Anticoagulation Reversal Guidelines

Our Lady of the Lake Regional Medical Center
Updated: December 2016

This document is based upon the current available evidence. It is intended to provide evidence based recommendations for reversal of commonly used anticoagulants. However, it is not intended to replace clinical judgment.

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 mg po	24-48 hours
INR ≥ 9	Hold warfarin dose. Vitamin K 2.5 – 5 mg PO. Repeat as needed	24-48 hours
Clinically significant bleeding		
Any INR	Hold warfarin therapy and give Vitamin K (5-10 mg by slow IV infusion**), supplement with 4-factor prothrombin complex concentrate (PCC) or FFP depending upon urgency***	12-24 hours *If 4 factor PCC used, recheck INR in 1 hour
Life-threatening bleed	Hold warfarin. 4 factor PCC, FFP***, plus vitamin K 5-10 mg by an injectable route	1 hour after 4 factor PCC

* 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.

Major life-threatening bleeding/ICH from warfarin (OLOL Powerplan)

If INR ≥ 1.5 – 2.0 administer:
- Administer FFP x 4 units
- Vitamin K 10 mg IVPB stat
- Vitamin K 5 mg IVPB x 2 days (to begin the following day)
  **May consider KCentra as an alternative to FFP

If INR 2.1 - <4.0 administer:
- Vitamin K 10 mg IVPB stat
- Vitamin K 5 mg IVPB x 2 days (to begin the following day)
- Kcentra 25 units/kg (max dose 2500 units) IV now
- Repeat PT / INR 30 minutes after administration of Kcentra

If INR 4.1 - <6.0 administer:
- Vitamin K 10 mg IVPB stat
- Vitamin K 5 mg IVPB x 2 days (to begin the following day)
- Kcentra 35 units/kg (max dose 3500 units) IV now
- Repeat PT / INR 30 minutes after administration of Kcentra

If INR >6.1 administer:
- Vitamin K 10 mg IVPB stat
- Vitamin K 5 mg IVPB x 2 days (to begin the following day)
- Kcentra 50 units/kg (max dose 5000 units) IV now
- Repeat PT / INR 30minutes after administration of Kcentra

**NOTE: If KCentra is ordered, review the patient's profile to ensure multiple doses are not administered. Current available evidence does not support redosing of KCentra

Heparin (Intravenous)

Timeframe since last IV dose	**Dose of Protamine**
<30 minutes	1mg per 100 units of IV heparin **(MAX single dose of 50mg)**
30 minutes to 2hr	0.5-0.75mg per 100 units of IV heparin
> 2 hours	0.25mg per 100 units of IV heparin

*Protamine sulfate by the IV route can cause hypotension and anaphylactoid reactions when given too rapidly. Therefore, doses should not exceed 5mg/min. It is intended for injection without further dilution, however, it may be diluted in D5W or NS.

Heparin (Subcutaneous)

Give 1-1.5mg of protamine per 100 units of heparin. This can be done by giving a portion of the dose (25-50mg) slowly by the IV route, followed by the remaining portion as a continuous infusion over 8-16 hours.

Enoxaparin

Timeframe since last SC/IV dose	**Dose**
≤8 hours	1mg of protamine per 1mg of enoxaparin (**MAX single dose of 50mg**)
> 8 hours,or as a second dose if bleeding continues	0.5mg of protamine per 1mg of enoxaparin

*Note that protamine does not fully reverse enoxaparin
**Protamine sulfate by the IV route can cause hypotension and anaphylactoid reactions when given too rapidly. Therefore, doses should not exceed 5mg/min. It is intended for injection without further dilution, however, it may be diluted in D5W or NS.

The following are strictly *recommendations* as there is a limited amount of data on this topic.

Reversal options for rivaroxaban, apixaban, and dabigatran

	Rivaroxaban	**Apixaban**	**Dabigatran**
Mild bleeding	Delay the next dose OR discontinue therapy	Delay the next dose OR discontinue therapy	Delay the next dose OR discontinue therapy
Moderate to severe bleeding	Above **PLUS** symptomatic treatment: • Mechanical Compression • Surgical Intervention • Symptomatic Treatment • Hemodynamic Support/Blood Transfusion • Oral Charcoal (if administered **<8 hours** prior)	Above **PLUS** symptomatic treatment: • Mechanical Compression • Surgical Intervention • Symptomatic Treatment • Hemodynamic Support/Blood Transfusion • Oral Charcoal (if administered **<8 hours** prior)	Above **PLUS** symptomatic treatment: • Mechanical Compression • Surgical Intervention • Symptomatic Treatment • Hemodynamic Support/Blood Transfusion • Oral Charcoal (if administered **<8 hours** prior)

Life threatening bleeding	Above **PLUS**: Kcentra™ 50 units/kg x 1 (max 5000 units) **Note: NOT dialyzable**	Above **PLUS** • Kcentra™ 50 units/kg x 1 (max 5000 units) • May consider Factor VIIa as an alternative (although studies indicate not as effective as PCC) **Note: NOT dialyzable**	Above **PLUS** • Praxbind® (idarucizumab) 5 gm IV x 1 • May consider hemodialysis (~60% removed)
******Consider the thrombotic effects of blood products*****			

*Recombinant Factor Xa antidote in preclinical development

REFERENCES

1. Garcia, D.A., Baglin, T.P., Weitz,J.I., Samama, M.M..Parenteral Anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis: ACCP Evidence Based Clinical Practice Guidelines, 9th edition. Chest. 2012;141: e24S-e43S. Available at www.chestjournal.chestpubs.org

2. Ansel J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the Vitamin K antagonists: ACCP Evidence Based Clinical Practice Guidelines, 8th edition. Chest. 2008;133;160S-198S. www.chestjournal.chestpubs.org

3. Eerenberg E, Kamphuisen P, Sijpkens M, Meijers J, Buller H, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124:1573-1579. doi: 10.1161/CIRCULATIONAHA.111.029017.

4. Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etixalate-a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103:1116-1127. doi:10.1160/TH09-11-0758.

5. Battinelli EM. Reversal of new oral anticoagulants. Circulation. 2011;124:1508-1510. doi:10.1161/CIRCULATIONAHA.111.054510.

6. Stangier J, Rathgen K, Stable H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etixalate: an open label, parallel-group, single centre study. Clin Pharmacokinet. 2010;49:259-268.

7. Kaatz, S., Kouides, P., Garcia, D., et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am. J. Hematol. 2012; 87: S141-S145.

8. Miyares, M., Davis, K. Newer oral anticoagulants: A review of laboratory monitoring options and reversal agents in the hemorrhagic patient. Am J Health-Syst Pharm. 2012; 69:e28-39.

9. Neurocritical Care Society. Emergency Neurological Life Support. Intracerebral Hemorrhage Protocol. Retrieved Oct 30 from http://enlsprotocols.org/pdf.html.