UNC EMERGENT ANTICOAGULATION REVERSAL

I. PURPOSE:

The purpose of these instructions is to provide guidelines for the reversal of or management of bleeding with anticoagulants. The following procedures/guidelines have been approved by the Pharmacy and Therapeutics Committee to promote the safe and effective use of the anticoagulation agents listed below:

II. GUIDELINES

A. Correction of Supratherapeutic Anticoagulation with Warfarin

Management of warfarin reversal and bleeding events is summarized below:

1. Management of life-threatening bleeds in patients on warfarin
   a. KCentra (4-factor PCC) is first line unless otherwise contraindicated
   b. Each dose of KCentra (4-factor PCC) will be rounded to the nearest vial size
   c. The responsibility of the clinical provider (MD, PA, NPP)
      i. Ensure patient is on warfarin
      ii. Ensure INR is obtained
      iii. Administration of KCentra should not be delayed for INR results
   d. The responsibility of the nurse:
      i. Administer the product within one hour of preparation

Developed by: Leah Hatfield, PharmD BCPS and Sheh-Li Chen, PharmD, BCOP
Reviewed by: Stephan Moll, MD, Abhi Mehrotra, MD, and Rhonda Cadena, MD

Last Updated: June 2014
**TABLE 1: MANAGEMENT OF WARFARIN RELATED BLEEDING EVENTS**

<table>
<thead>
<tr>
<th>INR</th>
<th>Bleeding</th>
<th>Risk Factors for Bleeding</th>
<th>Intervention</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratherapeutic, but &lt; 4.5</td>
<td>No</td>
<td>No/Yes</td>
<td>Lower or omit next VKA dose(s), reduce subsequent dose(s)</td>
<td>Recheck INR the next day</td>
</tr>
<tr>
<td>4.5-10.0</td>
<td>No</td>
<td>No/Yes</td>
<td>Ommit next VKA dose(s), reduce subsequent dose(s)</td>
<td>Recheck INR the next day</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>No</td>
<td>No/Yes</td>
<td>Vitamin K 2.5 – 5 mg PO* Omit next VKA dose(s); reduce subsequent dose(s)</td>
<td>Recheck INR the next day</td>
</tr>
<tr>
<td>Non-life threatening major bleed or surgery/procedure requiring emergent warfarin reversal</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vitamin K 10 mg IV + KCentra (4-factor PCC)</td>
<td>Recheck INR 10-30 minutes after 4-factor PCC administration. Due to short half-life of PCC, check INR q6hrs for 24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INR 2.0-3.9: KCentra 25 units/kg x 1 (Max 2500 units)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INR 4.0-6.0: KCentra 35 units/kg x 1 (Max 3500 units)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INR &gt; 6.0: KCentra 50 units/kg x 1 (Max 5000 units)</td>
<td></td>
</tr>
<tr>
<td>Serious, life threatening bleed at ANY INR in the ED</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vitamin K 10 mg IV + KCentra (4-factor PCC)</td>
<td>Recheck INR 10-30 minutes after 4-factor PCC administration. Due to short half-life of PCC, check INR q6hrs for 24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INR ≤ 6.0 or unknown: KCentra 35 units/kg x 1 (Max 3500 units)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>INR &gt; 6.0: KCentra 50 units/kg x 1 (Max 5000 units)</td>
<td></td>
</tr>
</tbody>
</table>

American Society of Hematology Self-Assessment Program, 2013
KCentra Package Insert, CSL Behring, 2013

* If patient is unable to tolerate PO, Vitamin K via IV route may be substituted for PO above
1. Additional Information about Warfarin Reversal
   a. Oral vitamin K is preferred for patients without severe bleeding.
   b. IV vitamin K should be ordered only if patient has life threatening bleeding, or needs an emergent procedure, where a shorter onset of anticoagulation reversal may be required.
   c. Subcutaneous or intramuscular doses are not recommended as routine care.
   d. Full effect of vitamin K on warfarin reversal occurs approximately 24 hours after administration. Partial effects may be seen in 6-12 hours.
   e. Doses of vitamin K greater than 10 mg are excessive and do not reverse anticoagulation more quickly.

