Reversal Strategies for DOAC-Related Bleeding: Patient Assessment and Current Evidence

PRESENTED AS A LIVE WEBINAR

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FACULTY

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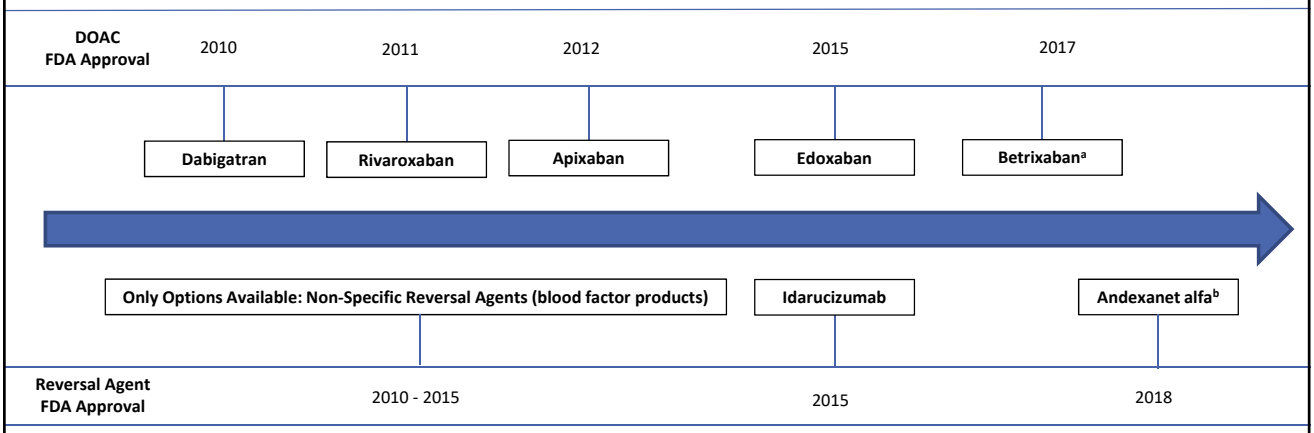
Learning Objectives

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

- Discuss the incidence, severity, and cost of bleeding complications associated with the use of direct-acting anticoagulant (DOAC) therapy.
- Given patient characteristics, develop a systematic patient assessment approach to identify the optimal anticoagulant reversal strategy.
- Summarize recent clinical evidence regarding the safety and efficacy of DOAC reversal.

Impact of Bleeding Complications Associated with the Use of DOAC Therapy

DOACs and Reversal Agents



[a]Recently discontinued by manufacturer.
[b]Coagulation factor Xa, recombinant [inactivated]-zhzo (also known as andexanet alfa).

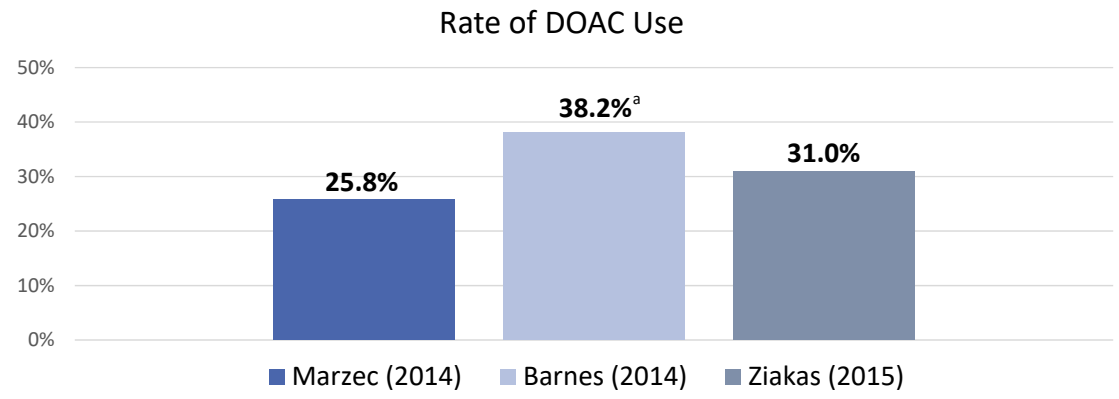
Kustos SA et al. *Medicines.* 2019;6:103. doi.org/10.3390/medicines6040103.

Increased Use of Oral Anticoagulants

- ↑Oral anticoagulant use in last 10 – 15 years
  - Atrial fibrillation guideline changes
    - $CHADS_2$ → CHA_2DS_2-VASc
      - More patients eligible
  - Underuse when warfarin was only option
    - DOACs may be viewed more favorably

Gadsbøll K et al. *Eur Heart J.* 2017; 38:899-906.
Barnes GD et al. *Am J Med*. 2015; 128:1300-5.

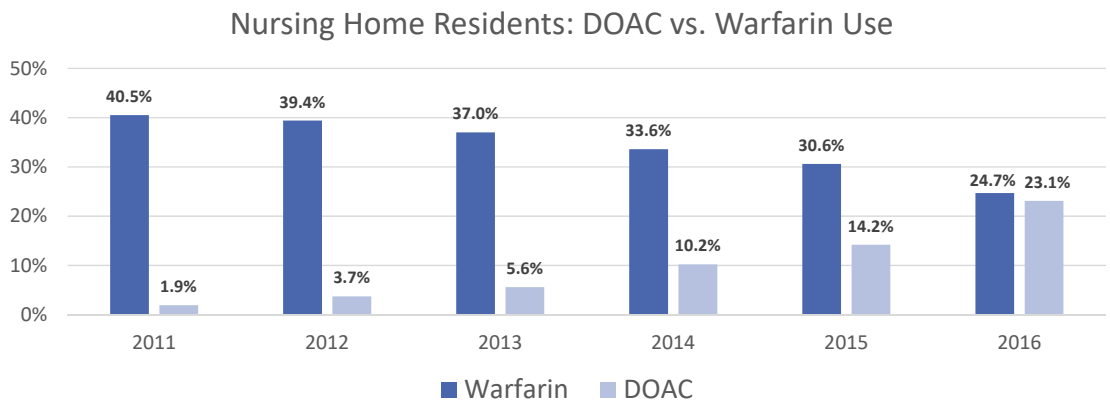
DOAC Use on the Rise



[a]Denotes % of office visits for DOAC use, not patients using DOACs

Barnes GD et al. *Am J Med*. 2015; 128:1300-5; Marzec LN et al. *J Am Coll Cardiol*. 2017; 69:2475-84; Ziakas PD et al. *PLoS One*. 2018; 13:e0198674.

