 10 mg IV, and platelets.
- Unresponsive upon transfer to our emergency department (ED).
- **At our hospital**: Anti-Xa (LMWH/UFH) was 4.74 IU/mL.
  - New CT reveals hematoma expansion with mild mass effect and right-to-left midline shift of 5 mm.
- The ED team stat-pages the pharmacist to discuss treatment options given new findings.

Three Main Questions

What is the urgency and reason for reversal?

What treatment options are available?

What patient-specific factors should be considered?



Available Treatment Options for DOAC Reversal

FDA Approved Options

- Idarucizumab for dabigatran reversal only
- Andexanet alfa for apixaban and rivaroxaban only
- PCC4 for VKA-reversal only

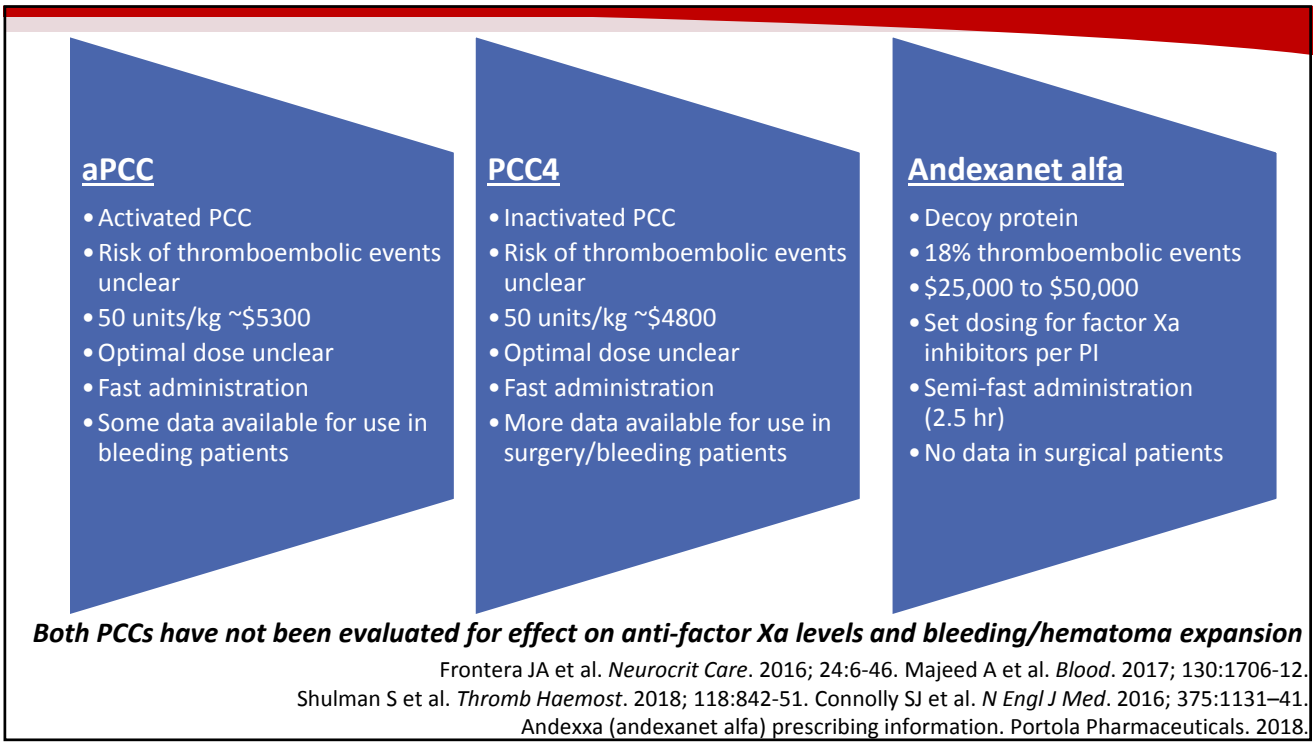
Non-FDA Approved Options

- PCC3
- PCC4
- aPCC (Factor VIII inhibitor bypassing activity, FEIBA)
- Recombinant activated factor VII
- Plasmapheresis
- Hemodialysis for dabigatran reversal only

