MC919C

Los Angeles County Department of Health Services
LAC-USC PRACTICE GUIDELINE

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]

<table>
<tr><th>Class</th><th>Anticoagulant</th><th>Half-life</th><th>Removed by HD</th><th>Strategies to reverse or minimize anticoagulant effects</th></tr>
<tr><td rowspan="4">Factor Xa Inhibitors</td><td>Apixaban (Eliquis®)</td><td>8-15 hrs (longer in renal impairment)</td><td>No</td><td rowspan="2">• General measures:
1. Stop DOAC (and antiplatelet medications)
2. Compression at bleeding site
3. 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 agent[ii]
1. Andexanet Alfa – see chart for dosing[iii]

<table><tr><th colspan="2"></th><th>Timing of last dose (rivaroxaban or apixaban)</th></tr><tr><th colspan="2"></th><th>Last dose < 8 hours ago or unknown</th><th>Last dose ≥ 8 hours ago</th></tr><tr><td rowspan="2">Strength of last dose</td><td>Rivaroxaban > 10 mg
OR
Apixaban > 5mg
OR
Unknown dose</td><td><u>High dose andexanet alpha</u>:
• 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>:
• 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>:
• Initial IV bolus: 400mg at 30mg/min
• Follow-On IV infusion: 4mg/min for up to 120 min</td></tr></table>
2. 4-factor PCC (Kcentra) 2000 units[iv]</td></tr>
<tr><td>Rivaroxaban (Xarelto®)</td><td>9-13 hrs (longer in renal impairment)</td><td>No</td></tr>
<tr><td>Edoxaban (Savaysa®)</td><td>10-14 hrs (longer in renal impairment)</td><td>~ 25%</td><td rowspan="2">No known reversal agent or specific antidote.[v],[vi] Consider off-label treatment with:
• Activated charcoal 100g (if ingested within the past 2 hours)[vii]
• 4-factor PCC (KCentra) 2000 units [Cuker 2019]
• High dose andexanet alfa (800 mg bolus followed by a continuous infusion of 8 mg/min for up to 120 min) [Cuker 2019]</td></tr>
<tr><td>Betrixaban (Bevyxxa®)</td><td>19-27 hrs</td><td>Unknown</td></tr>
</table>

	Fondaparinux (Arixtra®)	17-21 hrs (significantly longer in renal impairment)	No	• 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%	• 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%	• General measures: 1. Stop DOAC (and antiplatelet medications) 2. Compression at bleeding site 3. 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] 1. Idarucizumab (Praxbind®) 5g IV; administer as two 2.5g boluses no more than 15 min apart 2. Activated prothrombin complex concentrate (FEIBA) 50 units/kg IV[viii]
Low Molecular Weight Heparin	Dalteparin (Fragmin®)	3-5 hrs (longer in renal impairment)	~ 20%	• Use protamine for partial neutralization (~60%) • Degree of reversal can be assessed with Anti-factor Xa activity (order: "Anti Xa, LMWH") **Time since last dose of LMWH** < 8 hrs: • 1mg protamine (per 100 units dalteparin or per 1mg enoxaparin) • *or 50mg fixed dose* 8-12 hrs: • 0.5mg protamine (per 100 units dalteparin or per 1mg enoxaparin) • *or 25mg fixed dose* > 12 hrs: • Not likely to be useful unless CrCl < 30mL/min • *May consider 25mg fixed dose* **Initial dose of protamine[ix],[x]** **Second dose of protamine** (if aPTT remains prolonged 2-4 hrs after first dose): • May consider 0.5 mg protamine (per 100 units dalteparin or per 1 mg enoxaparin)
	Enoxaparin (Lovenox®)			

<table>
<tr><td>UFH</td><td>Heparin</td><td>30-90 min
(dose dependent)</td><td>Partial</td><td>• 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</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td colspan="5">Reversal of vitamin K antagonists</td></tr>
<tr><td rowspan="4">Vitamin K Antagonist</td><td rowspan="4">Warfarin
(Coumadin®)</td><td colspan="3">General Vitamin K Information:
• 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</td></tr>
<tr><td colspan="3">Serious or life-threatening bleeds (any INR)
• 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>
<tr><th>INR</th><th>4-factor PCC Dose[xii]</th></tr>
<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>
</table>
• Give FFP/Plasma if 4-factor PCC unavailable</td></tr>
<tr><td colspan="3">Non-life-threatening bleeds
<table>
<tr><th>INR</th><th>Clinical Situation</th><th>Management</th></tr>
<tr><td>< 4.5</td><td>No bleeding</td><td>• Hold warfarin</td></tr>
<tr><td></td><td>Rapid reversal required</td><td>• Hold warfarin; consider vitamin K 2.5mg oral</td></tr>
<tr><td>4.5 – 10</td><td>No bleeding</td><td>• Hold warfarin; consider vitamin K 2.5mg oral</td></tr>
<tr><td></td><td>Rapid reversal required</td><td>• Hold warfarin; consider vitamin K 2.5mg oral or 1mg IV infusion</td></tr>
<tr><td>> 10</td><td>No bleeding</td><td>• Hold warfarin; consider vitamin K 2.5mg oral or 1-2mg IV infusion</td></tr>
<tr><td></td><td>Rapid reversal required</td><td>• Hold warfarin; consider vitamin K 2.5mg oral or 1-2mg IV infusion</td></tr>
</table></td></tr>
</table>

References:

[i] Ollier E, Hodin S, Lanoiselee J, et al. Effect of activated charcoal on rivaroxaban complex absorption. Clinc Pharmcokinet. 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%20PI%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.