DOAC Use in Older Patients



Alcusky M et al. *J Am Heart Assoc.* 2019; 8:e012023. doi: 10.1161/JAHA.119.012023.

Risk Factors for DOAC-Related Bleeding

Patient Factors

- ↑ Age
- ↓ Kidney function
- Bleeding history
- Anemia

Medications

- Aspirin
- Nonsteroidal anti-inflammatory drugs
- Antiplatelet agents

Hylek EM et al. *J Am Coll Cardiol*. 2014; 63:2141-7; Sherwood MW et al. *J Am Coll Cardiol*. 2015; 66:2271-81; Eikelboom JW et al. *Circulation.* 2011; 123:2363-72.

Incidence of DOAC-Related Bleeding

Registry following 272,315 patients with atrial fibrillation (median follow-up = 4 years)

	Major/Life-Threatening Bleeding	Intracranial Bleeding
No anticoagulant	1.4 (1.3 – 1.4)	0.3 (0.3 – 0.3)
DOAC alone	2.2 (2.1 – 2.3)	0.5 (0.4 – 0.5)
DOAC + antiplatelet medication	4.0 (3.5 – 4.5)	0.6 (0.4 – 0.8)
DOAC triple therapy	8.8 (6.4 – 11.9)	0.9 (0.3 – 2.1)

Bleeding per 100 person years (95% confidence interval)

DOAC triple therapy = DOAC + aspirin + antiplatelet medication

van Rein N et al. *Circulation.* 2019; 139:775-86.

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.

DOAC-Related Bleeding Outcomes

3-year, prospective, cohort study

	DOAC-Related Bleeding
Total Patients	**401**
Age, years[a]	82 (75–88)
Patients followed up In-hospital death within 30 days Days in hospital if died[a] Days in hospital if discharged[a]	**393** 84 (21%) 3 (1–10) 6 (3–11)
Complications in hospital	85 (23%)

[a]Median (IQR)

IQR = interquartile range

Green L et al. *Haematologica*. 2018; 103:738-45.

Direct Costs of DOAC-Related Bleeding

Analysis of 456 patients admitted with DOAC related bleeding (2010 – 2015)

	Length of Stay Measure
Total LOS: Median (IQR)	5.4 (3.3 – 9.5) days
ICU utilization	27.7%
ICU LOS	3.4 (2.0 – 6.9) days

	Cost[a]
Total cost: Median (IQR)	$5237 ($2866 – $9566)
Blood product cost: Mean (SD)	$1456 ($1482)

GI = 61.6%
ICH = 21.3%

[a]Presented in 2017 Canadian dollars

LOS = length of stay, GI = gastrointestinal
ICH = intracranial hemorrhage

Xu Y et al. *Thromb Res*. 2019; 182:12-9.

Short- and Long-Term Cost of DOAC-Related Major/Life-Threatening Bleeding

Type of Bleeding	Total Index Hospital Cost (mean)
Overall	$28,059
Critical site	$37,254
Gastrointestinal	$19,819
Intracranial	$45,447
Procedural	$72,392
Trauma	$31,504

Standard deviation not reported

- 3081 patients
  - Atrial fibrillation and major/life-threatening bleeding related to factor Xa inhibitors
- Total bleeding-related costs within 30 days (excludes index event)
  - $6,181 ± $57,616
- Total bleeding-related costs within 12 months (excludes index event)
  - $9,796 ± $64,376

Deitelzweig S et al. *J Med Econ.* 2017; 20:1217-23.

Key Takeaways

- Oral anticoagulant use in general and DOAC use specifically has increased in the last several years
- Major/life-threatening bleeding is any bleeding that occurs in a critical site OR is associated with hemodynamic instability OR is associated with a hemoglobin decline of at least 2 g/dL or requiring at least 2 units of packed red blood cells
- DOAC-related bleeding has a significant impact on patient outcomes and costs

Identifying the Optimal Anticoagulant Reversal Strategy

Patient Case

- 67-year-old male
- PMH: HTN, HLD, AF, CVA, DM
- Social history: alcohol use

Pertinent Info	
Weight: 88 kg	BMI: 28 kg/m^2
Temperature: 99.7F	HR: 119 bpm
BP: 220/100 mm Hg	RR: 23
O_2 saturation: 93%, room air	
CrCl 82 mL/min	