B. Unfractionated Heparin (UFH)

1. Protamine sulfate is used to reverse the anticoagulant effect of heparin.
   a. Increased risk of hypersensitivity reaction, including anaphylaxis, in patients with a fish allergy or prior exposure to protamine.
   b. Pre-medicate with corticosteroids and antihistamines if at risk for protamine allergy.
      1. Hydrocortisone 50-100 mg IV x 1 over 15 minutes
      2. Diphenhydramine 50 mg IV/PO x1

2. Dose calculation
   a. 1 mg of protamine neutralizes approximately 100 units of UFH
   b. Use only the last 3 hours prior to reversal when considering the total amount of heparin administered to patient, due to the short half-life of UFH. If the patient is on a continuous infusion, calculate the total amount administered over the past three hours prior to reversal. If the patient is receiving SQ heparin, calculate the total amount administered within the past 3 hour prior to reversal only.
   c. Maximum single protamine dose is 50 mg

3. Administration
   a. IV heparin reversal
      i. Administer protamine IV with maximum infusion rate of 5 mg/min to prevent hypotension and bradycardia.
   b. SC heparin reversal
      ii. Administer bolus dose of protamine 25 mg and infuse remaining dose via intravenous infusion over 8 hours.

4. Monitor aPTT starting 5-15 minutes after protamine infusion.
   a. Onset of reversal effect is seen 5 minutes after administration
   b. Duration of reversal activity is approximately 2 hours.
   c. Multiple protamine doses may be required if bleeding or elevation of aPTT level persists.
C. Low-Molecular Weight Heparin (LMWH)

1. Protamine sulfate may be used as a partial reversal agent (neutralizes approximately 60% of LMWH’s anti-factor Xa activity).
2. Increased risk of hypersensitivity reaction, including anaphylaxis, in patients with a fish allergy or prior exposure to protamine.
   a. Premedicate with corticosteroids and antihistamines if at risk for protamine allergy.
3. Dose Calculation
   a. If last dose of LMWH was given in previous 8 hours, give 1 mg protamine for every 1 mg (or 100 units) of LMWH. Maximum total dose of protamine is 50 mg.
   b. If the last dose of LMWH was given in the previous 8-12 hours, give 0.5 mg protamine for every 1 mg (or 100 units) of LMWH. Max single dose of protamine is 50 mg.
   c. If the last dose of LMWH was given more than 12 hours earlier:
      i. Protamine is not recommended and an alternative agent may be needed to obtain hemostasis. If the patient requires other pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is recommended.
4. Administration
   a. Maximum protamine sulfate IV infusion rate is 5 mg/min to prevent hypotension and bradycardia.
   b. Repeat dose 0.5 mg protamine for every 1 mg (or 100 units) of LMWH if bleeding continues or elevated anti-factor Xa activity level after 2-4 hours.
D. Direct IV Thrombin Inhibitors (DTIs): Argatroban, Bivalirudin, Lepirudin

There is no specific reversal agent or pharmacologic antidote. Due to the short half-life of these agents (Argatroban 40-50 min; Bivalirudin 25 min; Lepirudin 80 min), management of hemorrhagic complications is primarily supportive and interruption of treatment will be sufficient to reverse the anticoagulant effect. If patients require pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is advised. Management of intravenous direct thrombin inhibitor related bleeding events is summarized below:

### TABLE 2: MANAGEMENT OF INTRAVENOUS DIRECT THROMBIN INHIBITOR RELATED BLEEDING EVENTS

<table>
<thead>
<tr>
<th>Mild</th>
<th>Delay next dose or discontinue IV direct thrombin inhibitor.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consider any of the following based on bleeding severity:</td>
</tr>
<tr>
<td></td>
<td>• Symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td>• Mechanical compression</td>
</tr>
<tr>
<td></td>
<td>• Surgical intervention</td>
</tr>
<tr>
<td></td>
<td>• Fluid replacement and hemodynamic support</td>
</tr>
<tr>
<td></td>
<td>• Blood product transfusion</td>
</tr>
<tr>
<td></td>
<td>If hemostasis is not achieved with the strategies outlined above, consider the administration of 2-4 units of fresh frozen plasma (FFP).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate</th>
<th>No agent has been shown to successfully reverse the anticoagulant effects of intravenous DTIs or treat DTI-related bleeding events. However, the interventions below may be considered.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1) Administer KCentra (4-factor PCC) 50 units/kg IV (max dose 5000 units) x 1 \</td>
</tr>
<tr>
<td></td>
<td>2) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, thrombin clotting time (TCT), CBC (platelets).</td>
</tr>
</tbody>
</table>
Dabigatran

