UNC MEDICAL CENTER GUIDELINE
Emergent Anticoagulation Reversal

The purpose of this guideline is to provide guidance for the reversal of or management of bleeding while on treatment with anticoagulants. Recommendations provided in this document reflect current guidelines, clinical evidence and institutional initiatives. These recommendations are not intended to replace clinical judgement, but are intended to serve as a tool for decision-making.

Table of Contents by Anticoagulant:
- Warfarin
- Dabigatran
- Edoxaban, Betrixaban, or Fondaparinux
- Apixaban or Rivaroxaban
- Unfractionated Heparin or Low Molecular Weight Heparin (Enoxaparin or Dalteparin)
- Argatroban or Bivalirudin
- Antiplatelet agents

I. Bleeding Definitions: See Appendix A

II. Emergent Reversal of Oral Anticoagulants

Figure 1. Management of Warfarin Related Bleeding Events

Patient currently taking warfarin

Non-major bleeding or routine/urgent procedure/surgery

See warfarin dosing guidelines for management of supratherapeutic international normalized ratio (INR) without bleeding

For minor bleeding or a routine/urgent procedure consider Vitamin K IV +/- 2 units of fresh frozen plasma (FFP)

Recheck INR in 6-12 hours

Major bleed or emergent procedure/surgery

Vitamin K 10 mg IV

AND

INR 1.50-3.99: KCentra® 25 units/kg x 1 dose (Max dose: 2500 units)

INR 4.00-6.00: KCentra® 35 units/kg x 1 dose (Max dose: 3500 units)

INR > 6.00: KCentra® 50 units/kg x 1 dose (Max dose: 5000 units)

Recheck INR 10-30 minutes after KCentra® administration and every 6 hours for 24 hours.
**Ordering and Administration**

A. Vitamin K

1. Subcutaneous or intramuscular doses are not recommended as routine care. Subcutaneous administration leads to erratic absorption and intramuscular administration may lead to the development of hematomas in the setting of therapeutic anticoagulation.

2. Full effect of vitamin K on warfarin reversal occurs approximately 24 hours after administration. Partial effects may be seen 6-12 hours after administration.

3. Doses of vitamin K greater than 10 mg are excessive and do not reverse anticoagulation more quickly.

B. 4-Factor Prothrombin Complex Concentration (KCentra®)

1. Ordering:
   
   i. KCentra® doses are calculated as units/kg using total body weight, with the maximum dosing weight of 100 kg.

   ii. During verification, the Sterile Products Area pharmacist will verify and prepare dose rounded to nearest vial size within 10% of originally ordered dose.

2. Administration:

   i. Administer via infusion pump at a rate of 3 units/kg/minute; do not exceed a rate of 8.4 mL/minute (504 mL/hour).

   ii. After KCentra® dose is complete, administer a 50 mL bag of normal saline using the same IV tubing at the same rate as KCentra® dose to ensure administration of full dose.
FIGURE 2. MANAGEMENT OF DABIGATRAN RELATED BLEEDING EVENTS

Patient currently taking dabigatran*

Non-major bleeding or routine/urgent procedure/surgery

Major bleeding or emergent procedure/surgery

Delay next dose or discontinue dabigatran

1) Administer idarucizumab (Praxbind®) 5 g (2 vials) IV x 1 dose
2) For persistent refractory bleeding (> 1 hour), consider a hematology consult
3) To investigate potential causes of bleeding obtain the following: serum creatinine (SCr), prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), complete blood count (CBC)

In the setting of acute renal failure, hemodialysis may be considered to assist with drug removal

*If presenting within 2 hours of ingestion of dabigatran dose, consider administering activated charcoal 50 g by mouth x 1 dose
-Avoid activated charcoal in patients who may require a gastrointestinal procedure for suspected or confirmed bleeding

Ordering and Administration

A. Idarucizumab (Praxbind®)
   1. Administration:
      i. Praxbind® is stored in the refrigerator.
      ii. Administer promptly once vials have been removed from box (stability after light exposure is 6 hours).
      iii. Administer both vials undiluted as an IV bolus (2.5 g in each vial) over 5 minutes via an infusion pump (pump entry defaults to 600 mL/hour).
      iv. The second vial should be administered no later than 15 minutes after the end of the first vial.
      v. After Praxbind® dose is complete; administer a 50 mL bag of normal saline using the same IV tubing at the same rate as Praxbind® dose to ensure administration of full dose.
FIGURE 3. MANAGEMENT OF EDOXaban, BETRIXaban, OR FONDAPARINUX RELATED BLEEDING EVENTS

