Our Lady of the Lake Regional Medical Center

Pharmacy Anticoagulation Stewardship

Anticoagulant Reversal Clinical Practice Guideline

1.1 Introduction

These clinical practice guideline recommendations are for patients on antithrombotic therapy requiring immediate, appropriate reversal.

1.2 Oral Anticoagulant Reversal

Medication Class: Factor Xa Inhibitors	**Reversal agent for Life threatening bleeding**
Rivaroxaban (Xarelto®) **Apixaban (Eliquis®)** **Edoxaban (Savaysa®)**	○ **4F-PCC (Kcentra®) Fixed Dosing** ▪ Dose: 2000 units IV x 1 ▪ Administration: Must be used within 4 hours of reconstitution • Other options ○ Activated charcoal 50 g orally for known recent ingestion within 2-4 hours
Dabigatran (Pradaxa®) Class: Direct Thrombin Inhibitor	• **First line** ○ **Idarucizumab (Praxbind®)** ▪ Dose: 5 g IV ▪ Administration: Administered as 2 separate 2.5 g doses no more than 15 minutes apart ▪ Onset: Less than 5 minutes • **Second line** ○ **4F-PCC (Kcentra®)** ▪ Dose: 50 units/kg IV (max dose: 5,000 units) ▪ Administration: Must be used within 4 hours of reconstitution ▪ Onset: Within 10 minutes • **Other options** ○ Activated charcoal 50 g orally for known recent ingestion within 2-4 hours ○ Consider hemodialysis in patient not receiving Idarucizumab (Praxbind). It removes about 57% of the drug.

1.2b: Warfarin

Clinical Scenario	Treatment of Elevated INR	Time to Recheck INR
No clinically significant bleeding, no urgent/emergent surgery, no dental extraction		
INR < 5	Hold warfarin dose and resume at lower dose when INR is therapeutic	24-48 hours
INR ≥ 5 but < 9	Patient at low risk for bleeding: Hold 1-2 doses of warfarin and resume at a lower dose when INR is therapeutic **OR** Patient at high risk for bleeding: Hold 1 dose of warfarin and give phytonadione (vitamin K) 2.5 – 5 mg PO	24-48 hours
INR > 9	Hold warfarin dose. Give Phytonadione (vitamin K) 2.5 – 5 mg PO. Repeat as needed	24-48 hours
Clinically significant bleeding		
Any INR	Hold warfarin therapy Give **Vitamin K (10 mg by slow IV infusion**)**, supplement prothrombin complex concentrate (PCC), depending upon urgency***; vitamin K injections may be needed q12h.	12-24 hours
Life-threatening bleed	Hold warfarin, Give 4 factor PCC ± FFP plus vitamin K 5-10 mg by slow IV infusion • **4F-PCC (Kcentra®) Fixed dosing** 1500 units x1 *Additional doses of 500 units at a time may be ordered once post-infusion INR has resulted if INR goal or clinical outcome not achieved	30 minutes after Kcentra infusion

* If continuing warfarin therapy is indicated after high doses of vitamin K, then heparin or low-molecular-weight heparin can be given until the effects of vitamin K have been reversed, and the patient becomes responsive to warfarin therapy.
**IV administration is associated with an increased risk of anaphylactoid reactions. Anaphylactoid reactions have occurred during the first infusion and in patients receiving IV phytonadione, which has been diluted and injected by slow IV infusion. Therefore, IV administration should be restricted to those situations where another route is not feasible and the increased risk involved is considered justified.
***Four-factor prothrombin complex concentrate preferred to plasma (Grade 2C—Chest 2012)
**NOTE:* If the IV route is used, phytonadione injection should be diluted prior to administration with preservative-free D5W, NS, or D5NS only and the infusion rate should not exceed 1 mg/minute.

2.0: Parenteral anticoagulant reversal

<table>
<tr><th>Medication</th><th>Reversal Agent</th></tr>
<tr><td>Argatroban

Class: Direct Thrombin Inhibitor</td><td>

4F-PCC (Kcentra®)

<u>Dose</u>: 50 units/kg IV (max dose: 5,000 units)
<u>Administration</u>: Must be used within 4 hours of reconstitution
<u>Onset</u>: Within 10 minutes

<u>Other options</u>

Hemodialysis

</td></tr>
<tr><td>Bivalirudin (Angiomax®)

Class: Direct Thrombin Inhibitor</td><td>

4F-PCC (Kcentra®)

<u>Dose</u>: 50 units/kg IV (max dose: 5,000 units)
<u>Administration</u>: Must be used within 4 hours of reconstitution
<u>Onset</u>: Within 10 minutes

<u>Other options</u>

Hemodialysis

</td></tr>
<tr><td>Heparin – Infusion</td><td>

Protamine

<u>Dose</u>: 50 mg for urgent reversal following heparin drip
(1 mg reverses 100 units of heparin with max single dose of 50 mg)

<table>
<tr><th>Time since UFH administration</th><th>Dose of Protamine to Neutralize 100 units of Heparin</th></tr>
<tr><td><30 min</td><td>1 mg to 1.5 mg</td></tr>
<tr><td>30-120 min</td><td>0.5 mg to 0.75 mg</td></tr>
<tr><td>>120 min</td><td>0.25 mg to 0.375 mg</td></tr>
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<u>Administration</u>: Slow IV push over 10 minutes
<u>Onset</u>: 5-15 minutes

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Heparin – Subcutaneous	• **Protamine** o Dose: 1 to 1.5 mg protamine per 100 units of heparin o Administration: May be done by administering a portion of the dose (e.g. 25 to 50 mg) by IV slowly followed by a continuous infusion of the remaining portion over 8 to 16 hours o Onset: 5-15 minutes
Enoxaparin (Lovenox®) Class: Low-Molecular Weight Heparin	• **Protamine** o Dose: 1 mg for every 1 mg of enoxaparin administered within the last 8 hours (max single dose: 50 mg) If enoxaparin administered > 8 hours: 0.5 mg for every 1 mg of enoxaparin o Administration: Slow IV push over 10 minutes o Onset: 5-15 minutes o Protamine reverses about 60% to 75% of enoxaparin
Fondaparinux (Arixtra®) Class: Factor Xa Inhibitor	• **4F-PCC (Kcentra®)** ▪ Dose: 50 units/kg IV (max dose: 5,000 units) ▪ Administration: Must be used within 4 hours of reconstitution ▪ Onset: Within 10 minutes

4F-PCC = 4-factor prothrombin complex concentrate

This Guideline Review and Revision information

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Last Date Reviewed: 07/2021

References:

1. Cuker et al. "Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum." *Am J Hematol*. 2019; 94:697-709
2. Garcia, David and Crowther, Mark. "Reversal of Warfarin: Case-Based Practice Recommendations." *Circulation.* 2012. 125: 2944-2947
3. Samuelson BT and Cuker A. "Measurement and Reversal of the Direct Oral Anticoagulants." *Blood Reviews.* 2017; 31(1): 77-84
4. Tomaselli et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. *Journal of the American College of Cardiology*. 2017; 70 (24): 3042-67