Reversal Strategies for DOAC-Related Bleeding: Promoting Optimal Use of Reversal Agents

PRESENTED AS A LIVE WEBINAR

Wednesday, March 10, 2021 & March 24, 2021
2:00 pm – 3:30 pm ET

HOME STUDY AVAILABLE

April 22, 2021 – May 13, 2022

FACULTY

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View faculty bios at
ashpadvantage.com/stopdoacbleed/webinar2/

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The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

- ACPE #: **0204-0000-21-403-H01-P**
- 1.5 hr, Application-based

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Supported by an educational grant from Alexion Pharmaceuticals, Inc.

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Learning Objectives

At the conclusion of this educational activity, participants should be able to

- Identify evidence-based protocols and guidelines related to the use of reversal agents for direct-acting oral anticoagulants (DOACS) that standardize clinical practice and address National Patient Safety Goals.
- Identify approaches for ensuring cost-effective use of anticoagulation reversal agents for DOAC-related bleeding.
- Develop a plan for establishing a standardized, evidence-based interprofessional approach for managing the use of DOAC reversal agents within the health system.

Using Evidence-Based Protocols and Guidelines Related to the Use of DOAC Reversal Agents

National Patient Safety Goals (NPSGs)

The Joint Commission. National patient safety goal for anticoagulant therapy. https://www.jointcommission.org/-/media/tjc/newsletters/ r3_19_anticoagulant_therapy_final2pdf.pdf?db=web&hash=710D79 BDAEFFCA6C833BB823E1EEF0C6 (accessed 2021 Feb 2).

Improve the Safety of Using Medications

- Anticoagulant medications are associated with increased risk of harm, when compared with other types
- Goal of NPSG (NPSG.03.05.01)
  - Reduce the likelihood of patient harm associated with the use of anticoagulant therapy
    - Consists of 8 elements of performance

The Joint Commission. National patient safety goal for anticoagulant therapy. https://www.jointcommission.org/-/media/tjc/newsletters/ r3_19_anticoagulant_therapy_final2pdf.pdf?db=web&hash=710D79 BDAEFFCA6C833BB823E1EEF0C6 (accessed 2021 Feb 2).

NPSG: Select Anticoagulation Goals

- Use approved protocols and evidence-based practice guidelines for
  - Initiation and maintenance of anticoagulant therapy
  - *Reversal of anticoagulation, and management of bleeding events related to each anticoagulant medication*
  - Perioperative management of all patients on oral anticoagulant
    - May address the use of bridging medications, timing for stopping an anticoagulant, and timing and dosing for restarting an anticoagulant

- Policy addressing the need for baseline and ongoing laboratory tests to monitor and adjust anticoagulant therapy

The Joint Commission. National patient safety goal for anticoagulant therapy. https://www.jointcommission.org/-/media/tjc/newsletters/ r3_19_anticoagulant_therapy_final2pdf.pdf?db=web&hash=710D79 BDAEFFCA6C833BB823E1EEF0C6 (accessed 2 Feb 2021).

DOAC Trends

- Thrombotic events/risks continue to rise annually in U.S.
  - Atrial fibrillation (AF) prevalence projected to increase from 5.2 million in 2010 to 12.1 million cases in 2030
  - Venous thromboembolism (VTE) annual risk is ~8 million people in the U.S.

- In 2015, approximately 2.9 million U.S. patients were treated with a DOAC

- Guideline recommendations: DOACs are preferred treatment for patients with nonvalvular AF and cancer patients with VTE

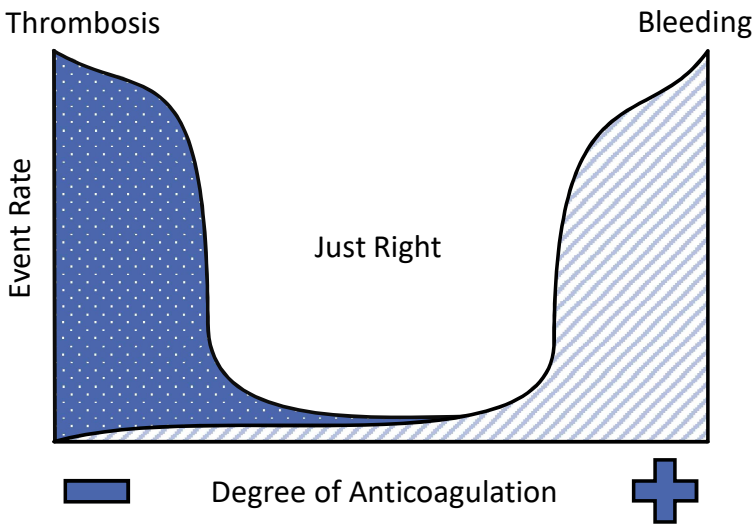
Milling T et al. *Am J Manag Care*. 2017;23(suppl 4):S67-S80; Lyman G et al. *Blood Adv*. 2021;5:927-74; Colilla S et al. *Am J Cardiol*. 2013;112:1142-7; January C et al. *J Am Coll Cardiol.* 2019;74:104-32; Deitelzweig S et al. *Ann Emerg Med.* 2016;68(4):S18.

DOAC-Related Bleeding

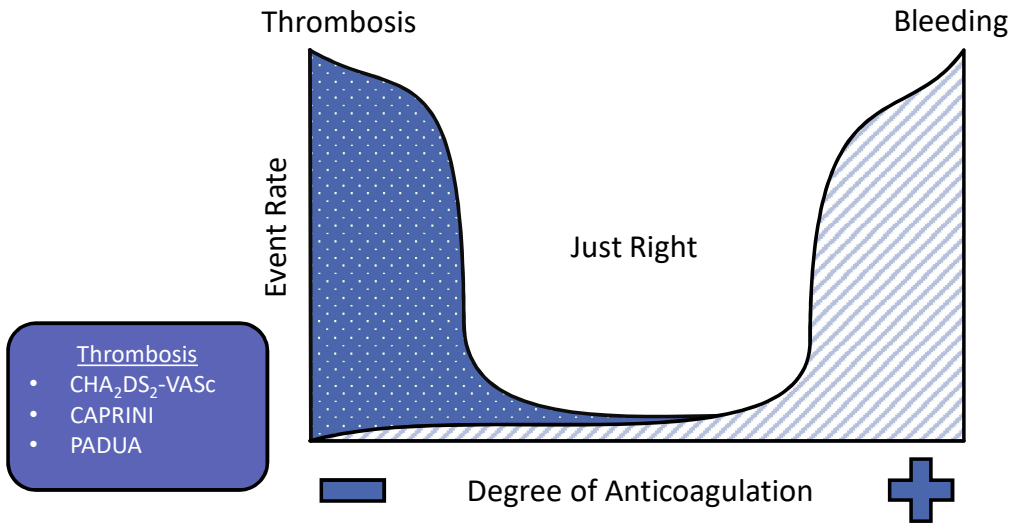
- The rate of DOAC related major/life-threatening bleeding is 2.0 per 100 patient years
  - AF: 48% GI vs. 13% ICH
  - VTE: 31% GI vs. 11% ICH
- DOAC-related hemorrhages: 30-day mortality
  - Major bleeds: 8.9 – 20.4%
  - ICH: 36 – 48%
- Withholding anticoagulant reversal in DOAC-related ICH is associated with 1.5-fold increase in risk of death and poor outcomes

Held C et al. *Eur Heart J.* 2015;36:1264-72; Piccini J et al. *Eur Heart J.* 2014;35:1873-80; Majeed A et al. *Circulation.* 2013;128:2325-32; Wilson D et al. *Neurology.* 2017;88:1693-700; Apostolaki-Hansson T et al. *Front Neurol.* 2020;11:760.

