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Anticoagulant Guidelines #2: **REVERSAL OF OR MANAGEMENT OF BLEEDING WITH ANTICOAGULANTS**	Origination Date:	09/12
	Revision Date:	09/12, 01/13, 11/13, 11/15
	Reviewed Date:	

POLICY KEY ELEMENTS

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 Medical Executive Committee to promote the safe and effective use of the anticoagulation agents listed below:

II. GUIDELINES

A. 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.
2. Dose calculation
    a. 1 mg of protamine neutralizes approximately 100 units of UFH
    b. Use only the last 3 hours when considering the amount of heparin administered to patient, due to the short half-life of UFH.
    c. Maximum protamine dose is 50 mg
    d. Protamine may have anticoagulant effects with excessive dosing.
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
        i. Administer bolus dose of protamine 25 mg and infuse remaining dose via intravenous infusion over 8 hours.
4. Monitor anti-factor Xa activity levels 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 anti-factor Xa activity level persists.

B. Low-Molecular Weight Heparin (LMWH)

1. Protamine sulfate may be used as a partial reversal agent (neutralizes approximately 60% of anti-factor Xa activity).
   a. Increased risk of hypersensitivity reaction, including anaphylaxis, in patients with a fish allergy or prior exposure to protamine.
   b. Premedicate with corticosteroids and antihistamines if at risk for protamine allergy.
2. 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.
   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.
   c. If the last dose of LMWH was given more than 12 hours earlier, 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 Transfusion Medicine consult is recommended.
3. 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.

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C. Direct Thrombin Inhibitors (DTIs)
Argatroban, Bivalirudin

1. There is no specific reversal agent or pharmacologic antidote.
2. Due to the short half-life of these agents, management of hemorrhagic complications is primarily supportive and interruption of treatment will be sufficient to reverse the anticoagulant effect.
3. For life-threatening hemorrhage, prothrombin complex concentrates may be used to manage bleeding.
   a. Recommend administration of prothrombin complex concentrate 20-25 IU/kg (requires approval from Transfusion Medicine PIC 50435)
4. Recombinant factor VIIa may also be used to manage bleeding (requires approval from Transfusion Medicine PIC 50435).
5. If patients require pharmacologic therapy to manage hemorrhagic complications, a Transfusion Medicine consult is recommended.

Dabigatran

1. Idarucizuman, a specific reversal agent for dabigatran, was approved by the FDA in October 2015. It is currently available, as needed, through the non-formulary process. .
2. Dabigatran is not highly protein bound and mostly excreted in the urine (80%), so appropriate diuresis must be maintained in order to promote adequate drug clearance.
3. Oral activated charcoal can be administered if the last dabigatran dose was ingested within 2 hours.
4. Hemodialysis is effective at removing approximately 60% of the dabigatran.
5. For uncontrolled bleeding, prothrombin complex concentrates or activated prothrombin complex concentrates may be used to manage bleeding.
   a. Recommend administration of prothrombin complex concentrate 25-50 IU/kg (requires approval from Transfusion Medicine PIC 50435)
   b. Alternatively, activated prothrombin complex concentrate (FEIBA) can be administered at a dose of 80 IU/kg (requires approval from Hematology)
6. Monitoring for efficacy or toxicity may be done using a dabigatran level (dilute thrombin time). This lab is a send out to Emory Medical Laboratories and only performed during business hours. As a result, treatment should not be delayed until a result is obtained; however, a baseline dabigatran level should be ordered to establish pharmacokinetics. A thrombin time or activated partial thromboplastin time (APTT) may also be used to assess for presence of dabigatran.
7. If patients require pharmacologic therapy to manage hemorrhagic complications, a Transfusion Medicine consult is required.

D. Factor Xa Inhibitors

Fondaparinux

1. There is no specific reversal agent or pharmacologic antidote so management of hemorrhagic complications is primarily supportive.
2. Fondaparinux is 94% protein bound and primarily renally excreted. Approximately 20% is removed by hemodialysis. The half-life is ≈17-21 hours and may be prolonged in patients with renal impairment and the elderly.
3. For uncontrolled bleeding, recombinant factor VIIa may be used as a reversal agent.
   a. Dose studied in literature was 90 mcg/kg, administered 2 hours after fondaparinux. (requires approval from Transfusion Medicine PIC 50435)
   b. Smaller doses may be appropriate.
4. Monitoring for efficacy or toxicity may be done using a fondaparinux level. This lab is a send out to Emory Medical Laboratories.
5. If patients require pharmacologic therapy to manage hemorrhagic complications, a Transfusion Medicine consult is required.