2300
- Found at base of stairs w/ altered mental status

2345
- Arrives to emergency department

0015
- CT head: Intracerebral hemorrhage w/midline shift

0130
- Apixaban identified as home medication

Emergency Department Management

BP 220/100 mm Hg

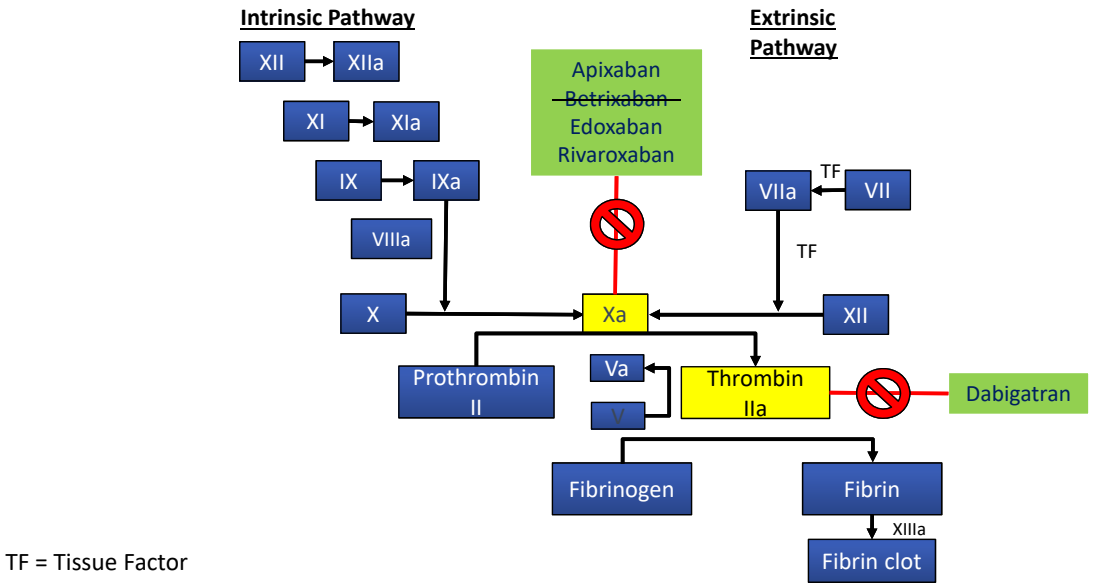
Nicardipine infusion

CT head– ICH with 4mm R→L midline shift

Andexanet alfa

Transferred to ICU

Coagulation Pathway: DOAC

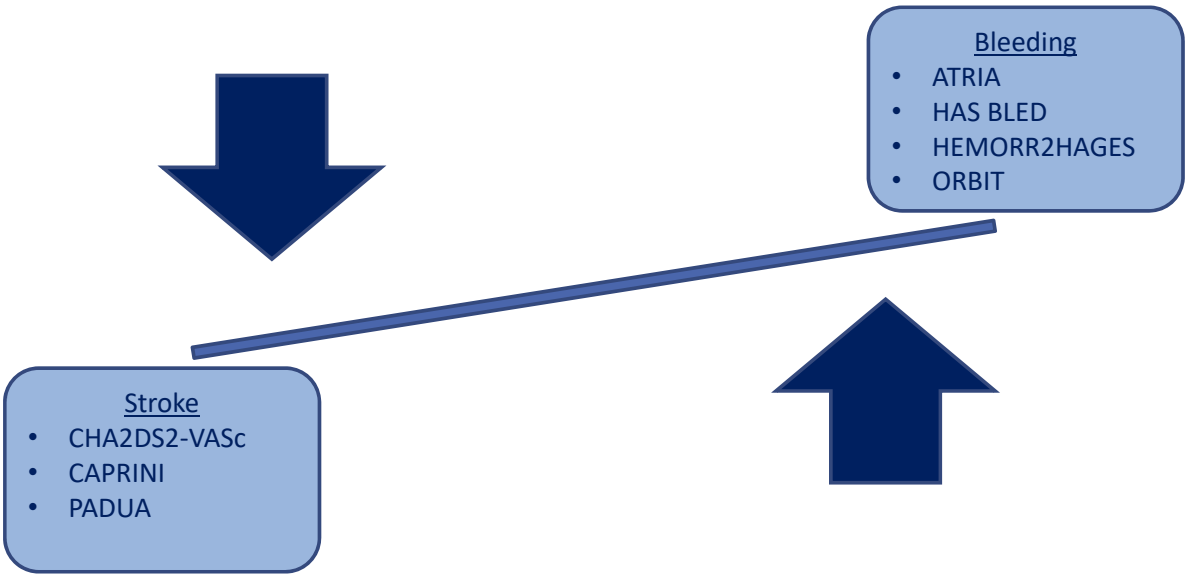


TF = Tissue Factor

Assessment Approach for Reversal

- Risk Stratification Tools
- Bleeding Severity, Immediate Surgery
- Medication History
- Laboratory Monitoring

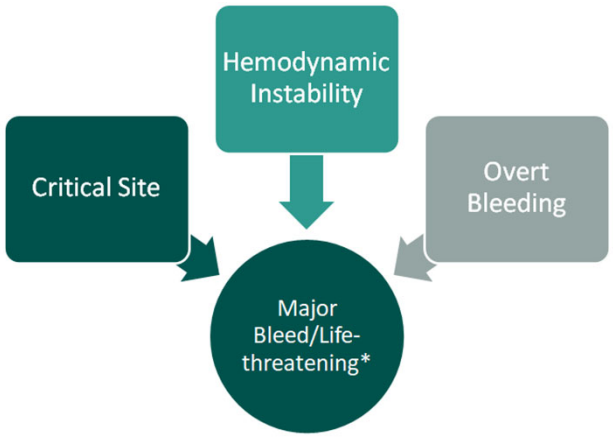
Risk Stratification



Bleeding Severity

Determine bleeding

- Severity
  - Major/life-threatening
  - Non-Major



* if ≥1 of the following applies the bleed is considered major/life-threatening

Medication History

- Accuracy is key
  - DOAC type
  - Dose
  - Last dose administered
- Other medications
  - Antiplatelets
  - Drug-drug interactions

DOAC Pharmacokinetics/Pharmacodynamics

	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Tmax (hr)	1-3	2-4	3-4	1-2
Vd (L)	50-70	50	21	107
Renal elimination (%)	80	36	27	50
$T_{1/2}$[a] (hr)	12-17	5-9	12	10-14

[a]In healthy adults

Pradaxa (dabigatran etexilate) prescribing information (PI). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2020 Jul; Xarelto (rivaroxaban) PI. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2020 Mar; Eliquis (apixaban) PI. Princeton, NJ and New York, NY: Bristol-Myers Squibb Company and Pfizer Inc; 2019 Nov; Savaysa (edoxaban) PI. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2020 Apr.