Balancing Act

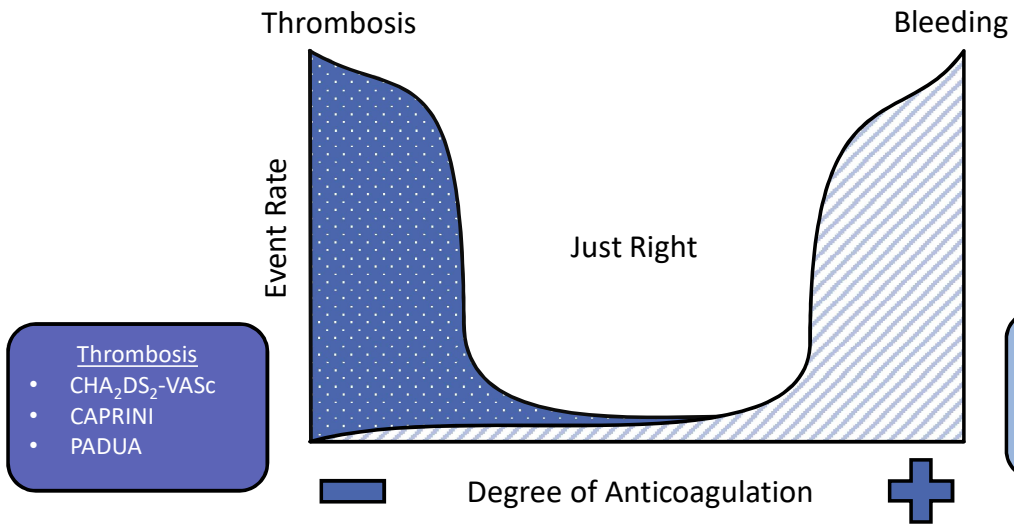


Balancing Act



Thrombosis
- CHA_2DS_2-VASc
- CAPRINI
- PADUA

Balancing Act



Thrombosis
- CHA_2DS_2-VASc
- CAPRINI
- PADUA

Bleeding
- HAS-BLED
- $HEMORR_2HAGES$
- ATRIA
- ORBIT

Bleeding Severity

Major/Life-Threatening Bleeding

Only one needed

- Occurring at critical site
- Hemodynamic instability
- Overt bleeding
  - Hemoglobin decrease ≥2 g/dL
    OR
  - Requiring ≥2 units of packed red blood cells

Non-Major Bleeding

- Any bleeding that is not major/life-threatening

Critical Site Bleeding

Site	Type of Bleed
Central nervous system	Intracranial Intraocular Spinal
Thoracic	Abdominal Airway Cardiac tamponade Hemothorax Retroperitoneal
Extremities	Intra-articular Intramuscular

Tomaselli GF et al. *J Am Coll Cardiol.* 2020; 76:594-622.

Invasive Procedures

Immediate

- Life-, limb-, organ-saving intervention
- Minutes

Urgent

- Potentially life-threatening, may threaten limb/organ, fixation of fractures, pain/distressing symptoms
- Defer for at least 12-24 hr if possible
- Lab monitoring ?

Expedite

- No immediate threat
- Can defer for days; only need to withhold DOAC

Laboratory Monitoring

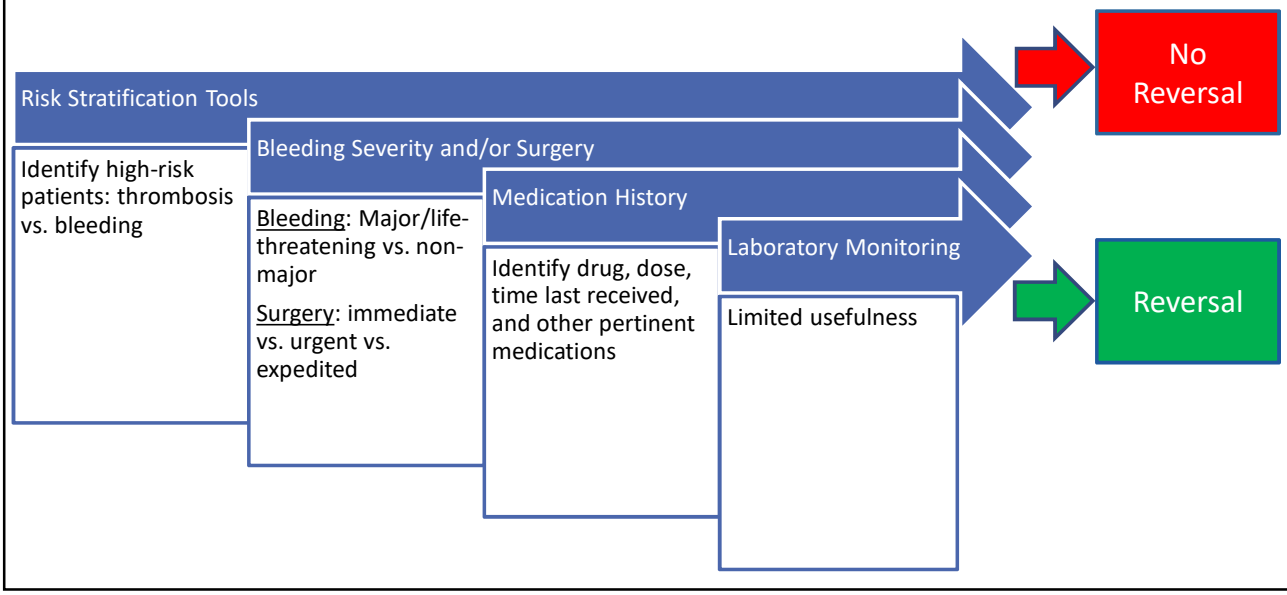
DOAC	Quantitative					Qualitative (Screening Assays)	
	dTT	ECA	ECT	Anti-Xa	LC-MS/MS	TT	Heparin or LMWH Anti-Xa*
Dabigatran	✓	✓	✓	-	✓	✓	-
Apixaban	-	-	-	✓	✓	-	✓
Edoxaban	-	-	-	✓	✓	-	✓
Rivaroxaban	-	-	-	✓	✓	-	✓

*ISTH suggests consideration of DOAC reversal in patients with a plasma DOAC concentration >50 ng/mL.