There is no specific reversal agent or pharmacologic antidote, thus management of hemorrhagic complications is primarily supportive. Hemodialysis is effective at removing approximately 60% of dabigatran. If patients require pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is advised. Management of dabigatran related bleeding events is summarized below:

**TABLE 3: MANAGEMENT OF DABIGATRAN RELATED BLEEDING EVENTS**

<table>
<thead>
<tr>
<th>Bleeding Severity</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Delay next dose or discontinue dabigatran.</td>
</tr>
</tbody>
</table>
| Moderate          | Consider any of the following based on bleeding severity:  
|                   |  - Symptomatic treatment  
|                   |  - Mechanical compression  
|                   |  - Surgical intervention  
|                   |  - Fluid replacement and hemodynamic support  
|                   |  - Blood product transfusion  
|                   |  - Oral activated charcoal (if previous dose ingested within 2 hours); Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose  
|                   | If hemostasis is not achieved with the strategies outlined above, consider the administration of 2-4 units of fresh frozen plasma (FFP). |
| Severe or Life-threatening | Consider any of the strategies outlined above based on bleeding severity. In the setting of acute renal failure, initiation of hemodialysis may be considered for the purpose of facilitating drug elimination. No agent has been shown to successfully reverse the anticoagulant effects of dabigatran or treat dabigatran-related bleeding events. However, the interventions below may be considered. |
|                   | 1) Administer KCentra (4-factor PCC) 50 units/kg IV x 1 (max dose 5000 units)  
|                   | 2) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, thrombin clotting time (TCT), Ecarin Time (ECT), CBC (platelets). |

*Table adapted from van Ryn. Thromb Haemost. 2010 Jun;103(6):1116-27;*
E. Factor Xa Inhibitors: Apixaban, Rivaroxaban, Fondaparinux

There is no specific reversal agent or pharmacologic antidote, thus management of hemorrhagic complications is primarily supportive. Rivaroxaban and apixaban are highly protein bound and are not dialyzable. If patients require pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is advised. Management of Factor Xa inhibitor-related bleeding events is summarized below:

**TABLE 4: MANAGEMENT OF FACTOR Xa INHIBITOR RELATED BLEEDING EVENTS**

<table>
<thead>
<tr>
<th>Bleeding Severity</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>Delay next dose or discontinue Factor Xa inhibitor.</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Consider any of the following based on bleeding severity:</td>
</tr>
<tr>
<td></td>
<td>• Symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td>• Mechanical compression</td>
</tr>
<tr>
<td></td>
<td>• Surgical intervention</td>
</tr>
<tr>
<td></td>
<td>• Fluid replacement and hemodynamic support</td>
</tr>
<tr>
<td></td>
<td>• Oral activated charcoal for apixaban or rivaroxaban (if previous dose ingested within 2 hours)</td>
</tr>
<tr>
<td></td>
<td>Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose</td>
</tr>
<tr>
<td></td>
<td>If hemostasis is not achieved with the strategies outlined above, proceed to the steps below.</td>
</tr>
<tr>
<td><strong>Severe or Life-threatening</strong></td>
<td>Consider any of the strategies outlined above based on bleeding severity. No agent currently available in the US has been shown to successfully reverse the anticoagulant effects of Factor Xa inhibitor-related bleeding events. However, the strategy below may be considered based on the currently available evidence. Therefore, the pharmacologic interventions below may be considered, but are not required in the management of Factor Xa inhibitor-related bleeding.</td>
</tr>
<tr>
<td></td>
<td>1) Administer KCentra (4-factor PCC) 50 units/kg IV x 1 (max dose 5000 units)</td>
</tr>
<tr>
<td></td>
<td>2) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, anti-Xa activity (send-out lab), CBC (platelets).</td>
</tr>
<tr>
<td></td>
<td>3) If PT prolonged, administer vitamin K 10mg IV x one dose (as there may be vitamin K deficiency present).</td>
</tr>
</tbody>
</table>