DOAC Plasma Levels

DOAC	Dose	Peak (ng/mL)	Trough (ng/mL)
Dabigatran[a]	150 mg twice daily (NVAF)	175 (117-275)	91 (61 -143)
	150 mg twice daily (PE/VTE)		60 (39-95)
Apixaban[b]	5 mg twice daily (NVAF)	171 (91-321)	103 (41-230)
	5 mg twice daily (PE/VTE)	132 (59-321)	63 (22-177)
Edoxaban[c,d]	60 mg daily (NVAF)	170 (125-245)[c]	36 (19-62)[c]
	60 mg daily (PE/VTE)	234 (149-317)[d]	19 (10-39)[d]
Rivaroxaban[e]	20 mg daily (NVAF)	249 (184-343)	44 (12-137)
	20 mg daily (PE/VTE)	270 (189 -419)	26 (6-87)

[a]Reported as mean (25^{th} – 75^{th} percentile), [b]Reported as median (5^{th} – 95^{th} percentile), [c]Reported as median (1.5x IQR)
[d]Reported as median (IQR), [e]Reported as mean (5^{th} – 95^{th} percentile)

NVAF = non-valvular atrial fibrillation, PE = pulmonary embolism, VTE = venous thromboembolism

Gosselin RC et al. *Thromb Haemost*. 2018; 118:437-50.

Laboratory Monitoring: Role in Assessment/Reversal

- Estimate degree of or presence of any activity
  - Special populations
    - Body weight extremes (>120 kg, <50 kg)
    - Elderly (>80 years)
    - Gastric surgery
    - Drug-drug interactions
  - Compliance concerns
  - Unplanned surgery
  - Major/life-threatening bleed

Unplanned Surgical Intervention

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 within days only need to withhold DOAC

Measuring DOAC Activity

Quantitative

Qualitative

Other

Quantitative Measures

DOAC	LC-MS/MS	dTT	ECT	ECA	Anti-Xa
Dabigatran	✓	✓	✓	✓	-
Apixaban	✓	-	-	-	✓
Edoxaban	✓	-	-	-	✓
Rivaroxaban	✓	-	-	-	✓

LC-MS/MS = liquid chromatography–tandem mass spectrometry
dTT = dilute thrombin time
ECT = ecarin clotting time
ECA = ecarin clotting assay

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

Quantitative Measures: Are We There Yet?

Accessibility	Standardization	Costs
• Availability • Turnaround time	• Calibrations • Degree of anticoagulation	• Direct • Indirect

Qualitative Measures

Exclusion of Clinically Relevant Drug Levels

- Refers to DOAC levels that may contribute to bleeding or surgical bleeding risk
  - >50 ng/mL serious bleed
  - >30 ng/mL bleeding risk

	aPTT	TT	PT	Anti-FXa (UFH/LMWH)
Medication				
Dabigatran[a]	✓	✓	-	-
Apixaban, edoxaban, rivaroxaban[b]	-	-	-	✓

[a]**Normal aPTT:** usually excludes clinically relevant levels, **Normal TT:** excludes clinically relevant levels, **Prolonged TT**: unclear if significant or insignificant levels

[b]**Normal PT and aPTT:** may not exclude on-therapy or above on-therapy levels, **Anti-FXa:** below lower limit of quantitation probably excludes clinically relevant levels

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

Qualitative Measures

On-Therapy OR Above On-Therapy Levels

	aPTT	PT
Medication		
Dabigatran[a]	✓	-
Apixaban, edoxaban, rivaroxaban[b]	-	✓

[a]**Normal aPTT:** may not exclude on-therapy levels, **Prolonged aPTT:** suggests on-therapy or above on-therapy levels are present

[b]**Normal PT:** may not exclude on-therapy or above on-therapy levels, **Prolonged PT:** suggests that on-therapy or above on-therapy levels are present

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

Other Monitoring Tools

- Viscoelastic hemostatic assay (VHA)
  - Rotational thromboelastometry (ROTEM)
  - Thromboelastography (TEG)
  - Measures the formation or degradation of a fibrin clot in whole blood or plasma in real time
- R-time, along with specific DOAC assays are most accurate
- Data are conflicting and require more validation and standardization before routine use can be recommended

Dias J et al. *J Trauma Acute Care Surg*. 2019; 87:364-70.
Artang R et al. *Res Pract Thromb Haemost*. 2019; 3:391-96.
Mahamad S et al. *J Thromb Thrombolysis.* 2019; 47:272-9.