Patient currently taking edoxaban*, betrixaban*, or fondaparinux

Non-major bleeding or routine/urgent procedure/surgery

Major bleeding or emergent procedure/surgery

Delay next dose or discontinue factor Xa inhibitor

1) Administer KCentra® 50 units/kg IV x 1 dose (Max dose: 5000 units)
2) For persistent refractory bleeding (> 1 hour), consider a hematology consult
3) To investigate potential causes of bleeding obtain the following: serum creatinine (SCr), prothrombin time (PT), activated partial thromboplastin time (aPTT), complete blood count (CBC)

*If presenting within 2 hours of ingestion of edoxaban or betrixaban dose, consider administering activated charcoal 50 g by mouth x 1 dose
-Avoid activated charcoal in patients who may require a gastrointestinal procedure for suspected or confirmed bleeding

ORDERING AND ADMINISTRATION

A. 4-Factor Prothrombin Complex Concentration (KCentra®)
   1. Ordering:
      i. KCentra® doses are calculated as units/kg using total body weight, with the maximum dosing weight of 100 kg.
      ii. During verification, the Sterile Products Area pharmacist will verify and prepare dose rounded to nearest vial size within 10% of originally ordered dose.
   2. Administration:
      i. Administer via infusion pump at a rate of 3 units/kg/minute; do not exceed a rate of 8.4 mL/minute (504 mL/hour).
      ii. After KCentra® dose is complete; administer a 50 mL bag of normal saline using the same IV tubing at the same rate as KCentra® dose to ensure administration of full dose.
**FIGURE 4. MANAGEMENT OF APIXABAN OR RIVAROXABAN RELATED BLEEDING EVENTS**

Patient currently taking apixaban* or rivaroxaban*

Non-major bleeding or routine/urgent procedure/surgery

Major bleeding or emergent procedure/surgery

All other bleeding or emergent procedure/surgery

Intracranial hemorrhage ONLY

Delay next dose or discontinue factor Xa inhibitor

1) Administer KCentra® 50 units/kg IV x 1 (Max dose: 5000 units)
2) For persistent refractory bleeding (> 1 hour), consider a hematology consult
3) To investigate potential causes of bleeding obtain the following: serum creatinine (Scr), prothrombin time (PT), activated partial thromboplastin time (aPTT), complete blood count (CBC)

1) Andexxa® with Neurocritical Care Attending approval only
2) See Table 1 for dosing recommendations

*If presenting within 2 hours of ingestion of apixaban or rivaroxaban dose, consider administering activated charcoal 50 g by mouth x 1 dose

-Avoid activated charcoal in patients who may require a gastrointestinal procedure for suspected or confirmed bleeding

**Ordering and Administration**

**A. 4-Factor Prothrombin Complex Concentration (KCenta®)**

1. Ordering:
   i. KCenta® doses are calculated as units/kg using total body weight, with the maximum dosing weight of 100 kg.
   ii. During verification, the Sterile Products Area pharmacist will verify and prepare dose rounded to nearest vial size within 10% of originally ordered dose.

2. Administration:
   i. Administer via infusion pump at a rate of 3 units/kg/minute; do not exceed a rate of 8.4 mL/minute (504 mL/hour).
   ii. After KCenta® dose is complete, administer a 50 mL bag of normal saline using the same IV tubing at the same rate as KCenta® dose to ensure administration of full dose.

**B. Coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa*)**

1. Ordering:
   i. Andexxa® is restricted to use for intracranial hemorrhage only and must be ordered or approved by a Neurocritical Care Attending
   ii. Select low or high dose based on anticoagulant dose and timing of last dose (see Table 1)

2. Administration:
i. Administer bolus and infusion using a 0.2 or 0.22 micron in-line filter (supplied by Central Pharmacy). The same tubing and filter should be used for the bolus and infusion.

ii. The infusion should begin within 2 minutes of completion of the bolus dose.

iii. After Andexxa® dose is complete, administer a 50 mL bag of normal saline using the same IV tubing and filter at the same rate as Andexxa® dose to ensure administration of full dose.