Table adapted from Eerenberg. Circulation. 2011 Oct 4; 124(14):1573-9
F. Antiplatelet agents that irreversibly inhibit platelet function: aspirin, clopidogrel, prasugrel

Antiplatelet agents that reversibly inhibit platelet function: dipyridamole, NSAIDs, ticagrelor

Duration of platelet inhibition by antiplatelet agents that irreversibly inhibit platelet function is not dependent on the agents’ half-life, but may persist for 5-7 days. Please utilize the chart below as a general guide for interpreting the peak and duration of action of these agents.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Time to Maximum Antiplatelet Effect</th>
<th>Elimination Half-Life</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>30 min</td>
<td>15-30 min</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>More rapid inhibition of platelet function is achieved with loading doses; antiplatelet effect lasts up to 10 days after stopping therapy.</td>
</tr>
<tr>
<td>Prasugrel (Effient)</td>
<td>30 min</td>
<td>7 hours</td>
<td>Antiplatelet effect lasts 5-7 days after stopping therapy.</td>
</tr>
<tr>
<td>Ticagrelor (Brilinta)</td>
<td>1.5 hours</td>
<td>7 hours</td>
<td>Antiplatelet effects are decreased to 30% activity after 2.5 days.</td>
</tr>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>1-3 hours</td>
<td>24-36 hours</td>
<td>Antiplatelet effect lasts 5-7 days after stopping therapy.</td>
</tr>
</tbody>
</table>

Table adapted from Ortel TL. Blood 2012 Dec 6; 120(24):4699-705.

1. Management of antiplatelet agent associated bleeding events:
   a. There are no specific reversal agents for antiplatelet agents.
   b. Treatment of bleeding involves general hemostatic measures.
   c. Discontinuation of antiplatelet agents due to a bleeding event 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.
   d. Antiplatelet agents should be reinstated as soon as hemostasis is obtained
   e. 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.
   f. Desmopressin is likely not a safe option, as it can lead to arterial vasospasm.
III. REFERENCES:

- UNCH Blood Derivative Compendium v02014 04.
- www. Clotconnect.org
### APPENDIX A: Summary of Anticoagulation Reversal Recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination Half-Life</th>
<th>Removed by Dialysis</th>
<th>Summary of emergent reversal for life-threatening bleeding</th>
</tr>
</thead>
</table>
| **Apixaban (Eliquis)** | 12 hours (longer in renal impairment) | no                  | If ingested within 2 hours, give activated charcoal 1 g/kg (max 50 g)  
Administer KCentra® (4-factor PCC) 50 units/kg x 1 at 3 units/kg/min (max dose 5000 units)  
Monitor PT/INR and anti-Factor Xa activity level to confirm reversal|
| **Argatroban**      | 40-50 minutes         | 20%                 | Turn off infusion.  
Monitor aPTT/TCT to confirm clearance  
Consider KCentra® (4-factor PCC) 50 units/kg x 1 at 3 units/kg/min (max dose 5000 units) |
| **Bivalirudin (Angiomax)** | 25 minutes (up to 1 hr in severe renal impairment) | 25%                 | Turn off infusion.  
Monitor aPTT/TCT to confirm clearance  
Consider KCentra® (4-factor PCC) 50 units/kg x 1 at 3 units/kg/min (max dose 5000 units) |
| **Dabigatran (Pradaxa)** | 14 hours (up to 34 hrs in severe renal impairment) | 62-68%              | If ingested within 2 hours, give activated charcoal 1g/kg (max 50 g)  
Administer KCentra® (4-factor PCC) 50 units/kg x 1 at 3 units/kg/min (max dose 5000 units)  
Monitor aPTT/TCT to confirm reversal |
| **Enoxaparin (Lovenox)** | 3-5 hours (longer in severe renal impairment) | 20%                 | Protamine partially reverses the anticoagulant effect of LMWHs (~60%).  
Administer protamine: (do not exceed rate 5 mg/min, max dose 50 mg)  
If last dose was < 8 hours prior:  
For each 1 mg of enoxaparin, administer 1 mg of protamine  
If last dose was 8-12 hours prior:  
For each 1 mg of enoxaparin, administer 0.5 mg protamine  
If last dose was >12 hours prior:  
Protamine is unlikely to be beneficial  
For refractory or life threatening bleeding:  
Administer KCentra® (4-factor PCC) 50 units/kg x 1 at 3 units/kg/min (max dose 5000 units)  
Monitor anti Factor Xa activity level to confirm reversal |
| **Fondaparinux (Arixtra)** | 17-21 hours (significantly longer in renal impairment) | no                  | Administer KCentra® (4-factor PCC) 50 units/kg x 1 at 3 units/kg/min (max dose 5000 units)  
Monitor aPTT/anti Factor Xa activity level to confirm reversal |
| **Heparin**         | 30-90 minutes (dose-dependent) | partial             | Protamine neutralizes heparin  
Administer protamine:  
For each 100 units of heparin, administer 1 mg of protamine  
Do not exceed rate of 5 mg/min, max dose is 50 mg |
### UNC Healthcare ED Anticoagulation Reversal Guidelines