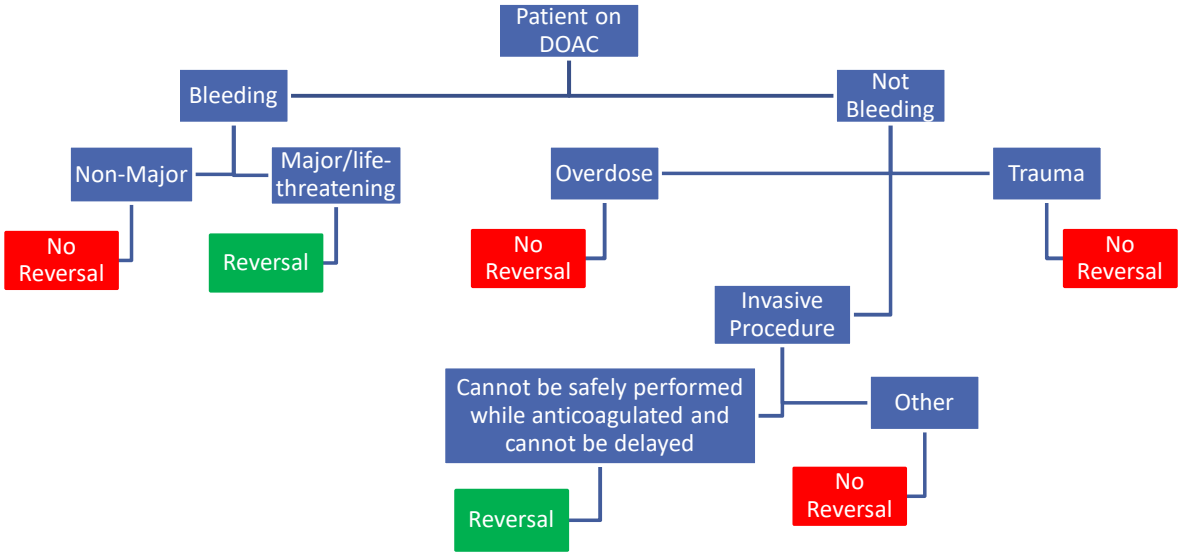
dTT = dilute thrombin time
ECA = ecarin clotting assay
ECT = ecarin clotting time
LC-MS/MS = liquid chromatography–tandem mass spectrometry
TT = thrombin time
LMWH = low molecular weight heparin
ISTH = International Society on Thrombosis and Haemostasis

Levy J et al. *J Thromb Haemost.* 2016;14:623-7.
Cuker A et al. *Am J Hematol.* 2019;94:697-709.
Tomaselli GF et al. *J Am Coll Cardiol*. 2020;76:594-622.

Assessment Approach for Reversal



Reversal Algorithm



Cuker A et al. *Am J Hematol*. 2019;94:697-709.

Patient Case

- 67-year-old male
- PMH: HTN, HLD, AF, CVA, DM
- Social history: none

Pertinent Info	
Weight: 88 kg	BMI: 28 kg/m^2
Temperature: 99.7F	HR: 109 bpm
BP: 127/68 mm Hg	RR: 23
O_2 saturation: 93%, room air	
CrCl 82 mL/min	

2300
- Fell down set of stairs and hit his head and is found w/abrasion to his scalp

2345
- Arrives to emergency department

0015
- CT head: subdural hematoma

0130
- Apixaban identified as home medication

Patient Case Continued

Apixaban 5 mg last taken at 1800, currently 0130 the following day. He remains GCS of 15, neurosurgery consulted with no intervention, and transferred to ICU.

Which of the following strategies would you implement?

a. PCC4 2000 units
b. PCC4 25 units/kg
c. PCC4 50 units/kg
d. Andexanet alfa low dose
e. None of the above

Patient Case Continued

Patient is now with a 48-hr stable head CT, no neurological deficits, and ready to downgrade outside of the ICU.

At this point, which of the following strategies would you implement?

a. Withhold anticoagulation indefinitely
b. Restart apixaban today
c. Start VTE prophylaxis, assess apixaban restart at 7-day f/u
d. No VTE prophylaxis, restart anticoagulation in 4 weeks

Reversal Strategies

Supportive	DOAC Removal	Non-specific	Specific
• Compression • Blood Products • Fluid Resuscitation • Surgical Hemostasis	• Charcoal • Hemodialysis	• PCC4 • aPCC	• Idarucizumab • Andexanet Alfa

Factor Replacement

	FFP	rFVIIa (NovoSeven RT)	PCC3 (Profilnine SD)	PCC4 (Kcentra)	aPCC (FEIBA)
Origin	Single donor plasma	Recombinant	Pooled human plasma	Pooled human plasma	Pooled human plasma
Factor content	All	VIIa	II, IX, X	II, VII, IX, X	II, VIIa, IX, X

NovoSeven RT (coagulation factor VIIa, recombinant) PI. Plainsboro, NJ: Novo Nordisk Inc; 2020 Jul.
Profilnine SD (factor IX complex) PI. Los Angeles, CA: Grifols Biologicals Inc.; 2010 Aug.
Kcentra (prothrombin complex concentrate, human) PI. Kankakee, IL: CSL Behring LLC; 2018 Oct.
FEIBA (anti-inhibitor coagulant complex) PI. Lexington, MA: Baxalta US Inc.; 2020 Feb.

Summary of Non-Specific Reversal

- Off-label use for DOAC reversal
- Limited to observational data
  - Conflicting data for both laboratory and clinical endpoints
- Majority of data with PCC4 vs. aPCC
- Dosing is guideline dependent
  - Fixed dosing: 2000 units
  - Weight-based dosing: 25-50 units/kg

Milling T et al. *Am J Emerg Med.* 2020;1890-903; Panos NG et al. *Circulation*. 2020;141:1681-9; Majeed A et al. *Blood*. 2017;130:1706-12; Schulman S et al. *Thromb Haemost*. 2018;118:842-51.

Specific Reversal Agents

Idarucizumab

- Monoclonal antibody fragment
- FDA-approved for reversal of dabigatran
- Binds free and thrombin bound dabigatran
- PK/PD
  - Onset: minutes
  - Duration: ~24 hr
  - Elimination T1/2: 47 min (initial), 10.3 hr (terminal)

Andexanet Alfa

- Modified human FXa decoy protein
- FDA-approved for reversal of apixaban and rivaroxaban
- Binds and sequesters FXa inhibitor; increases thrombin potential
- PK/PD
  - Onset: rapid
  - Duration
    - Anti-FXa activity: 2 hr post infusion completion
    - Thrombin generation: 22 hr
  - Elimination T1/2: ~1 hr

Andexxa (coagulation factor Xa, recombinant [inactivated]-zhzo) PI. South San Francisco, CA: Portola Pharmaceuticals, Inc.; 2020 Sep; Praxbind (idarucizumab) PI. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2018 Apr.

Idarucizumab Dosing and Preparation

- Dosing: 5 g IV x1
  - Administered as two consecutive infusions or as two boluses of 2.5 g no more than 15 minutes apart
- Preparation: 5 g boxed kit
  - Ready-to-use sterile glass vial containing 50 mL of 50 mg/mL concentration (2500 mg/vial), x2 vials

Praxbind (idarucizumab) PI. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2018 Apr.

RE-VERSE AD Trial

Idarucizumab for dabigatran reversal — full cohort analysis	
Methods	Multicenter, prospective, single-cohort study
Patients	≥ 18 years of age at entry on dabigatran etexilate Group A: overt, uncontrollable, or life-threatening hemorrhage Group B: Required surgery that could not be delayed for at least 8 hours and normal hemostasis required
Interventions	Idarucizumab 2.5 g x1 then repeat 2.5 g x1 within 15 min. Total of 5 g
Outcomes	**Primary outcome**: max % reversal based on dTT or ECT (100%) **Secondary outcomes**: Group A: extent of bleeding and hemodynamic stability (68% bleeding cessation at 24 hr, remaining patients it was unclear) Group B: hemostasis during intervention classified by physician as normal or as mildly, moderately, or severely abnormal (93.4%, 5.1%, 1.5%, 0%) 30-day Mortality; Thrombosis

Pollack CV Jr et al. *N Engl J Med.* 2017;377:431-41.

Andexanet Alfa Dosing and Preparation

	Last Dose	< 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	
Edoxaban[a]	Any dose	High dose	Limited data

Low dose: Bolus 400 mg at target rate 30 mg/min followed by continuous infusion 4 mg/min for ≤ 120 min

High dose: Bolus 800 mg at target rate 30 mg/min followed by continuous infusion 8 mg/min for ≤ 120 min

[a]Andexanet alfa is not FDA approved for reversal of edoxaban.