Summary of DOAC Lab Monitoring

- Quantitative
  - Would be best but lacks readily available tests
  - Requires validated calibration
- Qualitative
  - Ruling out “on-therapy” OR “clinically relevant” levels
  - Highly variable, reagent dependent
- VHA
  - R-time is the most sensitive parameter
  - Results are varying with conflicting data
  - Still requires further validation and standardization

Assessment Approach for Reversal

Risk Stratification Tools

- Identify high-risk patients: thrombosis vs. bleeding

Bleeding Severity and/or Surgery

- Bleeding: Major/life-threatening vs. non-major
- Surgery: immediate vs. urgent vs. expedited

Medication History

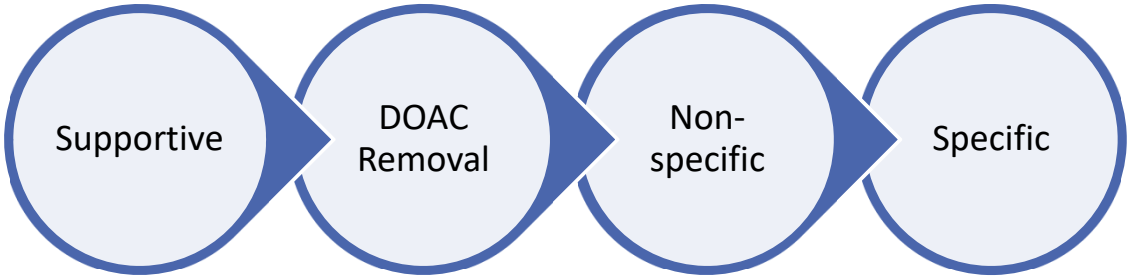
- Identify drug, dose (strength and last recevied), other pertinent medications

Laboratory Monitoring

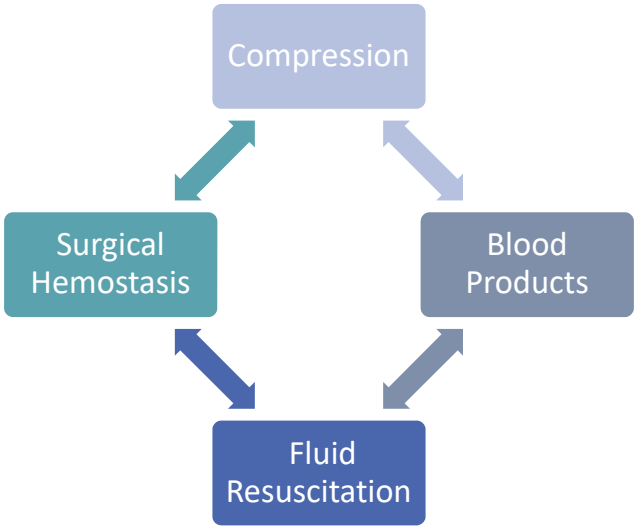
- Limited usefulness

DOAC Reversal Options

Reversal Strategies



Supportive Care



Removal Options

Activated charcoal

- Within 2 to 4 hr of last dose
- Based on T1/2 of the medication
- Risks: Aspiration
- A 50 g dose of activated charcoal reduced apixaban T1/2 from 13.4 hr to 5 hr
- Case reports suggest almost 100% neutralization when taken within 2 hr of dabigatran

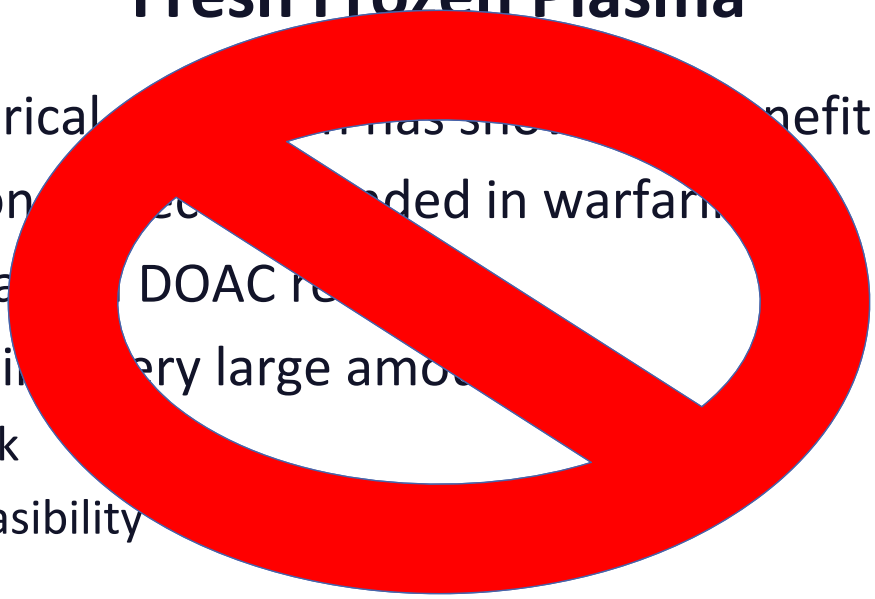
Hemodialysis

- Dabigatran
- Based on case reports/case series
- Limited recommendation with no reversal availability
- Can be used in overdose with extremely high levels
- Or those with AKI and markedly reduced renal function

Fresh Frozen Plasma

- Historical use which has shown no benefit
- No longer recommended in warfarin
- No data in DOAC reversal
- Requires very large amounts
  - Risk
  - Feasibility

Fresh Frozen Plasma



- Historical [illegible] nefit
- No lon[illegible]ded in warfar[illegible]
- No da[illegible] DOAC re[illegible]
- Requi[illegible]ery large amo[illegible]
  - Risk
  - Feasibility

Mechanism of Action: PCC in DOAC Reversal

- Unclear MOA for PCC in DOAC reversal
- Overwhelm anticoagulant effect
- Local site of injury activity
  - Thrombin generation
    - Inactivated PCC → activated enhancing local hemostasis
  - Activated PCC→ Provides high levels of activated factor at sites of bleeding

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.