Factor Xa Inhibitor Reversal

- **Andexanet alfa** is FDA Approved for patients with **life threatening major bleeding** on apixaban or rivaroxaban
- **PCC4** and **aPCC** are options to consider for Factor Xa inhibitor reversal for both **life threatening bleeding** and those requiring **urgent surgery/procedures**
- Withholding the factor Xa inhibitor will promote clearance in those with normal renal function

Tomaselli GF. *J Am Coll Cardiol*. 2017; 70:3042-67.
Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.



Both PCCs have not been evaluated for effect on anti-factor Xa levels and bleeding/hematoma expansion

Frontera JA et al. *Neurocrit Care*. 2016; 24:6-46. Majeed A et al. *Blood*. 2017; 130:1706-12.
Shulman S et al. *Thromb Haemost*. 2018; 118:842-51. Connolly SJ et al. *N Engl J Med*. 2016; 375:1131–41.
Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.

Andexanet Alfa coagulation factor Xa (recombinant), inactivated-zhzo

- Recombinant modified human factor Xa decoy protein that is catalytically inactive but that retains the ability to bind factor Xa inhibitors in the active site with high affinity
- FDA approved May 2018
  - Only for life threatening bleeding with rivaroxaban and apixaban
  - Different dosing strategy for agent, dose, and time since last dose

Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.

Andexanet Alfa Dosing

- Different dosing strategy for agent, dose, and time since the last dose
  - dependent on family/patient involvement

Factor Xa inhibitor	FXa inhibitor dose	Timing of FXa inhibitor last dose before coagulation Factor Xa (andexanet alfa)	
		<8 hours or unknown	≥8 hours
Rivaroxaban	≤10 mg	Low dose	Low dose
	>10 mg, or unknown	High dose	
Apixaban	≤5 mg	Low dose	
	>5 mg, or unknown	High dose	

Dose	Initial IV bolus	Follow-up IV infusion
Low dose	400 mg at a target rate of 15-30 min	4 mg/min for 120 minutes (480 mg)
High dose	800 mg at a target rate of 15-30 min	8 mg/min for 120 minutes (960 mg)

Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.

What is the recommended dose of andexanet alfa for a patient presenting with ICH whose last dose of apixaban 5 mg was 10 hours ago?

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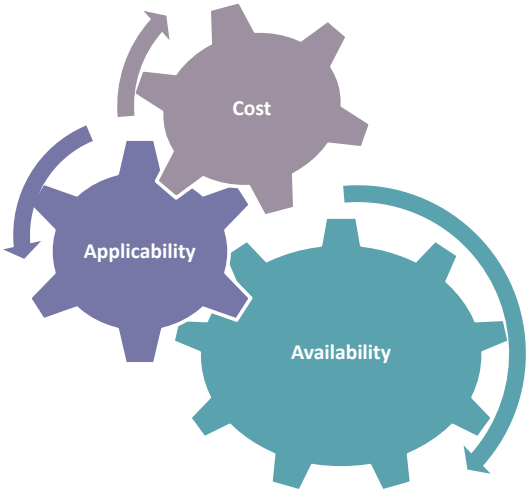
Andexanet Alfa

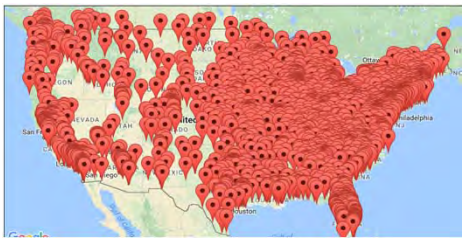


Other considerations:

- Availability
- Vial size
- Tubing
- One compounded bag vs. two
- Bleeding vs. surgery
- Outside hospital transfer
- Drug levels vs. standard tests
- Formulary addition & stewardship oversight
- Guideline development & education

Availability

Idarucizumab



Andexanet alfa

- Early supply program offered to high-enrolling ANEXXA-4 institutions
- Considerations for loaning/borrowing from other hospitals that do not carry andexanet

https://www.andexxa.com/
https://www.praxbind.com/

Reconstitution & Administration Considerations for Andexanet Alfa

- Currently available as 100 mg vials
  - 9-18 vials required for the low and high dose
  - 200 mg vials in the pipeline
- Reconstitution
  - Bolus +/- maintenance infusion in one IV bag
- Tubing
  - ½ the dose remains in the line if not flushed post bolus and infusion
  - OSH transfers and pump compatibility between hospitals

Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.