#### Drug Elimination Half-Life Removed by Dialysis Summary of emergent reversal for life-threatening bleeding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination Half-Life</th>
<th>Removed by Dialysis</th>
<th>Clinical Setting</th>
<th>Therapeutic Options</th>
</tr>
</thead>
</table>
| Rivaroxaban (Xarelto) | Health: 5-9 hrs Elderly: 11-13 hrs (longer in renal impairment) | no | | If ingested within 2 hours, give activated charcoal 1g/kg (max 50g)  
Administer KCentra® (4-factor PCC) 50 units/kg x 1 at 3 units/kg/min, (max dose 5000 units)  
Monitor PT/INR and anti-Factor Xa activity level to confirm reversal |

<table>
<thead>
<tr>
<th>INR</th>
<th>Clinical Setting</th>
<th>Therapeutic Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (Coumadin, Jantoven)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR &lt; 4.5</td>
<td>No bleeding</td>
<td>Hold warfarin until INR in therapeutic range</td>
</tr>
</tbody>
</table>
| Rapid reversal required | Hold warfarin  
Consider vitamin K 2.5 mg po* |
| INR 4.5 – 10 | No bleeding | Hold warfarin until INR in therapeutic range  
Consider vitamin K 2.5 mg po* |
| Rapid reversal required | Hold warfarin  
Give vitamin K 2.5 - 5 mg po* |
| INR > 10 | No bleeding | Hold warfarin until INR in therapeutic range  
Consider vitamin K 2.5 – 5 mg po* |
| Rapid reversal required | Hold warfarin  
Give vitamin K 2 mg IV infusion |
| Any INR | Non-life threatening major bleed or surgery/procedure requiring emergent warfarin reversal | Hold warfarin  
Give vitamin K 10 mg IV infusion over 30 minutes  
Give KCentra (4-factor PCC)  
INR 2.0 – 3.9 : 25 units/kg (max 2500 units)  
INR 4.0 – 6.0 : 35 units/kg (max 3500 units)  
INR > 6.0 : 50 units/kg (max 5000 units) |
| Any INR | Serious or life threatening bleeding | Hold warfarin  
Give vitamin K 10 mg IV infusion over 30 minutes  
Give KCentra (4-factor PCC)  
INR unknown: 35 units/kg (max 3500 units)  
INR 1.5 – 6.0: 35 units/kg (max 3500 units)  
INR > 6.0 : 50 units/kg (max 5000 units)  
Repeat x 2 q15mins prn if INR remains > 1.5 |

*If patient is unable to tolerate PO vitamin K, IV route may be substituted*

Developed by: Leah Hatfield, PharmD BCPS and Sheh-Li Chen, PharmD, BCOP  
Last Updated: June 2014  
Reviewed by: Stephan Moll, MD, Abhi Mehrotra, MD, and Rhonda Cadena, MD