- 100-mg vial: Low dose = 9 vials, High dose = 18 vials
- 200-mg vial: Low dose = 5 vials, High dose = 9 vials
- Gently swirl vial until complete dissolution, DO NOT shake
- Typical dissolution time 3 to 5 minutes

Andexxa (coagulation factor Xa, recombinant [inactivated]-zhzo) PI. South San Francisco, CA: Portola Pharmaceuticals, Inc.; 2020 Sep.

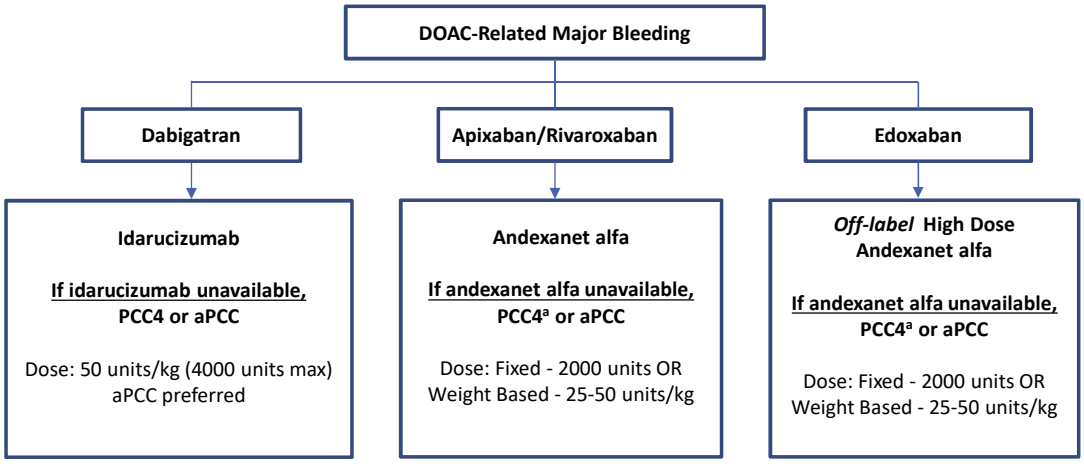
Connolly SJ et al. *N Engl J Med.* 2019; 380:1326-35.

ANNEXA-4

Andexanet Alfa for the Reversal of FXa Inhibitor Activity	
Methods	Multicenter, prospective, open-label single group study
Inclusion	> 18 years of age FXa inhibitor or LMWH within past 18 hr with acute major bleed
Exclusion	Planned surgery within 12 hr, ICH GCS < 7 or estimated hematoma volume > 60 mL, expected survival < 1 month, thrombotic event within 2 weeks of enrollment, use of VKAs, dabigatran, PCC, FVIIa, whole blood or plasma within 7 days
Interventions	Andexanet alfa bolus and continuous infusion: High dose OR low dose
Outcomes	Co-Primary Efficacy Outcomes: Percent change from baseline in anti-FXa activity **(apixaban/rivaroxaban 92%, enoxaparin 75%),** Percentage of patients with excellent or good hemostatic efficacy 12 hr after infusion **(82%)** Safety Outcomes: Death (14%), thrombotic events **(10%),** and the development of antibodies to andexanet alfa or to native FX and FXa (0%)

Connolly SJ et al. *N Engl J Med.* 2019;380:1326-35.

DOAC Dependent Reversal



[a]Guidelines note stronger evidence for PCC4 for FXa antagonist reversal.

Cuker A et al. *Am J Hematol.* 2019;94:697-709; Tomaselli G et al. *J Am Coll Cardiol*. 2020;76:594-622.

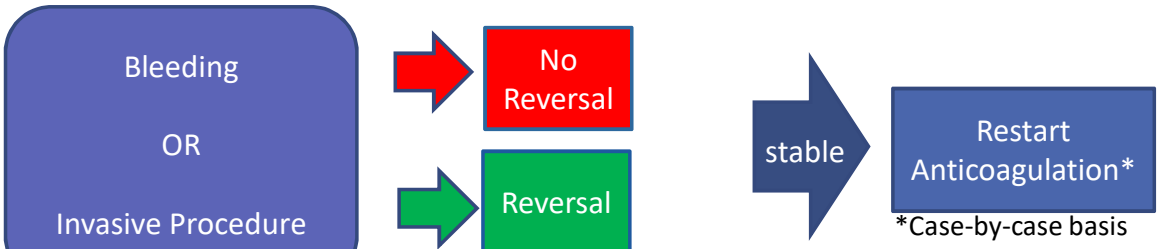
DOAC Reversal Guidelines: Summary

Guideline	Year	Indication	1st line	Alternative
NCS/SCCM	2016	ICH	DTI: idarucizumab FXa inhibitor: aPCC or PCC4 (50 units/kg)	DTI: PCC4 or aPCC (50 units/kg)
ASH[a]	2018	Life-threatening bleed	DTI: idarucizumab FXa inhibitor: andexanet alfa	FXa inhibitor: PCC4
ESO	2019	ICH	DTI: idarucizumab Apixaban/rivaroxaban: andexanet alfa Edoxaban: PCC4 (50 units/kg)	Apixaban/rivaroxaban: PCC4 (37.5–50 units/kg)
ACC/AHA/HRS	2019	Life-threatening bleed or surgery	DTI: idarucizumab FXa inhibitor: andexanet alfa	-
Anticoagulation Forum	2019	Major and life-threatening bleed	DTI: idarucizumab Apixaban/rivaroxaban: andexanet alfa[b] Edoxaban: andexanet alfa (high dose)	DTI: aPCC (50 units/kg) FXa inhibitor: PCC4 (2000 units)
ACC ECDP2	2020	Major bleed	DTI: idarucizumab Apixaban/rivaroxaban: andexanet alfa[b] Edoxaban: andexanet alfa (high dose)	DTI: PCC4 or aPCC (50 units/kg) FXa inhibitor: PCC4 (2000 units) or aPCC (50 units/kg)

[a]Does not recommend either PCC4 or andexanet alfa over the other.
[b]According to DOAC dose and timing of last administration.

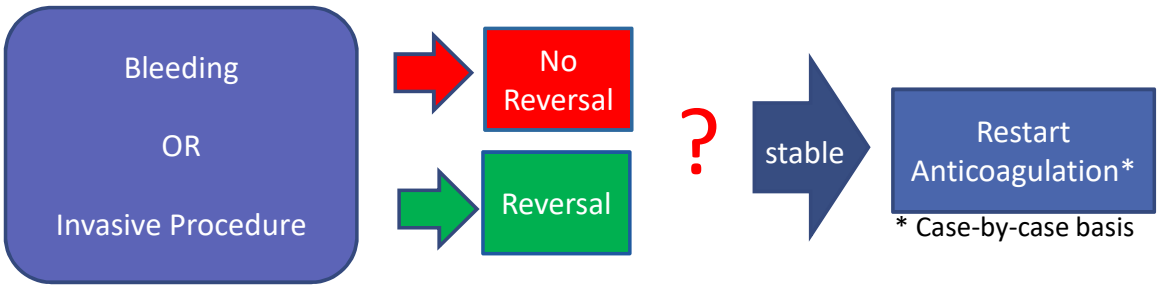
See Selected Resources slide for guideline citations.

Restarting Anticoagulation



Steffel J et al. *Eur Heart J*. 2018;39:1330–93.
Halvorsen S et al. *Eur Heart J*. 2017;38:1455-62.
Tomaselli G et al. *J Am Coll Cardiol*. 2020;76:594-622.