Indication for Use of Andexanet Alfa

- Life threatening bleeding on apixaban or rivaroxaban
  - within 18 hr of last dose
- Currently not indicated for:
  - Non life threatening major bleeding
  - Surgery in the next 12 hours or that can be delayed
  - Bleeding managed with supportive measures

Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.

Our Experience

- 15 patients as of October 2018
- Many patients would not have met ANNEXA-4 criteria
  - 7 received PCC
  - 1 recent thrombotic event
  - 3 had surgery within 12 hours

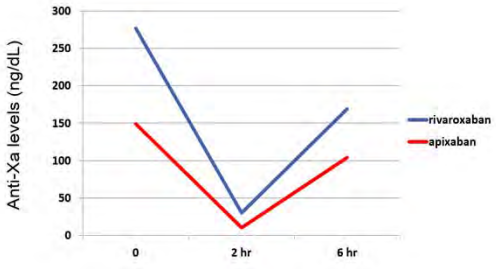
Culbreth SE, Rimsans J et al. *Am J Hematol*. 2018; [epub ahead of print].

Considerations/Indication for Use

- Outside hospital transfer s/p PCC treatment
  - Hematoma expansion on CT
  - Anti-Xa (LMWH/UFH) level remains elevated
- Elevated standard coagulation tests vs. chromogenic drug levels
  - Anti-Xa (LMWH/UFH) vs. drug concentration
  - Not indicated unless evidence of bleeding/expansion

Considerations in Using Andexanet Alfa

- Doses of factor Xa inhibitor greater than 18 hours prior
- Life threatening bleeding on factor Xa inhibitor other than apixaban or rivaroxaban
- Andexanet alfa + surgery
  - Rebound anti-Xa levels 2-4 hr post infusion
  - Consideration for continuous infusion for length of surgery
  - Not approved by FDA at this time



Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.

Considerations After Andexanet Alfa Administration

- Rebound in anti-Xa observed 2-4 hours
  - Monitor for re-bleeding and elevated anti-Xa levels
  - Educate clinicians on rebound and timing of procedures
- Medicare New Technology Add on Payment (NTAP) approved October 1, 2018
  - Need to submit appropriate coding
  - Up to $14,062.50
  - Resources available on website
- Restarting anticoagulation when hemostasis achieved

Andexxa (andexanet alfa) prescribing information. Portola Pharmaceuticals. 2018.

Implementing Use of Andexanet Alfa

- Formulary review
- Guidelines for use
- Electronic medical record decision support
- Education for emergency medicine, hematology, pharmacy, and anesthesiologists

Patient Case: MS

- MS is an 85 YOF who presents with sudden onset of abdominal pain associated with watery diarrhea, chills, and arrives to the ED by ambulance at 10 pm
- Past medical history: severe aortic stenosis w/ preserved ejection fraction, pacemaker, peripheral artery disease, atrial fibrillation 4 months prior, hypertension, diabetes mellitus, hypothyroid
- Current medications: aspirin 81 mg/day, apixaban 2.5 mg twice daily, atorvastatin 40 mg/day, levothyroxine 75 mcg/day, metoprolol 25 mg/day, furosemide 20 mg/day
- On exam: blood pressure 124/72 mmHg, heart rate 77 bpm, Remainder of exam is normal
- Labs: hemoglobin 10.4 g/dL, hematocrit 32.3%, platelets 188 k/uL, Serum creatinine 0.65 mg/dL, PT 14.3 seconds, INR 1.1
- CT: approx. 20 cm length of mid ileum demonstrates circumferential wall thickening, adjacent mesenteric fat stranding→ concern for mesenteric ischemia requiring emergent exploratory laparotomy

Patient Case (continued)

- Upon further discussion, last dose of apixaban was last night, 24-26 hours ago
- Team consults with the pharmacist about how to reverse apixaban to emergently bring this patient to the operating room (OR) for exploratory laparotomy.

