Update on Reversal Agents for DOACs

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Timothy K. Liem financial disclosures:

- None

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Rate of DOAC-Associated Major Bleeding

Study	DOACs	Major bleeding	ICH	GIB
Rocket-af [37]	Rivaroxaban	3.60%	0.50%	3.20%
Dresden [38]	Rivaroxaban	3.40%	0.21%	1.49%
Aristotle [36]	Apixaban	2.13%	0.33%	0.76%
Averroes [39]	Apixaban	1.40%	0.40%	0.40%
OLDW [40]	Apixaban	2.33%	0.29%	1.78%
	Dabigatran	2.37%	0.28%	1.97%
	Rivaroxaban	4.04%	0.44%	3.26%
Gloria AF Registry [41]	Dabigatran	0.68 per 100 patients/year	0.18 per 100 patients/year	0.35 per 100 patients/year
	Apixaban	0.93 per 100 patients/year	0.24 per 100 patients/year	0.31 per 100 patients/year
Xantus [42]	Rivaroxaban	1.90%	0.40%	0.80%
ETNA-AF-Europe [43]	Edoxaban	1.05%	0.24%	0.40%

Al Aseri, J Cardiovasc Pharm Therapeut 2023

Annual Bleeding Risk:

- Rivaroxaban 2-4%
- Apixaban 1-2%

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Reversal Agents for DOACs

Idarucizumab	
Structure/mechanism	Monoclonal **antibody Fab fragment against dabigatran**
FDA indications	For patients treated with dabigatran when reversal is needed for emergency surgery/ urgent procedures, in life-threatening or uncontrolled bleeding
Dosing	Initial IV Bolus 5 g — Follow-On IV Infusion 5 g
Half-life (hrs)	47 min
Precaution	Thromboembolic risk, re-elevation of coagulation parameters, hypersensitivity
Cost	**AWP = $3600-$3800 per dose**

Monoclonal Ab fragment

- Irreversible binding to free- and thrombin-bound dabigatran
- Increases dabigatran elimination

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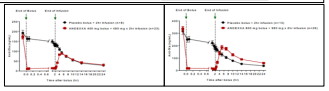
Reversal Agents for DOACs

Andexanet alfa	
Structure/mechanism	Recombinant truncated decoy human F Xa variant
FDA indications	**For patients treated with rivaroxaban and apixaban**, when reversal is needed due to life-threatening or uncontrolled bleeding
Dosing - Low Dose - High Dose	Bolus 400 mg IV 800 mg IV — Follow-On Infusion 480 mg IV over 2 hrs 960 mg IV over 2 hrs

FXa Inhibitor	Last Dose	<8 hrs or unknown	≥8 hrs
Rivaroxaban	≤10 mg >10 mg/ unknown	Low Dose High Dose	Low Dose
Apixaban	≤5 mg >5 mg/ unknown	Low Dose High Dose	

2022: 55% decrease in wholesale cost
Low-dose $12,500
High-dose $22,500



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Connolly, N Engl J Med 2019
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EXPERT CONSENSUS DECISION PATHWAY

2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

VKA (warfarin and other coumarins)	DTI (dabigatran)	FXa Inhibitor (apixaban and rivaroxaban)	FXa Inhibitor (betrixaban and edoxaban)
• Administer 4F-PCC†: -INR 2 to <4, 25 units/kg -INR 4-6, 35 units/kg -INR >6, 50 units/kg Or low fixed-dose option -1000 units for any non-intracranial major bleed -1500 units for ICH • If 4F-PCC is not available, use plasma 10–15 mL/kg(1)	• Administer 5g idarucizumab IV‡ • If idarucizumab is not available, administer PCC or aPCC§ • Consider activated charcoal for known recent ingestion (within 2-4 h)	• Administer andexanet alfa‖¶# • If andexanet alfa is not available, administer PCC or aPCC§ • Consider activated charcoal for known recent ingestion (within 2-4 h)	• Administer off-label treatment with high-dose andexanet alfa## • If andexanet alfa is not available, administer PCC or aPCC§ • Consider activated charcoal for known recent ingestion (within 2-4 h)

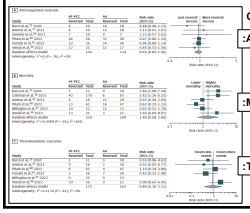
Tomaselli, JACC 2020

Andexanet vs 4F-PCC in ICH: Meta-analysis

JAMA Network Open. Evaluation of Direct Oral Anticoagulant Reversal Agents in Intracranial Hemorrhage: A Systematic Review and Meta-analysis

Meta-analysis of 36 studies (1832 pts)

	4F-PCC (967 pts)	Andexanet (525 pts)	Idarucizumab (340 pts)
Anticoag reversal	77%	75%	82%
All-cause mortality	26%	24%	11%
Thrombosis events	8%	14%	5%



Comparison of 4F-PCC vs Andexanet Alfa for Proportion of:

:Anticoagulation reversal

:Mortality

:Thrombosis events

CONCLUSIONS AND RELEVANCE: In the absence of randomized clinical comparison trials, the overall anticoagulation reversal, mortality, and thromboembolic event rates . . . appeared similar among available DOAC reversal agents for managing ICH. Cost, institutional formulary status, and availability may restrict reversal agent choice…

Chaudhary, JAMA 2022

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The NEW ENGLAND JOURNAL of MEDICINE

Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

Connolly, N Engl J Med 2024

Event	Andexanet (N = 263)	Usual Care (N = 267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	—
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (−0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	−0.4 (−2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	−1.9 (−4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (−1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (−5.0 to 10.0)	0.51

530 pts who had taken a FXa inhibitor within 15 hrs of an acute ICH were randomized to Andexanet vs Usual Care (85.5% PCC).