Table 1. Andexxa® Dosing By Anticoagulant and Time of Last Dose

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Anticoagulant Last Dose Administered (mg taken)</th>
<th>Timing of Anticoagulant Last Dose</th>
<th>&lt; 8 hours or unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>&lt; 5 mg</td>
<td>Low dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 5 mg or unknown mg dose</td>
<td>High dose</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>&lt; 10 mg</td>
<td>Low dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 10 mg or unknown mg dose</td>
<td>High dose</td>
<td></td>
</tr>
</tbody>
</table>

**Low dose:** 400 mg IV bolus (30 mg/min (180 mL/hour)) followed by 480 mg (4 mg/min (24 mL/hour)) over 2 hours

**High dose:** 800 mg IV bolus (30 mg/min (180 mL/hour)) followed by 960 mg (8 mg/min (48 mL/hour)) over 2 hours
### III. Emergent Reversal of Intravenous and Subcutaneous Anticoagulants

**FIGURE 5. MANAGEMENT OF UNFRACTIONATED HEPARIN (UFH) OR LOW-MOLECULAR WEIGHT HEPARIN (LMWH) RELATED BLEEDING EVENTS**

#### Ordering and Administration

A. **Protamine Sulfate**
   1. **Administration:**
      i. Administer protamine sulfate as a slow IV push with maximum rate of 5 mg/minute to prevent hypotension and bradycardia
      ii. Patients with history of fish allergies or prior exposure to protamine should receive pre-medications with hydrocortisone and diphenhydramine.

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<table>
<thead>
<tr>
<th>Patient currently taking UFH or LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-major bleeding or routine/urgent procedure/surgery</td>
</tr>
<tr>
<td>Major bleeding or emergent procedure/surgery</td>
</tr>
<tr>
<td>Delay next dose or discontinue heparin infusion or low molecular weight heparin injections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unfractionated Heparin (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) <strong>Administer protamine sulfate</strong>: Max dose: 50 mg</td>
</tr>
<tr>
<td>a. Calculate the units of heparin administered within the last 3 hours</td>
</tr>
<tr>
<td>b. Administer 1 mg of protamine for every 100 units of heparin administered in last 3 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unfractionated Heparin (subcut)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) <strong>Administer protamine sulfate</strong>: Max dose: 50 mg</td>
</tr>
<tr>
<td>a. Calculate the units of heparin administered within the last 3 hours</td>
</tr>
<tr>
<td>b. Administer 1 mg of protamine for every 100 units of heparin administered in last 3 hours</td>
</tr>
<tr>
<td>c. Monitor activated partial thromboplastin time (aPTT) every 3 hours and consider repeat protamine (0.5 mg per 100 units of heparin administered) if bleeding continues</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low Molecular Weight Heparin:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) <strong>Administer protamine sulfate</strong>: Max dose: 50 mg</td>
</tr>
<tr>
<td>a. <strong>Enoxaparin</strong>: Determine timing of last dose</td>
</tr>
<tr>
<td>i. If dose within the last 8 hours, give 1 mg of protamine for every 1 mg of enoxaparin administered</td>
</tr>
<tr>
<td>ii. If dose within the last 8-12 hours, give 0.5 mg of protamine for every 1 mg of enoxaparin administered</td>
</tr>
<tr>
<td>iii. If dose more than 12 hours ago, protamine sulfate is not recommended. Consider checking LMWH anti-factor Xa level in the setting of renal failure. Administer 0.5 mg of protamine for every 1 mg of enoxaparin administered if level elevated.</td>
</tr>
<tr>
<td>b. <strong>Dalteparin</strong>: Determine timing of last dose</td>
</tr>
<tr>
<td>i. If dose within last 8 hours, give 1 mg of protamine for every 100 units of dalteparin administered</td>
</tr>
</tbody>
</table>

*Patients with fish allergies or prior exposure to protamine are at increased risk for hypersensitivity reactions, including anaphylaxis, pre-medicate with the following:
- Hydrocortisone 50 mg IV x 1 dose
- Diphenhydramine 50 mg IV or by mouth x 1 dose
FIGURE 6. MANAGEMENT OF DIRECT THROMBIN INHIBITOR RELATED BLEEDING EVENTS