Non-Specific Reversal: PCC4

Study Design	Patients	Intervention	Outcomes	Critique/Comments
Majeed A et al. 2017 Prospective, observational multi-center cohort study	N=84 Rivaroxaban n=4 Apixaban n=39 Bleed type ICH n=59 Non-ICH n=25	<65 kg PCC4 1500 units >65 kg PCC4 2000 units Additional dose allowed at physician discretion, allowed TXA administration	**Primary outcome**: Hemostatic efficacy: Overall 69% (58/84), ICH 73% (43/59) **Secondary outcome**: Thrombotic events: 3.5% (3/84) 30-day all-cause mortality: 32% (27/84); 20 were ICH	ISTH criteria for hemostatic efficacy, timing of PCC4 from last dose (12.5 hr), 67% of patients received TXA, 3 patients with additional PCC4 dose
Schulman S et al. 2018 Prospective, observational multi-center cohort study	N=66 Rivaroxaban n=37 Apixaban n=29 Bleed type ICH n=36 GI bleed n=16 Other n=14	PCC4 2000 units; allowed TXA administration	**Primary outcome**: Hemostatic efficacy: 85% (56/66) **Secondary outcome**: Thrombotic events: 8% (5/66) 30-day mortality: 14% (9/66), 8 with ICH	ISTH criteria for hemostatic efficacy, timing of PCC4 from last dose (18 hr), 26% of patients received TXA, 2 patients with additional PCC4 dose

Majeed A et al. *Blood*. 2017; 130:1706-12.; Schulman S et al. *Thromb Haemost*. 2018; 118:842-51.

PCC4 in DOAC-Related ICH

Factor Xa Inhibitor-Related Intracranial Hemorrhage: Results from a Multicenter, Observational Cohort Receiving Prothrombin Complex Concentrates	
Methods	Retrospective, observational multi-center cohort study
Patients	N= 663, (AF n=521 [78.6%]), apixaban 55.2%, rivaroxaban 55.8% ICH type: Intracerebral 172/433, SAH 68/433, SDH 193/433
Interventions	PCC4 (activated and inactivated)
Outcomes	**Primary outcome**: Hemostatic efficacy: Excellent or good - 354/433 (81.8% [95% CI, 77.9-85.2]) **Secondary outcome**: Thrombotic events: 25 (3.8%) patients had a total of 26 thrombotic events, 22 w/in 14 days after PCC4; In-hospital mortality was 144 (19.0%); LOS: ICU – 2 days, Hospital – 6 days; infusion-related reaction - 1 patient
Critique/Comments	Modified Sarode criteria for hemostatic efficacy, similar patient selection to ANNEXA4, no report the time between onset of bleeding and brain imaging, repeat dosing in 5.1% of patients, time to PCC 2.6 hr

Panos NG et al. *Circulation*. 2020; 141:1681-9.

Direct Thrombin Inhibitor Reversal: Idarucizumab

- Only FDA-approved reversal agent for dabigatran
- MOA: Humanized monoclonal antibody fragment (Fab) that binds dabigatran and metabolites and rapidly neutralizes the anticoagulant effects
- PK/PD
  - Onset: minutes
  - Duration: ~24 hr
  - T1/2: 47 min (initial), 10.3 hr (terminal)
- Preparation: Sterile glass vial containing 50 mL of 50 mg/mL concentration (2,500 mg/vial), x2 vials
- Dosing: 5 g IV, administered as two consecutive infusions of 2.5 g no more than 15 minutes apart

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 **Secondary outcomes**: Group A: extent of bleeding and hemodynamic stability Group B: hemostasis during intervention classified by physician as normal or as mildly, moderately, or severely abnormal 30-day Mortality; Thrombosis

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

RE-VERSE AD: Patient Groups

Group A: Overt Bleeding (N = 301)[a]

- Gastrointestinal bleeding: 137 (45.5%)
- Intracranial bleeding: 98 (32.6%)
  - SDH: 39 (13.0%)
  - SAH: 26 (8.6%)
  - ICH: 53 (17.6%)
- Major/life-threatening bleed: 265 (88%)
  - Hemodynamic instability: 114 (37.9%)

[a]May have had more than one type of bleed.

Group B: Surgery (N = 202)

- Hernia/peritoneal infection: 49 (24.3%)
- Hip/femur fracture or septic arthritis: 41 (20.3%)
- CV condition: pacemaker implantation, aneurysm repair: 37 (18.3%)
- Craniotomy: 17 (8.4%)

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

RE-VERSE AD Trial: Lab Reversal

- Prolonged dTT or ECT at baseline: 91.7% (461)
  - Group A: n = 276/301
  - Group B: n = 185/202
- Median maximum % reversal at 4 hrs: 100% (95% CI 100 to 100)

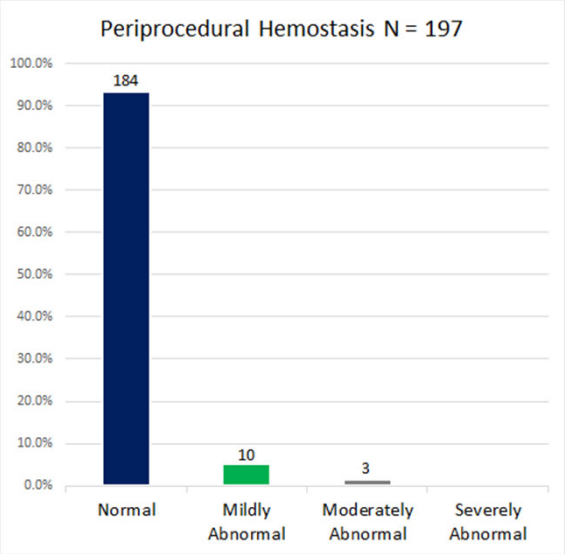
Group A Clinical Outcomes

- Time to cessation of bleeding
  - ICH patients not evaluated
  - Remaining patients: 203/301
    - Bleeding cessation within 24 hr 134/203 (68%)
    - Median time to hemostasis 2.5 hr (95% CI (2.2-3.9))

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

Group B Clinical Outcomes

- Local hemostasis determined at time of surgery
- 197 of 202 (97.5%) of patients underwent surgery/procedures
- Median time from administration of 1st vial to procedure was 1.6 hr