What do you recommend?

a. Andexanet alfa 400 mg bolus followed by 480 mg infusion over 2 hours
b. PCC4 25 units/kg
c. Andexanet alfa continuous infusion for the duration of the procedure
d. aPCC 25 units/kg
e. Nothing – withholding the apixaban is sufficient given normal renal function

Outcome

- Last dose ~24 hours prior, normal renal function
- Stat anti-factor Xa (LMWH/UFH) was 1.15 IU/mL
- No data at this time supporting andexanet alfa for surgery
- Allowed PCC4 to be in the OR if bleeding occurred that was not typical for this procedure
- No PCC or transfusion of blood products were required
- Estimated blood loss reported: “minimal; 10 mL”

Key Takeaways

Anticoagulant associated bleeding requires

- Patient assessment
  - Site, Severity, Anticoagulant, Images, Timing, Labs
  - Worsening, Stable, Improving
- Hospital resources
  - Blood factors and/or reversal agents
- Expertise/teamwork
  - Drug prescribing, drug prep, drug administration
- Follow up
  - When to restart anticoagulation

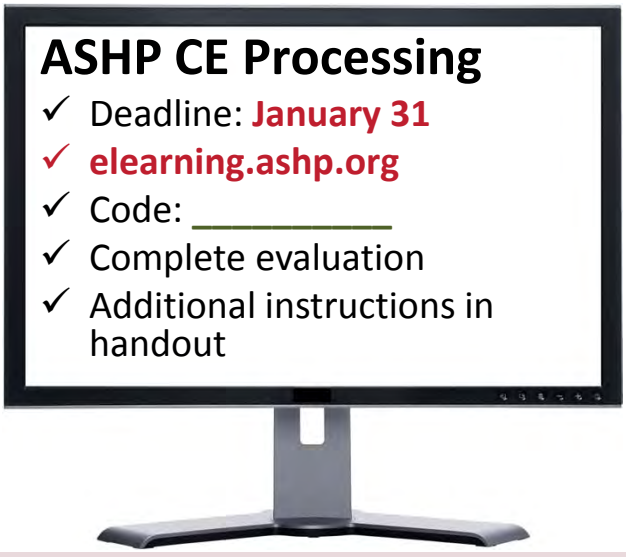
Consider these practice changes. Which will you consider making after this activity?

1. Educate colleagues on the need for close follow-up and management of patients on anticoagulant therapy.
2. Be proactive in counseling patients on bleeding risk when using DOACs on a long-term basis.
3. Read my institutional protocols for bleeding management in patients experiencing a life-threatening bleed or requiring emergency surgery.
4. Review which DOAC reversal agents are available at my institution (e.g., andexanet alfa, idarucizumab, PCC4).
5. Discuss with colleagues how to assess the need for reversal of the DOACs in special populations.
6. Investigate appropriate use of DOAC reversal agents, including timing of the dose, potential for excessive levels, and adapting to other co-factors.

A patient on a new oral anticoagulant…

- Is going to the OR for an emergent procedure
  - INR is 2.5 and no liver disease or warfarin on board.
  - What if the INR was >6 (with heart failure and acute kidney failure)
- With history of multiple PE has a massive GI bleed, Hgb is 5 and BP dropping
- Who fell yesterday and CT today shows an epidural hemorrhage
- Is stable and has some blood in their stool

Thank You for Joining Us



Coming Soon

On-demand archive of today's presentation

- Available early March 2019

Download the handout at **www.ashpadvantagemedia.com/doac-reversal**

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4. Click **Claim** for any session.
5. Complete the Evaluation.
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On-demand activity of today's live symposium coming in March 2019
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