Patient currently taking argatroban or bivalirudin

Non-major bleeding or routine/urgent procedure/surgery

Discontinue direct thrombin inhibitor continuous infusion

Major bleeding or emergent procedure/surgery

1) Administer KCentra® 50 units/kg IV x 1 (max dose: 5000 units)
2) For persistent refractory bleeding, consider a hematology consult
3) To investigate potential causes of bleeding obtain the following: serum creatinine (SCr), prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), complete blood count (CBC)

Ordering and Administration

A. 4-Factor Prothrombin Complex Concentration (KCentra®)
   1. Ordering:
      i. KCentra® doses are calculated as units/kg using total body weight, with the maximum dosing weight of 100 kg.
      ii. During verification, the Sterile Products Area pharmacist will verify and prepare dose rounded to nearest vial size within 10% of originally ordered dose.
   2. Administration:
      i. Administer via infusion pump at a rate of 3 units/kg/minute; do not exceed a rate of 8.4 mL/minute (504 mL/hour).
      ii. After KCentra® dose is complete, administer a 50 mL bag of normal saline using the same IV tubing at the same rate as KCentra® dose to ensure administration of full dose.
III. Management of Antiplatelet Agent Related Bleeding Events

Duration of platelet inhibition by antiplatelet agents that irreversibly inhibit platelet function is not dependent on the agent half-life, but rather may persist for 5-7 days. Utilize Table 2 below as a guide for interpreting the peak and duration of action of these agents.

Table 2. Antiplatelet PK/PD profiles

<table>
<thead>
<tr>
<th>Agent</th>
<th>Time to Maximum Antiplatelet Effect</th>
<th>Elimination Half-Life</th>
<th>Platelet Inhibition</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>30 minutes</td>
<td>15-30 minutes</td>
<td>Irreversible</td>
<td>Antiplatelet effects begin within one hour of dose and persist for at least 4 days after stopping therapy.</td>
</tr>
<tr>
<td>Clopidogrel (Plavix®)</td>
<td>3-7 days</td>
<td>8 hours</td>
<td>Irreversible</td>
<td>More rapid inhibition of platelet function is achieved with loading doses; antiplatelet effect persists for up to 10 days after stopping therapy.</td>
</tr>
<tr>
<td>Prasugrel (Effient®)</td>
<td>30 minutes</td>
<td>7 hours</td>
<td>Irreversible</td>
<td>Antiplatelet effect persists for 5-7 days after stopping therapy.</td>
</tr>
<tr>
<td>Ticagrelor Brilinta®</td>
<td>1.5 hours</td>
<td>7 hours</td>
<td>Reversible</td>
<td>Antiplatelet effects are decreased to 30% activity after stopping therapy for 2.5 days.</td>
</tr>
<tr>
<td>Ticlopidine (Ticlid®)</td>
<td>1-3 hours</td>
<td>24-36 hours</td>
<td>Reversible</td>
<td>Antiplatelet effect persists for 5-7 days after stopping therapy.</td>
</tr>
<tr>
<td>Cangrelor (Kengreal®)</td>
<td>Seconds with IV administration</td>
<td>2-5 minutes</td>
<td>Reversible</td>
<td>Normal platelet function returns by 60 minutes after infusion is stopped.</td>
</tr>
</tbody>
</table>

Table adapted from Ortel TL. Blood. 2012;120(24):4699-4705.

1. Management strategies for antiplatelet associated bleeding events:
   a. There are no specific reversal agents for antiplatelet agents, therefore treatment of bleeding involves general hemostatic measures.
   b. Discontinuation of antiplatelet agents due to bleeding must be weighed against the patient’s risk of arterial thrombosis. The risk of thrombosis is particularly high within 1 month of receiving a bare metal coronary stent and within 3 months of receiving a drug eluting coronary stent. Premature cessation of dual anti-platelet therapy in these situations can lead to stent thrombosis, which can potentially be fatal.
   c. Antiplatelet agents should be reinstated as soon as hemostasis is obtained.
   d. Platelet infusion may be considered as additional measure for severe critical bleeds, or prevention of bleeds before emergency surgery, but it may confer a risk of arterial thrombosis.
   e. Tranexamic acid (Lysteda®) or Aminocaproic acid (Amicar®) can be considered
      i. Tranexamic acid: 10 mg/kg IV bolus administered over 10 minutes (maximum bolus dose: 1000 mg IV once)
      ii. Aminocaproic acid: 50 mg/kg IV bolus administered over 60 minutes (maximum bolus dose: 5000 mg IV once)
      iii. Continuation of tranexamic acid or aminocaproic acid after the bolus can be considered for continued bleeding
   f. DDAVP is likely not a safe option, as it can lead to arterial vasospasm.
   g. Hematology/Coagulation Consult Service may be consulted if a risk versus benefit evaluation is required.
References:
15. www. Clotconnect.org

