

SUBJECT/TITLE: Anticoagulation reversal in adult patients

PURPOSE: To provide evidence-based guidance regarding the reversal of anticoagulation therapy. This guide should not replace clinical judgement or expert consultation

Abbreviations: FFP = fresh frozen plasma DOAC = direct oral anticoagulant PCC = prothrombin complex concentrate [KCentra]
 HD = hemodialysis CrCl = creatinine clearance APCC = activated prothrombin complex concentrate [FEIBA]

Class	Anticoagulant	Half-life	Removed by HD	Strategies to reverse or minimize anticoagulant effects												
Factor Xa Inhibitors	Apixaban (Eliquis®)	8-15 hrs (longer in renal impairment)	No	<ul style="list-style-type: none"> General measures: <ol style="list-style-type: none"> Stop DOAC (and antiplatelet medications) Compression at bleeding site Provide volume support and transfusions Activated charcoal 100g (if ingested within the past 8 hours)ⁱ When bleeding is life-threatening, into a critical organ, or has not responded to maximal supportive measures, consider a reversal agentⁱⁱ <ol style="list-style-type: none"> Andexanet Alfa – see chart for dosingⁱⁱⁱ 												
	Rivaroxaban (Xarelto®)	9-13 hrs (longer in renal impairment)	No													
			<table border="1"> <thead> <tr> <th colspan="2">Timing of last dose (rivaroxaban or apixaban)</th> </tr> <tr> <th colspan="2">Last dose < 8 hours ago or unknown</th> </tr> <tr> <th colspan="2">Last dose ≥ 8 hours ago</th> </tr> </thead> <tbody> <tr> <td rowspan="2" style="writing-mode: vertical-rl; transform: rotate(180deg);">Strength of last dose</td> <td>Rivaroxaban > 10 mg OR Apixaban > 5mg OR Unknown dose</td> <td> <u>High dose andexanet alpha:</u> <ul style="list-style-type: none"> Initial IV bolus: 800mg at 30mg/min Follow-On IV infusion: 8mg/min (up to 120 min) </td> <td> <u>Low dose andexanet alpha:</u> <ul style="list-style-type: none"> Initial IV bolus: 400mg at 30mg/min Follow-On IV infusion: 4mg/min (up to 120 min) </td> </tr> <tr> <td>Rivaroxaban ≤ 10mg OR Apixaban ≤ 5mg</td> <td colspan="2"> <u>Low dose andexanet alpha:</u> <ul style="list-style-type: none"> Initial IV bolus: 400mg at 30mg/min Follow-On IV infusion: 4mg/min for up to 120 min </td> </tr> </tbody> </table>		Timing of last dose (rivaroxaban or apixaban)		Last dose < 8 hours ago or unknown		Last dose ≥ 8 hours ago		Strength of last dose	Rivaroxaban > 10 mg OR Apixaban > 5mg OR Unknown dose	<u>High dose andexanet alpha:</u> <ul style="list-style-type: none"> Initial IV bolus: 800mg at 30mg/min Follow-On IV infusion: 8mg/min (up to 120 min) 	<u>Low dose andexanet alpha:</u> <ul style="list-style-type: none"> Initial IV bolus: 400mg at 30mg/min Follow-On IV infusion: 4mg/min (up to 120 min) 	Rivaroxaban ≤ 10mg OR Apixaban ≤ 5mg	<u>Low dose andexanet alpha:</u> <ul style="list-style-type: none"> Initial IV bolus: 400mg at 30mg/min Follow-On IV infusion: 4mg/min for up to 120 min
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Edoxaban (Savaysa®)	10-14 hrs (longer in renal impairment)	~ 25%	No known reversal agent or specific antidote. ^{v,vi} Consider off-label treatment with: <ul style="list-style-type: none"> Activated charcoal 100g (if ingested within the past 2 hours)^{vii} 4-factor PCC (KCentra) 2000 units [Cuker 2019] 													

	Betrixaban (Bevyxxa®)	19-27 hrs	Unknown	<ul style="list-style-type: none"> High doseandexanet alfa (800 mg bolus followed by a continuous infusion of 8 mg/min for up to 120 min) [Cuker 2019]
	Fondaparinux (Arixtra®)	17-21 hrs (significantly longer in renal impairment)	No	<ul style="list-style-type: none"> 4-factor PCC (Kcentra) 50 units/kg—max 5000 units [Christos 2016]

Class	Anticoagulant	Half-life	Removed by HD	Strategies to reverse or minimize anticoagulant effects
Direct Thrombin Inhibitors	Argatroban	40-50 min	~ 20%	<ul style="list-style-type: none"> Turn off infusion
	Bivalirudin (Angiomax®)	25 min (up to 1 hr in severe renal impairment)	~ 25%	
	Dabigatran (Pradaxa®)	14-17 hrs (up to 34 hrs in severe renal impairment)	~ 65%	<ul style="list-style-type: none"> General measures: <ol style="list-style-type: none"> Stop DOAC (and antiplatelet medications) Compression at bleeding site Provide volume support and transfusions Activated charcoal 100g (if ingested within the past 2 hours) For patients with pre-existing vascular access, consult nephrology to consider dialysis When bleeding is life-threatening, into a critical organ, or has not responded to maximal supportive measures, consider a reversal agent [Cuker 2019] <ol style="list-style-type: none"> Idarucizumab (Praxbind®) 5g IV; administer as two 2.5g boluses no more than 15 min apart Activated prothrombin complex concentrate (FEIBA) 50 units/kg IV^{viii}
Low Molecular Weight Heparin	Dalteparin (Fragmin®)	3-5 hrs (longer in renal impairment)	~ 20%	<ul style="list-style-type: none"> Use protamine for partial neutralization (~60%) Degree of reversal can be assessed with Anti-factor Xa activity (order: “Anti Xa, LMWH”)
	Enoxaparin (Lovenox®)			