	Andexanet	Usual Care (PCC)	
– Hemostatic efficacy	67.0%	53.1%	P=.003
– ↓ anti-factor Xa activity	94.5%	26.9%	P<.001
– Modified Rankin 0-3	28%	31%	NS
– Mortality	27.8%	25.5%	p=.51
– Thrombotic events	10.3%	5.6%	p=.048

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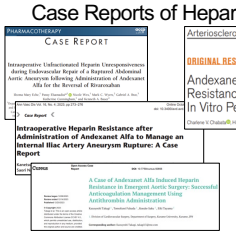
Case Reports of Heparin Resistance after Andexanet Alpha



Intraoperative Heparin Resistance after Administration of Andexanet Alfa to Manage an Internal Iliac Artery Aneurysm Rupture: A Case Report

Eche, Pharmacotherapy 2019

Chabata, Arterioscl Thromb Vasc Biol 2024

A Case of Andexanet Alfa Induced Heparin Resistance in Emergent Aortic Surgery: Successful Anticoagulation Management Using Antithrombin Administration

Nagao, Ann Vasc Dis 2023

Takagi, Cureus 2023

Andexanet prevents UFH prolongation of ACT and TEG

- Low doses — supraTx UFH overcomes
- High doses — supraTx UFH does not overcome

3-phase interaction between Andexanet/ UFH/ antithrombin

- Initial UFH unresponsiveness
- Normal UFH response after Andexanet depletion
- Antithrombin depletion

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Guidance from the International Society for Thrombosis and Haemostasis

Reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

Levy, J Thromb Haemost 2024

Guidance on Indications for Use

Andexanet alfa[a] Licensed for reversal of rivaroxaban and apixaban in major hemorrhage since 2019	PCC[b] Not licensed for specific DOAC reversal
• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding
• Bleeding in a critical organ or closed space	• Bleeding in a critical organ or closed space
• Urgent relief surgery for intracranial hemorrhage	• Urgent or emergency surgery or intervention that cannot be delayed in patients with a high risk for procedural bleeding, ie, neurosurgery
	• Might be useful in trauma patients with dilution coagulopathy due to massive blood loss

Levy, J Thromb Haemost 2024

Guidance When Not To Use

• Urgent or emergency surgery or intervention (not licensed, will interfere with perioperative heparin treatment)	
• Elective surgery	• Elective surgery
• Gastrointestinal bleeds that can be stopped by local supportive measures	• Gastrointestinal bleeds that can be stopped by local supportive measures
• High DOAC drug levels without associated bleeding	• High DOAC drug levels without associated bleeding
• Need for surgery or intervention that can be delayed long enough to permit drug clearance	• Need for surgery or intervention that can be delayed long enough to permit drug clearance

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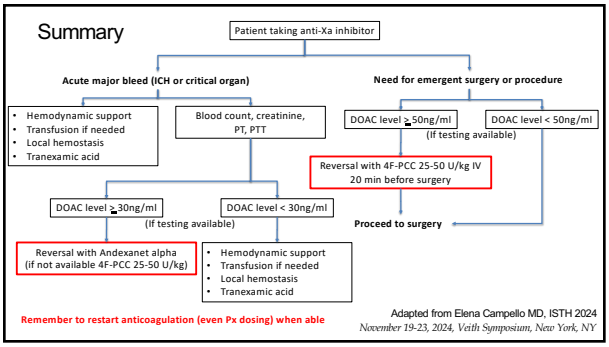
Summary
Patient taking anti-Xa inhibitor
Acute major bleed (ICH or critical organ)
Need for emergent surgery or procedure
• Hemodynamic support
• Transfusion if needed
• Local hemostasis
• Tranexamic acid
Blood count, creatinine, PT, PTT
DOAC level ≥ 50ng/ml
(If testing available)
DOAC level < 50ng/ml
Reversal with 4F-PCC 25-50 U/kg IV
20 min before surgery
DOAC level ≥ 30ng/ml
(If testing available)
DOAC level < 30ng/ml
Proceed to surgery
Reversal with Andexanet alpha
(if not available 4F-PCC 25-50 U/kg)
• Hemodynamic support
• Transfusion if needed
• Local hemostasis
• Tranexamic acid
Remember to restart anticoagulation (even Px dosing) when able
Adapted from Elena Campello MD, ISTH 2024
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