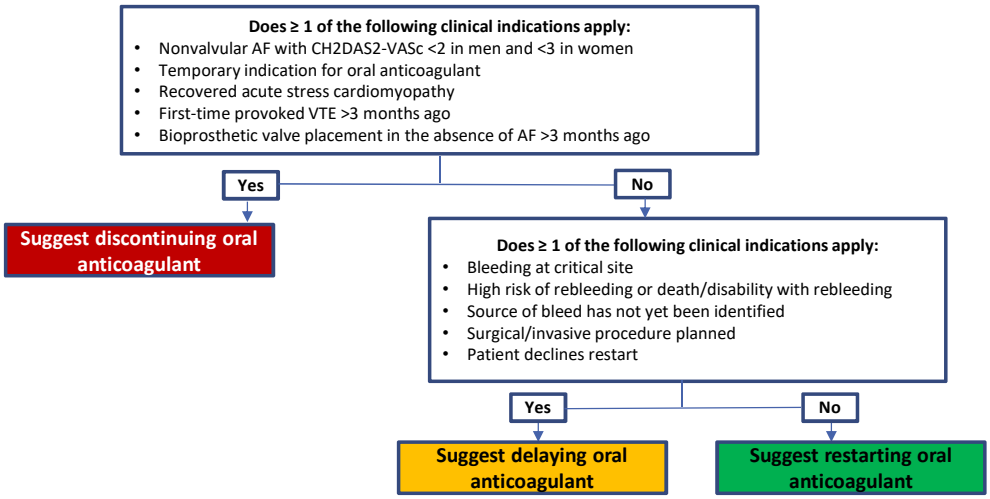
Restarting Anticoagulation



- Timing is controversial and dependent on bleed type and/or postoperative bleed risk
- Discontinue if inappropriate
- If unable to restart, consider alternative interventions
  - Left arterial appendage (LAA) occlusion
  - Inferior vena cava (IVC) filter

Steffel J et al. *Eur Heart J*. 2018;39:1330-93.
Halvorsen S et al. *Eur Heart J*. 2017;38:1455-62.
Tomaselli G et al. *J Am Coll Cardiol*. 2020;76:594-622.

Considerations for Restarting Anticoagulation



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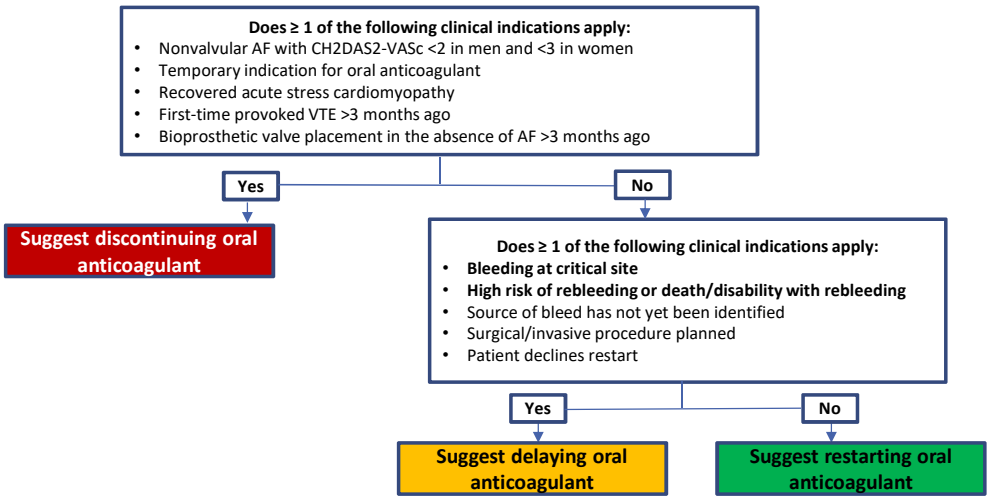
Considerations for Restarting Anticoagulation



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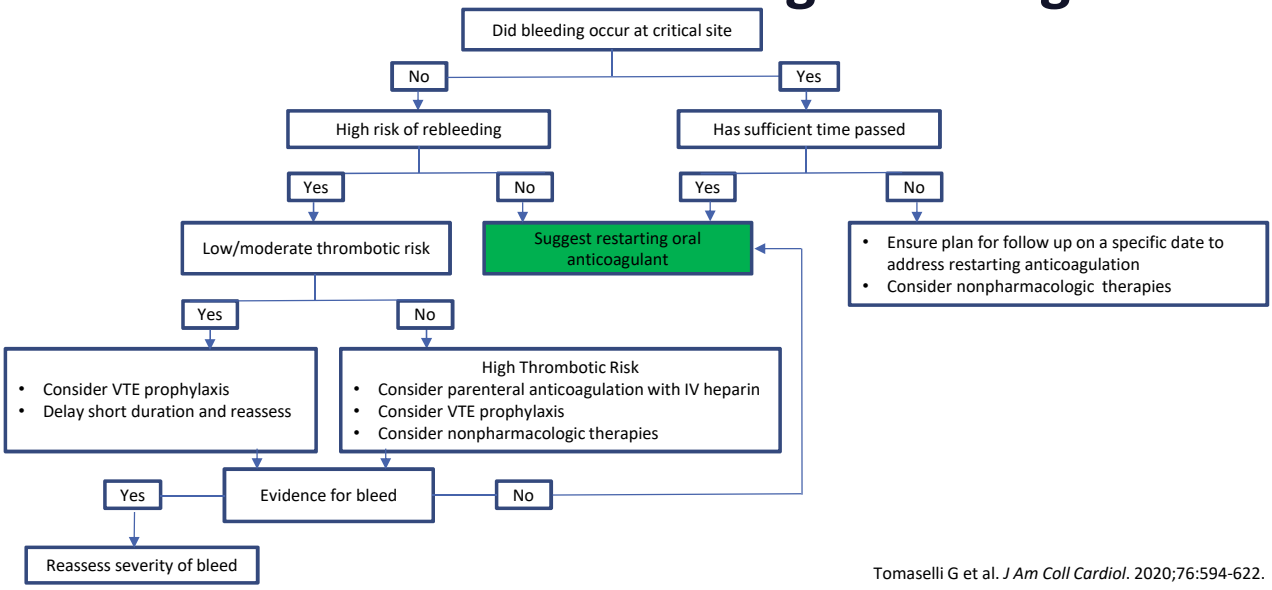
Considerations for Restarting Anticoagulation