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

Thrombosis Follow-Up

30-day Thrombotic Event

- Total Event: 4.8% (24/503)
  - Group A: 14 patients
  - Group B: 10 patients

90-day Thrombotic Event

- Total Event: 6.8% (34/503)
  - Group A: 19 patients
  - Group B: 15 patients

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

Reinitiation of Antithrombotic Therapy

- Anticoagulation or antiplatelet restart
  - Group A
    - 72.8% of patients, mean 13.2 days
  - Group B
    - 90.1% of patients, mean 3.5 days
- Antithrombotic therapy restart: 72 hr post reversal
  - Group A: 23%
  - Group B: 67%

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

Andexanet Alfa

- FDA approved for reversal of apixaban and rivaroxaban
- MOA: decoy protein to and sequesters FXa inhibitors, neutralizing their anticoagulant effect by preventing them from binding to endogenous factor Xa. Additionally, increases TF-initiated thrombin generation.
- 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.

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	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

- 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.

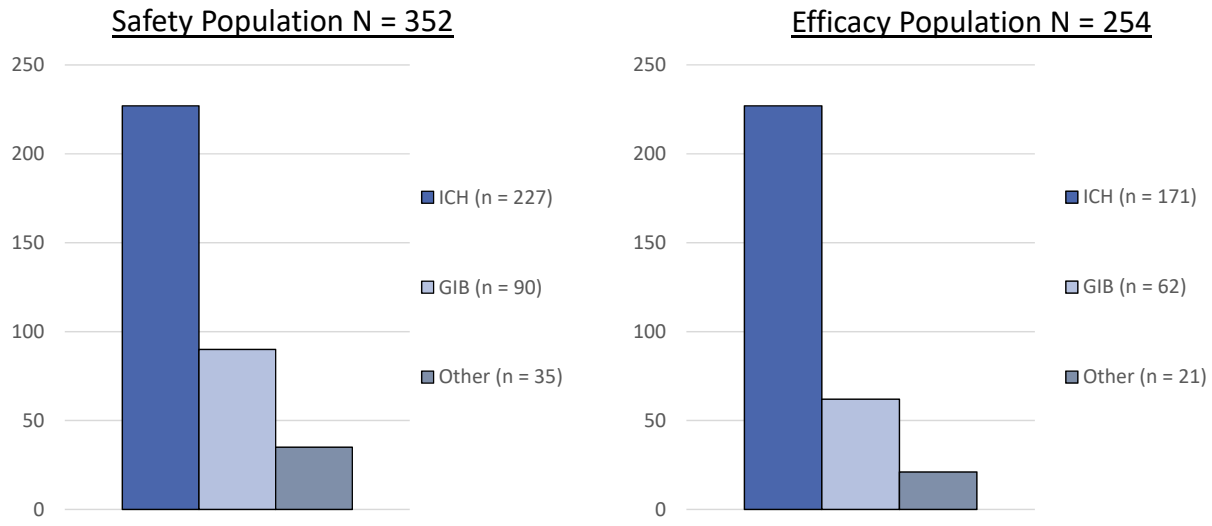
Connolly SJ et al. *N Engl J Med.* 2019; 380:1326-35.

ANNEXA-4

Andexanet Alfa for the Reversal of FXa Inhibitor Activity	
Methods	Multicenter, prospective, open-label single group study
Inclusion	> 18 years of age Apixaban (n = 194), rivaroxaban (n = 128), edoxaban (n = 10), enoxaparin (n = 20) within past 18 h 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 before 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, Percentage of patients with excellent or good hemostatic efficacy 12 hr after andexanet alfa infusion Safety Outcomes: Death, thrombotic events, and the development of antibodies to andexanet alfa or to native FX and FXa

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

ANNEXA-4: Bleeding Site



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

ANNEXA-4: Efficacy Results

Anti-FXa Activity

- Apixaban (n = 134)
  - 92% reduction (95% CI, 91 to 93)
- Rivaroxaban (n = 100)
  - 92% reduction (95% CI, 88 to 94)
- Enoxaparin (n = 16)
  - 75% reduction (95% CI, 66 to 79)

Hemostatic Efficacy

- Evaluated at 12 hours (249/254)
- Excellent or good (n = 204)
  - 82% (95% CI, 77 to 87)
    - Excellent n = 171
    - Good n = 33
  - GI bleed
    - 85% (95% CI, 76 to 94)
  - ICH
    - 80% (95% CI, 74 to 86)

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

Biomarker Efficacy Correlation

- Relationship of change of anti-FXA level and hemostatic efficacy measured measured by receiver-operating-characteristic (ROC) curves
  - All patients
    - AUC 0.53 (95% CI, 0.44 to 0.62).
  - ICH patients
    - AUC 0.64 (95% CI, 0.53 to 0.74).
- No relationship between hemostatic efficacy and reduction in anti-FXa activity during andexanet alfa treatment

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

ANNEXA-4: Safety Results

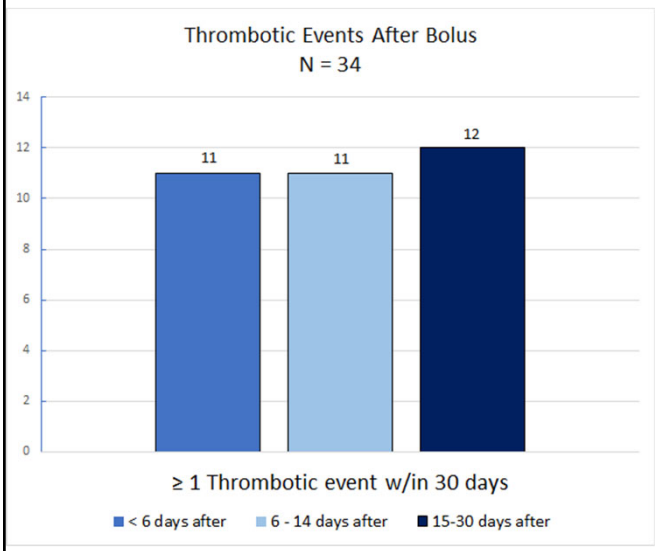
30-day Thrombotic Event Rate
- 10% (34/352)