Appendix A: Bleeding Definitions

Major Bleeding:
- Symptomatic bleeding into a critical site:
  - Intracranial
  - Intraspinal
  - Intraocular
  - Retroperitoneal
  - Intraarticular
  - Pericardial
  - Intramuscular with compartment syndrome
- Bleeding leading to \( \geq 2 \) g/dL hemoglobin decrease
- Bleeding leading to transfusion of \( \geq 2 \) units of packed red blood cells
- Activation of the massive transfusion protocol
- Bleeding leading to hypotension requiring vasopressors

Minor Bleed:
- Bleeding leading to \(< 2 \) g/dL hemoglobin decrease
- Bleeding leading to transfusion of \(< 2 \) units of packed red blood cells
- Gross hematuria not associated with trauma
- Epistaxis and oral bleeding that is prolonged and unresponsive to topical therapies
- Bruising, bleeding gums, oozing from injection sites
- Bleeding at a compressible site
### Appendix B: Anticoagulant Pharmacokinetic Considerations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination Half-Life</th>
<th>Mechanism of Clearance</th>
<th>Removed by Dialysis</th>
<th>In-House Laboratory Values for Detecting Drug Presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>12 hours (prolonged in renal impairment)</td>
<td>Renal/Hepatic</td>
<td>No</td>
<td>Prothrombin time (PT) (prolonged or normal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LMWH anti-factor Xa level (elevated)</td>
</tr>
<tr>
<td>Argatroban</td>
<td>40-50 minutes (prolonged in hepatic dysfunction)</td>
<td>Hepatic</td>
<td>20%</td>
<td>Activated partial thromboplastin time (aPTT) (prolonged)</td>
</tr>
<tr>
<td>Betrixaban (Bevyxxa®)</td>
<td>19 to 27 hours</td>
<td>Renal/Hepatic</td>
<td>No</td>
<td>Prothrombin Time (PT) (prolonged or normal)</td>
</tr>
<tr>
<td>Bivalirudin (Angiomax®)</td>
<td>25 minutes (up to 1 hr in severe renal impairment)</td>
<td>Renal</td>
<td>25%</td>
<td>Prothrombin time (PT) (prolonged)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombin time (TT) (prolonged)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Activated partial thromboplastin time (aPTT) (prolonged)</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>14 hours (up to 34 hrs in severe renal impairment)</td>
<td>Renal</td>
<td>62-68%</td>
<td>Thrombin time (TT) (prolonged)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Activated partial thromboplastin time (aPTT) (prolonged)</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>10 to 14 hours (prolonged in renal impairment)</td>
<td>Renal/Hepatic</td>
<td>No</td>
<td>Prothrombin time (PT) (prolonged or normal)</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox®)</td>
<td>3-5 hours (prolonged in renal impairment)</td>
<td>Renal</td>
<td>20%</td>
<td>LMWH anti-factor-Xa (elevated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prothrombin time (PT) (prolonged)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombin time (TT) (prolonged)</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra®)</td>
<td>17-21 hours (significantly prolonged in renal impairment)</td>
<td>Renal</td>
<td>No</td>
<td>Prothrombin time (PT) (prolonged or normal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Activated partial thromboplastin time (aPTT) (prolonged)</td>
</tr>
<tr>
<td>Heparin</td>
<td>30-90 minutes</td>
<td>Hepatic</td>
<td>Partial</td>
<td>Activated partial thromboplastin time (aPTT) (prolonged)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UFH anti-factor Xa level (elevated)</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>Healthy: 5-9 hours Elderly: 11-13 hours (prolonged in renal impairment)</td>
<td>Renal/Hepatic</td>
<td>No</td>
<td>Prothrombin time (PT) (prolonged or normal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LMWH anti-factor Xa level (elevated)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>20-60 hours</td>
<td>Hepatic</td>
<td>No</td>
<td>Prothrombin time (PT) (prolonged)</td>
</tr>
</tbody>
</table>