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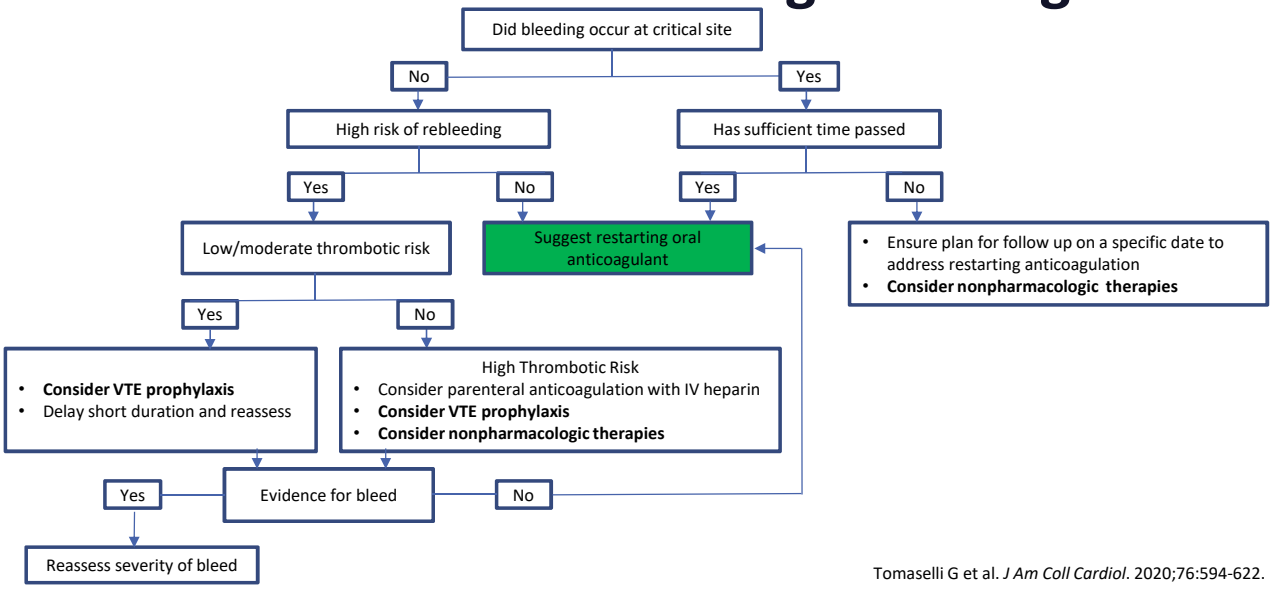
Considerations for Restarting Anticoagulation



Tomaselli G et al. *J Am Coll Cardiol*. 2020;76:594-622.

Thrombosis Rates

Study	Atrial Fibrillation	Stroke	VTE	MI
RE-VERSE AD	95.7%	25.0%	53.6%	21.4%
ANNEXA-4	70.0%	37.5%	56.3%	6.2%
Panos et. al	78.6%	30.8%	61.5%	7.7%

% shown as event rates

Panos NG et al. *Circulation*. 2020;141:1681-9.
Connolly SJ et al. *N Engl J Med.* 2019;380:1326-35.
Pollack CV Jr et al. *N Engl J Med.* 2017;377:431-41.

Key Takeaways

- NPSGs are developed in order to provide safe administration of medications regarding anticoagulation management
- Given the risks of thrombotic events, patients should be appropriately selected for reversal and a plan should be developed for restarting anticoagulation
- DOAC reversal should consist of specific agents if available; non-specific blood factor products could be used as an alternative

Establishing a Cost-Effective, Standardized Institutional Approach to DOAC Reversal

The Cost of DOAC Reversal Agents

	~$5,800/pt	~$3,700/pt	~$29,000 – $58,000/pt
	Options Available: Non-Specific Reversal Agents (blood factor products)	**Idarucizumab**	**Andexanet Alfa**
Reversal Agent FDA Approval	2010 - 2015	2015	2018
Data to Support Use	Limited, observational: reversal for **bleeding or surgery**	Prospective, single cohort: reversal for **bleeding or surgery**	Prospective, single cohort: reversal for **bleeding ONLY**[a]

[a]Data with apixaban and rivaroxaban, limited or no data with edoxaban or betrixaban

Cost-effective?

Smith MN et al. *J Thromb Thrombolysis.* 2019;48:250-5; Buchheit J et al. *Crit Pathw Cardiol.* 2016;15(3):77-81.

Cost vs. Benefit of Andexanet Alfa

- True cost-effectiveness studies not available
- Some papers estimate andexanet alfa cost based on PCC4 data
  - Smith et al.
    - Estimated cost Δ between PCC4 and andexanet alfa: ~$53K/patient
  - Frontera et al.
    - Estimated cost of andexanet alfa > hospital reimbursement for 74% of patients who received PCC4
      - 2018 New Technology Add-on Payment (NTAP): ~$14K/patient

Frontera JA et al. *J Thromb Thrombolysis*. 2020;49:121-31. Smith MN et al. *J Thromb Thrombolysis.* 2019;48:250-5.

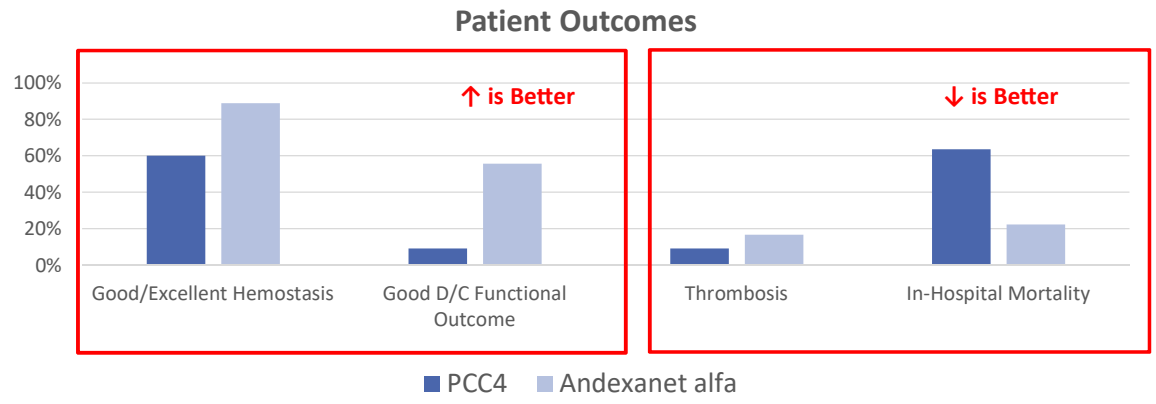
New Technology Add-on Payment (NTAP)

- Mechanism for CMS to address delays in updating DRG payments when new treatments emerge
- Hospitals can submit for NTAP for andexanet alfa used to treat Medicare patients IN ADDITION TO MS-DRG PAYMENT
- Additional payment equal to the lesser of (i) 65% of the cost of andexanet alfa being directly paid for in addition to the MS-DRG payment, or (ii) 65% of the amount by which the costs of the case exceed the standard MS-DRG payment
  - Maximum payment of $18,281.25 per patient
    - Since 10/1/2019

CMS = Centers for Medicare & Medicaid Services
MS-DRG = Medicare severity diagnosis-related group

Alexion Pharmaceuticals, Inc. Access and reimbursement. https://andexxa.com/ordering/#reimbursement (accessed 2021 Feb 4).

Case Series: Evaluation of Outcomes + Cost



29 patients (PCC4: 11; andexanet alfa: 18) with intracranial hemorrhage associated with apixaban or rivaroxaban

D/C = discharge

Barra ME et al. *J Thromb Haemost*. 2020;18:1637-47.