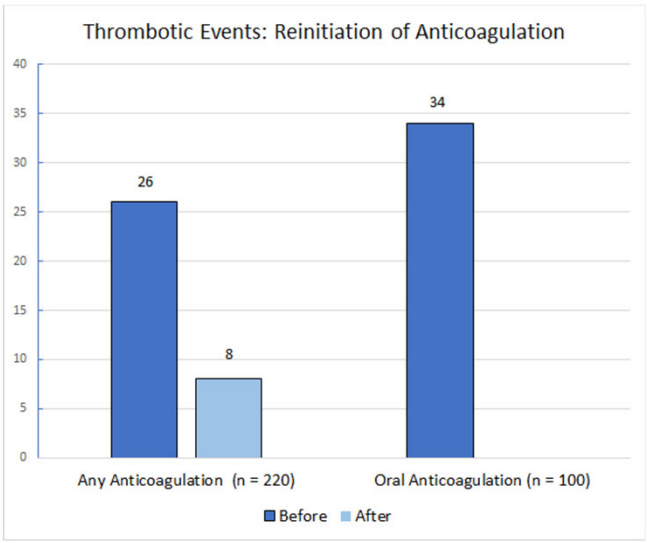
30-day Mortality
- 14% (49/352)

Antibodies or Neutralizing Antibodies
- Zero

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

ANEXXA-4: Thrombosis





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

Conclusion – ANNEXA-4

- No significant relationship between hemostatic efficacy and reduction in anti-FXa activity during andexanet alfa treatment
- Relationship between hemostatic efficacy and reduction in anti-FXa activity during andexanet alfa treatment in ICH; however, not robust
- Andexanet alfa markedly reduced anti-FXa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hr

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

Future Andexanet Alfa Trial in ICH

Trial of Andexanet Alfa in ICH Patients Receiving an Oral FXa Inhibitor	
Methods	Randomized, prospective, open-label single group study
Inclusion	Acute intracranial hemorrhage within 6 hr of symptom onset and within 15 hr of taking an oral factor Xa inhibitor
Interventions	Andexanet alfa bolus and continuous infusion: High dose OR low dose
Outcomes	Primary Outcomes: Proportion of patients with good or excellent hemostatic efficacy Secondary Outcomes: Change from baseline in anti-FXa activity, Change from baseline in NIHSS, Change from baseline in GCS, Proportion of neurological deterioration as defined by NIHSS increase > 4 or GCS decrease > 2

https://clinicaltrials.gov/ct2/show/record/NCT03661528 (accessed 2021 Jan 28).

Ciraparantag (PER977, Aripazine)

- Oral FXa inhibitors, dabigatran, unfractionated heparin, LMWH, fondaparinux
- Small synthetic, water-soluble molecule
- Inactivates via strong, non-covalent hydrogen bonds
- No procoagulant effect
- Not FDA approved

Mlling T Jr et al. *Am J Emerg Med*. 2016; 34:39-45.

Key Takeaways

- Always assess thrombosis risk and bleeding severity along with medication history
- Current laboratory parameters are not specific but may help guide therapy
- Clotting factor concentrates may be used for DOAC reversal; however, optimal dose unknown, limited data
- Specific antidotes are 1st line if available and may assist in the management of life-threatening hemorrhage

DOAC Reversal Guidelines: Summary

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

Selected Resources

Christensen H, Cardonnier C, Korv J et al. European Stroke Organisation guideline on reversal or 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
AKI	acute kidney injury
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
ASH	American Society of Hematology
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
BMI	body mass index
BP	blood pressure
CHA2DS2-VASc	congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category
CrCl	creatinine clearance
CT	computed tomographic
CV	cardiovascular
CVA	cerebrovascular accident
DM	diabetes mellitus
DOAC	direct-acting oral anticoagulant
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
FX	factor X
FXa	activated factor X
GCS	Glasgow Coma Scale
GI	gastrointestinal
HAS BLED	hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol
HEMORR2HAGES	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
HLD	hyperlipidemia

HR	heart rate
HRS	Heart Rhythm Society
HTN	hypertension
ICH	intracranial hemorrhage
ICU	intensive care unit
IQR	interquartile range
ISTH	International Society on Thrombosis and Haemostasis
LC-MS-MS	liquid chromatography–tandem mass spectrometry
LKW	last known well
LMWH	low molecular weight heparin
LOS	length of stay
MOA	mechanism of action
MTP	massive transfusion protocol
NCS	Neurocritical Care Society
NIHSS	National Institutes of Health Stroke Scale
NVAF	nonvalvular atrial fibrillation
ORBIT	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
PCC3	three-factor prothrombin complex concentrate
PCC4	four-factor prothrombin complex concentrate
PE	pulmonary embolism
PMH	past medical history
PI	prescribing information
PRBCs	packed red blood cells
PT	prothrombin time
rFVIIa	recombinant activated factor VII
ROTEM	rotational thromboelastometry
RR	respiratory rate
SAH	subarachnoid hemorrhage
SCCM	Society of Critical Care Medicine
SD	standard deviation
SDH	subdural hematoma
TEG	thromboelastography
TXA	tranexamic acid
UFH	unfractionated heparin
VHA	viscoelastic hemostatic assay
VKA	vitamin K antagonist
VTE	venous thromboembolism