					Initial dose of protamine^{ix, x}	
				Time since last dose of LMWH	< 8 hrs	<ul style="list-style-type: none"> 1mg protamine (per 100 units dalteparin or per 1mg enoxaparin) or 50mg fixed dose
					8-12 hrs	<ul style="list-style-type: none"> 0.5mg protamine (per 100 units dalteparin or per 1mg enoxaparin) or 25mg fixed dose
					> 12 hrs	<ul style="list-style-type: none"> Not likely to be useful unless CrCl < 30mL/min May consider 25mg fixed dose
					Second dose of protamine (if aPTT remains prolonged 2-4 hrs after first dose)	
					<ul style="list-style-type: none"> May consider 0.5 mg protamine (per 100 units dalteparin or per 1 mg enoxaparin) 	

UFH	Heparin	30-90 min (dose dependent)	Partial	<ul style="list-style-type: none"> Turn off infusion Administer 1mg of protamine for every 100 units of heparin (maximum single dose: 50mg)^{xi} When administered as continuous IV, only consider heparin given in the preceding 2-3 hours
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Reversal of vitamin K antagonists

Vitamin K Antagonist	Warfarin (Coumadin®)	General Vitamin K Information:												
		<ul style="list-style-type: none"> Intravenous Vitamin K works faster than oral vitamin K, but is associated with anaphylactic reaction in 3/10,000 patients. Subcutaneous injection of vitamin K is not recommended; effect is delayed and unpredictable. Use of high doses of vitamin K (e.g. 10 to 15mg) may cause warfarin resistance for up to 1 week or more 												
		Serious or life-threatening bleeds (any INR)												
		<ul style="list-style-type: none"> Hold warfarin Give vitamin K 10mg IV infusion over 30 minutes 4-factor PCC (Kcentra) is preferred over FFP for life-threatening bleeds (see table) <table border="1"> <thead> <tr> <th>INR</th> <th>4-factor PCC Dose^{xii}</th> </tr> </thead> <tbody> <tr> <td>2-4</td> <td>25 units/kg (max 2500 units)</td> </tr> <tr> <td>4-6</td> <td>35 units/kg (max 3500 units)</td> </tr> <tr> <td>> 6</td> <td>50 units/kg (max 5000 units)</td> </tr> </tbody> </table> <ul style="list-style-type: none"> Give FFP/Plasma if 4-factor PCC unavailable 			INR	4-factor PCC Dose ^{xii}	2-4	25 units/kg (max 2500 units)	4-6	35 units/kg (max 3500 units)	> 6	50 units/kg (max 5000 units)		
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		Rapid reversal required	• Hold warfarin; consider vitamin K 2.5mg oral or 1mg IV infusion
	> 10	No bleeding	• Hold warfarin; consider vitamin K 2.5mg oral or 1-2mg IV infusion
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References:

- ⁱ Ollier E, Hodin S, Lanoiselee J, et al. Effect of activated charcoal on rivaroxaban complex absorption. *Clin Pharmacokinet*. 2017 Jul; 56(7):793-801
- ⁱⁱ Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. *Am J Hematol*. 2019; 1-13
- ⁱⁱⁱ Andexanet alfa prescribing information. <https://www.andexxa.com/wp-content/uploads/Andexxa%20P1%20US%202.8-dec2018.pdf>. Accessed May 2019.
- ^{iv} Majeed A, Agren A, Holmstrom M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 2017; 130:1706-1712.
- ^v Savaysa: highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed June 2019.
- ^{vi} Byexxa: Full Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208383s000lbl.pdf. Accessed June 2019.
- ^{vii} Christos S, Naples R. Anticoagulation reversal and treatment strategies in major bleeding: update 2016. *West J Emerg Med*. 2016 May; 17(3): 264-70.
- ^{viii} Schulman S, Ritchie B, Nahirniak S, et al. Reversal of dabigatran-associated major bleeding with activated prothrombin complex concentrate: a prospective cohort study. *Thromb Res*. 2017; 152:44-48.
- ^{ix} Lovenox: highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020164s085lbl.pdf. Accessed June 2019.
- ^x Fragmin: highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020287s050lbl.pdf. Accessed June 2019.
- ^{xi} Garcia DA, Baglin TP, Weitz JI, et al. Parenteral Anticoagulants. *Antithrombotic Therapy and Prevention of Thrombosis*, 9th ed: American College of Chest Physicians. CHEST 2012; 141(2)(Suppl):e24S–e43S
- ^{xii} Tomaselli, GF, et al. 2017 ACC Expert Consensus Decision Pathway on management of Bleeding in Patients on Oral Anticoagulants. *J Am Coll Cardiology*
- Raval A, Cigarroa J, Chung M. Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting. *Circulation*. 2017;135:00–00.
- Hatfield L and Chen SL. University of North Carolina Healthcare Anticoagulation Reversal Guidelines. June 2014.
- UW Guidelines for reversal of anticoagulants. <https://depts.washington.edu/anticoag/home/sites/default/files/GUIDELINES%20FOR%20REVERSAL%20OF%20ANTICOAGULANTS.pdf>. Accessed June 2019.