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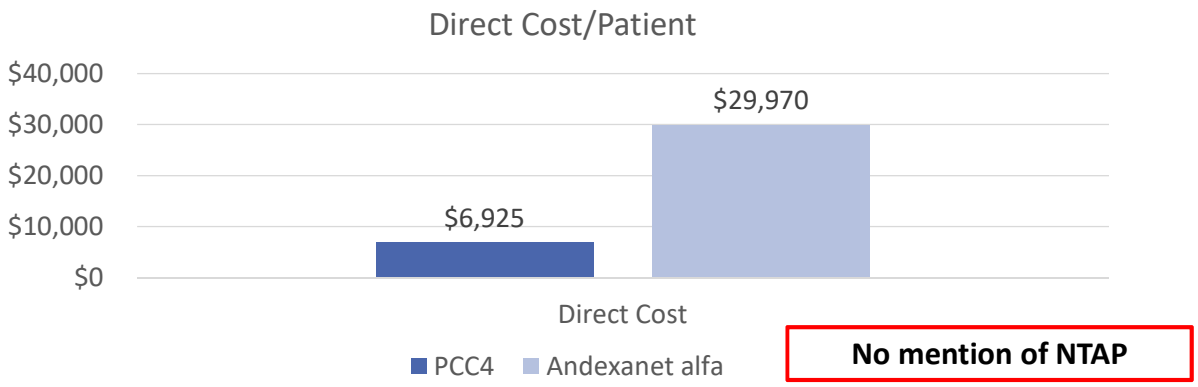
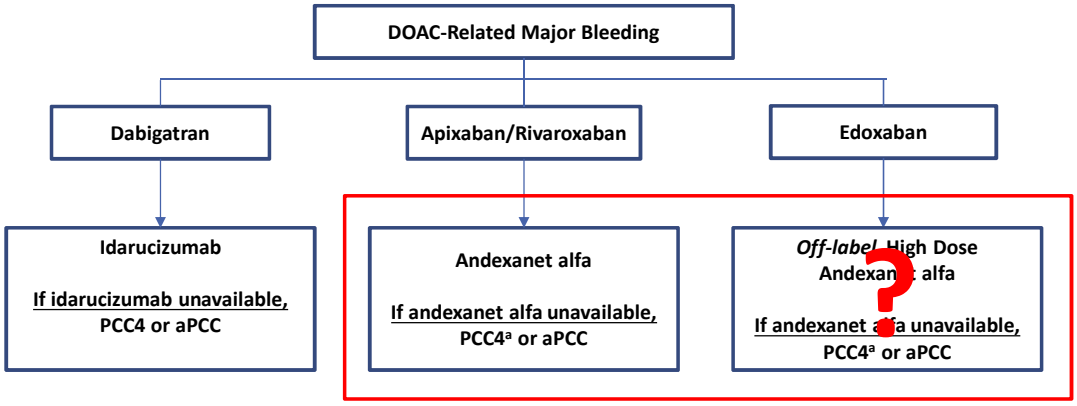


29 patients (PCC4: 11; andexanet alfa: 18) with intracranial hemorrhage associated with apixaban or rivaroxaban

Barra ME et al. *J Thromb Haemost*. 2020;18:1637-47.

Newest Guidelines Recommend…



[a]Guidelines note stronger evidence for PCC4 for FXa antagonist reversal.

Cuker A et al. *Am J Hematol.* 2019;94:697-709; Tomaselli GF et al. *J Am Coll Cardiol*. 2017;76:594-622.

Reversal for Urgent or Immediate Surgery?

- Non-specific reversal agents
  - Some data for non-bleeding patients requiring surgery/procedure
- Idarucizumab
  - RE-VERSE AD: Included bleeding and non-bleeding patients requiring surgery/procedure
- Andexanet alfa
  - ANNEXA 4: Included only bleeding patients

Limit andexanet alfa use to those with overt life-threatening bleeding or who require immediate (life- or limb-saving) surgery

Connolly SJ et al. *N Engl J Med.* 2019; 380:1326-35; Pollack CV Jr et al. *N Engl J Med.* 2017; 377:431-41.

Formulary Management Considerations

Should newer agents be part of your hospital's reversal approach?

- What type of patient population is at your site?

Characteristics	Hospital A	Hospital B	Hospital C
Location	Suburban	Urban	Rural
Beds	225	900	100
ED Volume	50,000 visits/year	150,000 visits/year	60,000 visits/year
Teaching	No	Yes	No
Trauma	Level 3	Level 1	Level 4
Neurosurgery	Within System	Yes	No
ICU Beds	16 MICU/12 SICU	70 MICU/40 SICU/40 CVICU/16 Neuro	6 mixed ICU beds
Dedicated ED Pharmacy Services	16 hours/day 7 days/week	24 hours/day 7 days/week	None
Bleeding Patients	0 – 1 patient/month	2 – 5 patients/month	2 – 3 patients/year

Survey: Anticoagulation Reversal

Respondents (n)	281
Critical care pharmacists	48%
Emergency medicine pharmacists	48%
United States	97.2%
Teaching hospital	64.1%
> 500 beds	55.2%
200 to 500 beds	37.7%
< 200 beds	7.1%
24-hour Emergency Department Pharmacy Services	21%

Rowe AS et al. *Hosp Practice.* 2020;48:123-7.

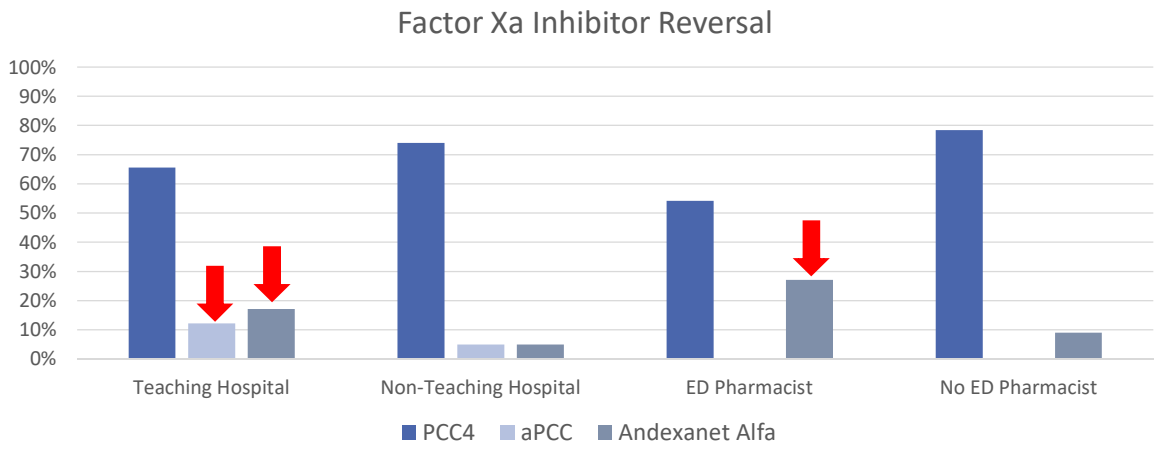
Survey: Anticoagulation Reversal

	PCC4	aPCC	Idarucizumab	Andexanet Alfa
Dabigatran	3.2%	0.4%	**96.4%**	n/a
Factor Xa Inhibitors	**73.3%**	12.8%	n/a	9.6%

n/a = not applicable

Rowe AS et al. *Hosp Practice.* 2020;48:123-7.

Survey: Factor Xa Inhibitor Reversal



Rowe AS et al. *Hosp Practice.* 2020;48:123-7.

Hospital Characteristics

- Frequency of patients presenting with life-threatening bleeding
- Emergency department volume
- Types of patients presenting with bleeding
  - Neurologic
  - Trauma
  - GI
- Experience with blood factor product strategy
- 340b eligible

Faine BA et al. *Am J Health-Syst Pharm.* 2018;75:72-7; Rowe AS et al. *Hosp Practice.* 2020;48:123-7.

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Non-Specific or Specific Reversal Agents?

Hospital A

- Lower ED volume
- Won't get many trauma or neuro patients
- Some MICU – GI bleeds?
- Some ED pharmacy services but not 24/7
- Infrequent bleeding patients
- Part of a larger system

Non-Specific or Specific Reversal Agents?

Hospital B

- Very high ED volume
- Many trauma and neuro patients
- Likely a referral center
- Many MICU beds
- Capability to manage many complex patient populations
- 24/7 ED pharmacy services
- Many bleeding patients
- Likely the "flagship" of a larger system
- Maybe 340B eligible?

Non-Specific or Specific Reversal Agents?

Hospital C

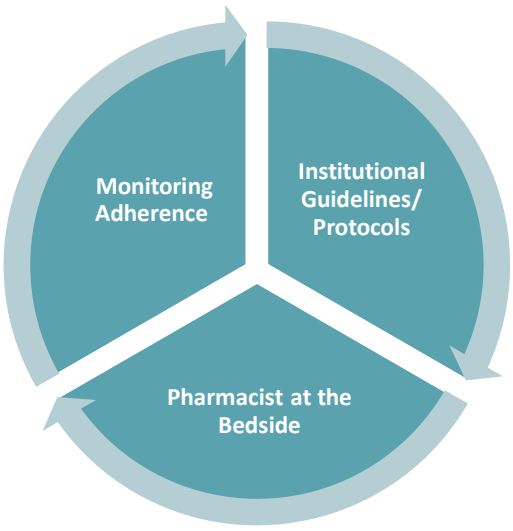
- Lower ED volume
- Won't get many trauma or neuro patients
- No trauma or neurosurgery
- Limited ICU capacity
- No dedicated ED pharmacy services
- Rarely see bleeding patients
- Rural, not part of a system, stabilize and transfer

Formulary Management Considerations

Should newer agents be part of your hospital's reversal approach?

- Do you have a mechanism to standardize and monitor use?

Standardizing DOAC Reversal



79.7% of hospitals surveyed have a DOAC reversal protocol

0 of 103 rural and community hospitals with low volume ED surveyed have a DOAC reversal protocol

Faine BA et al. *Am J Health-Syst Pharm.* 2018;75:72-7; Rowe AS et al. *Hosp Practice.* 2020;48:123-7.

Standardizing Use of Reversal Agents

Institution-wide Approach

- Establish guidelines or protocols and build into electronic medical record system
  - Pharmacy leadership and interprofessional participation are critical
  - **How** to reverse, rather than **who** to reverse
  - Meets The Joint Commission National Patient Safety Goal Element of Performance 2 (TJC NPSG EP2)

Institutional Reversal Guidelines

Standardize the following

- Reversal strategy for each anticoagulant
- Reversal agent dosing
- Monitoring
- Administration information (IV push vs. infusion)
- Interpretation tips for lab values
- Guidance for reinitiating anticoagulation

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

Monitoring Adherence to Guidelines and Protocols

Formal Stewardship Program

- University of North Carolina Medical Center
- Benign hematology pharmacist became part of a coagulation consult service team
  - Review of all patients requiring blood factor products
- Overall: $4 million in savings over approximately 4 years
  - Lower doses
  - Continuous infusions instead of bolus dosing → less drug
  - Optimized blood factor selection

Amerine LB et al. *Am J Health-Syst Pharm.* 2015;72:1579-84.

Anticoagulation Stewardship Team

Team consisted of 2 pharmacists and 1 hematologist

	Before Stewardship Service Implementation (Apr to Jun 2015)	After Stewardship Service Implementation (Sep 2015 to Jul 2016)
Inappropriate* PCC4 orders	55.8%	2.6%
Cost of inappropriate orders	$104,274	$10,831

***Inappropriate = not aligned with institutional guidelines**

Wychowski MK et al. *J Thromb Thrombolysis.* 2017;43:380-6.

Assuring Appropriate Reversal Approach

Pharmacy Continuum of Care

Emergency Department Pharmacist	Pharmacist Verifying Order	ICU Pharmacist	Step-Down Unit Pharmacist
Right candidate	Right candidate	Right candidate	Response to therapy
Right drug	Right drug	Right drug	VTE prophylaxis
Right dose	Right dose	Right dose	Identify potential causes
Expedite preparation	Expedite preparation	Response to therapy	Restart anticoagulation
Response to therapy		VTE prophylaxis	

Key Takeaways

- PCC4 and idarucizumab are similar in cost, while andexanet alfa is considerably more costly. Whether these newer reversal agents differ from PCC4 in efficacy is unclear.
- NTAP is an extra payment that can help health systems recoup some of the cost of andexanet alfa.
- The pharmacist can play a key role in ensuring a standardized, safe, and cost-effective institutional approach to DOAC reversal.

Selected Resources

Christensen H, Cardonnier C, Korv J et al. European Stroke Organisation guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. *Eur Stroke J.* 2019; 4:294-306.

Cuker A, Burnett A, Triller D et al. Reversal of direct oral anticoagulants: guidance from the Anticoagulation Forum. *Am J Hematol*. 2019; 94:697-709.

Frontera JA, Lewin JJ III, Rabinstein AA et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care.* 2016; 24:6-46.

January CT, Wann LS, Calkins H et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2019;74:104-32.

Tomaselli GF, Mahaffey KW, Cuker A et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020; 76:594-622.

Witt DM, Nieuwlaat R, Clark NP et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv.* 2018; 2:3257-91.

How will you change your practice?

- Educate the healthcare team about assessing the need for DOAC reversal
- Help select the reversal strategy (right drug, right dose) for individual patients with or at risk for DOAC-associated bleeding
- Address the practical issues related to preparation of reversal agents
- Begin establishing a standardized interprofessional approach for managing use of DOAC reversal agents
- Implement policies, protocols, or guidelines designed to provide anticoagulation reversal in the most cost-effective manner
- Evaluate the need to restart anticoagulation after treatment for bleeding

Take a moment to reflect on changes you would make based on what you learned today

Abbreviations Used in Presentation

ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
aPCC	activated prothrombin complex concentrate
ASH	American Society of Hematology
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
BMI	body mass index
BP	blood pressure
CHA_2DS_2-VASc	congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category
CMS	Centers for Medicare & Medicaid Services
CrCl	creatinine clearance
CT	computed tomographic
CVA	cerebrovascular accident
CVICU	cardiovascular intensive care unit
D/C	discharge
DM	diabetes mellitus
DOAC	direct-acting oral anticoagulant
DRG	diagnosis-related group
DTI	direct thrombin inhibitor
dTT	dilute thrombin time
ECA	ecarin clotting assay
ECDP	expert consensus decision pathway
ECT	ecarin clotting time
ED	emergency department
ESO	European Stroke Organisation
FDA	Food and Drug Administration
FFP	fresh frozen plasma
FVIIa	activated factor VII
FX	factor X
FXa	activated factor X
FXaI	activated factor X inhibitor
GCS	Glasgow Coma Scale
GI	gastrointestinal
HAS BLED	hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol

HEMORR$_2$HAGES	hepatic or renal disease, ethanol abuse, malignancy history, older (age >75), reduced platelet count or function, rebleeding risk, hypertension (uncontrolled), anemia, genetic factors, excessive fall risk, stroke history
HR	heart rate
HRS	Heart Rhythm Society
HTN	hypertension
ICH	intracranial hemorrhage
ICU	intensive care unit
ISTH	International Society on Thrombosis and Haemostasis
IVC	inferior vena cava
LAA	left arterial appendage
LC-MS/MS	liquid chromatography–tandem mass spectrometry
LMWH	low molecular weight heparin
MICU	medical intensive care unit
MS-DRG	Medicare severity diagnosis-related group
NCS	Neurocritical Care Society
NPSG	National Patient Safety Goal
NTAP	New Technology Add-On Payment
ORBIT	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
PCC	prothrombin complex concentrate
PCC3	three-factor prothrombin complex concentrate
PCC4	four-factor prothrombin complex concentrate
PI	prescribing information
PMH	past medical history
rFVIIa	recombinant activated factor VII
RR	respiratory rate
SCCM	Society of Critical Care Medicine
SICU	surgical intensive care unit
TT	thrombin time
VKA	vitamin K antagonist
VTE	venous thromboembolism