Apixaban, Edoxaban, Rivaroxaban

1. There is no specific reversal agent or pharmacologic antidote so management of hemorrhagic complications is primarily supportive.
2. Oral activated charcoal can be administered if last apixaban, edoxaban or rivaroxaban dose was ingested within 2 hours.
3. Apixaban, edoxaban, and rivaroxaban are highly protein bound and not dialyzable.
4. For uncontrolled bleeding, prothrombin complex concentrates may be used to manage bleeding.
   a. Dose studied in literature was 50 IU/kg; however, smaller doses may be appropriate.
   b. Recommend administration of prothrombin complex concentrate 20-25 IU/kg (requires approval from Transfusion Medicine PIC 50435)
5. Monitoring for efficacy or toxicity may be done using a prothrombin time (PT); however, PT reagents are relatively insensitive to apixaban and there is little published information for edoxaban..
   a. Monitoring for efficacy or toxicity may be done using a rivaroxaban level (anti-Xa activity calibrated for rivaroxaban). This lab is a send out to Emory Medical Laboratories and only performed during business hours. As a result, treatment should not be delayed until a result is obtained; however, a baseline level should be ordered to establish pharmacokinetics.
   b. There is no currently available laboratory test to specifically measure the anticoagulant effect of apixaban or edoxaban.
6. If patients require pharmacologic therapy to manage hemorrhagic complications, a Transfusion Medicine consult is required.

E. Correction of Supratherapeutic Anticoagulation with Warfarin

<table>
<tr><th>INR</th><th>Recommendation if Rapid Reversal is NOT Necessary</th></tr>
<tr><td>Above therapeutic range, but < 5</td><td>Lower the warfarin dose AND/OR hold next few warfarin doses. Resume at a lower dose when INR is therapeutic. If only minimally above therapeutic range, no dose reduction may be required.</td></tr>
<tr><td>≥ 5, but < 9</td><td>Patient at low risk for bleeding: Hold 1-2 doses of warfarin and resume at lower dose when INR is therapeutic.

Patient at high risk for bleeding: Hold warfarin dose and administer vitamin K 2.5 mg orally x 1. Resume warfarin at lower dose when INR is therapeutic. May repeat vitamin K if necessary.</td></tr>
<tr><td>≥ 9</td><td>Hold warfarin and give vitamin K 2.5 to 5 mg orally x 1. Monitor closely. May repeat vitamin K 2.5 mg orally in 24-48 hours. Resume warfarin at lower dose when INR is therapeutic.</td></tr>
<tr><th colspan="2">Rapid Reversal Indicated (Significant Bleeding or Urgent/Emergent Procedure Planned)</th></tr>
<tr><td>≥ 5, but < 9 and urgent procedure needed</td><td>Hold warfarin and give vitamin K 2.5 to 5 mg orally. If INR does not decrease within 24 hours, may repeat vitamin K 2.5 mg orally. Resume warfarin at lower dose when INR therapeutic or with surgeons approval.</td></tr>
<tr><td>Serious bleeding or urgent procedure
(any elevated INR)</td><td>Hold warfarin and give vitamin K 10 mg by slow intravenous infusion (not greater than 1 mg/min). May repeat every 12 hours as needed.

Check INR at least every 6 to 12 hours.

Administer Fresh Frozen Plasma (FFP) 2 – 4 units every 6 – 12 hours as needed for borderline elevations. If more aggressive reversal is necessary, consult with Transfusion Medicine for additional recommendations.</td></tr>
<tr><td>Life-threatening bleeding or emergency procedure
(any elevated INR)</td><td>Hold warfarin and give vitamin K 10 mg by slow intravenous infusion (not greater than 1 mg/min), may repeat every 12 hours as necessary.

Administer: Prothrombin complex concentrate (Kcentra™) according to the table below IV x 1. Repeat dosing
<table>
<tr><td>Pre-treatment INR</td><td>2 - > 4</td><td>4 - 6</td><td>> 6</td></tr>
<tr><td>Dose / kg Body Weight</td><td>25</td><td>35</td><td>50</td></tr>
<tr><td>Maximum Dose (Factor IX IU)</td><td>Do Not Exceed 2500</td><td>Do Not Exceed 3500</td><td>Do Not Exceed 5000</td></tr>
</table>
Monitor INR within 30 minutes of completion of the infusion.

Kcentra™ requires pre-approval with the exception of attending providers from the Emergency Department, Neurocritical Care, Neurosurgery, or Transfusion Medicine services.</td></tr>
<tr><td>Intracranial Hemorrhage</td><td>See warfarin reversal diagram below.</td></tr>
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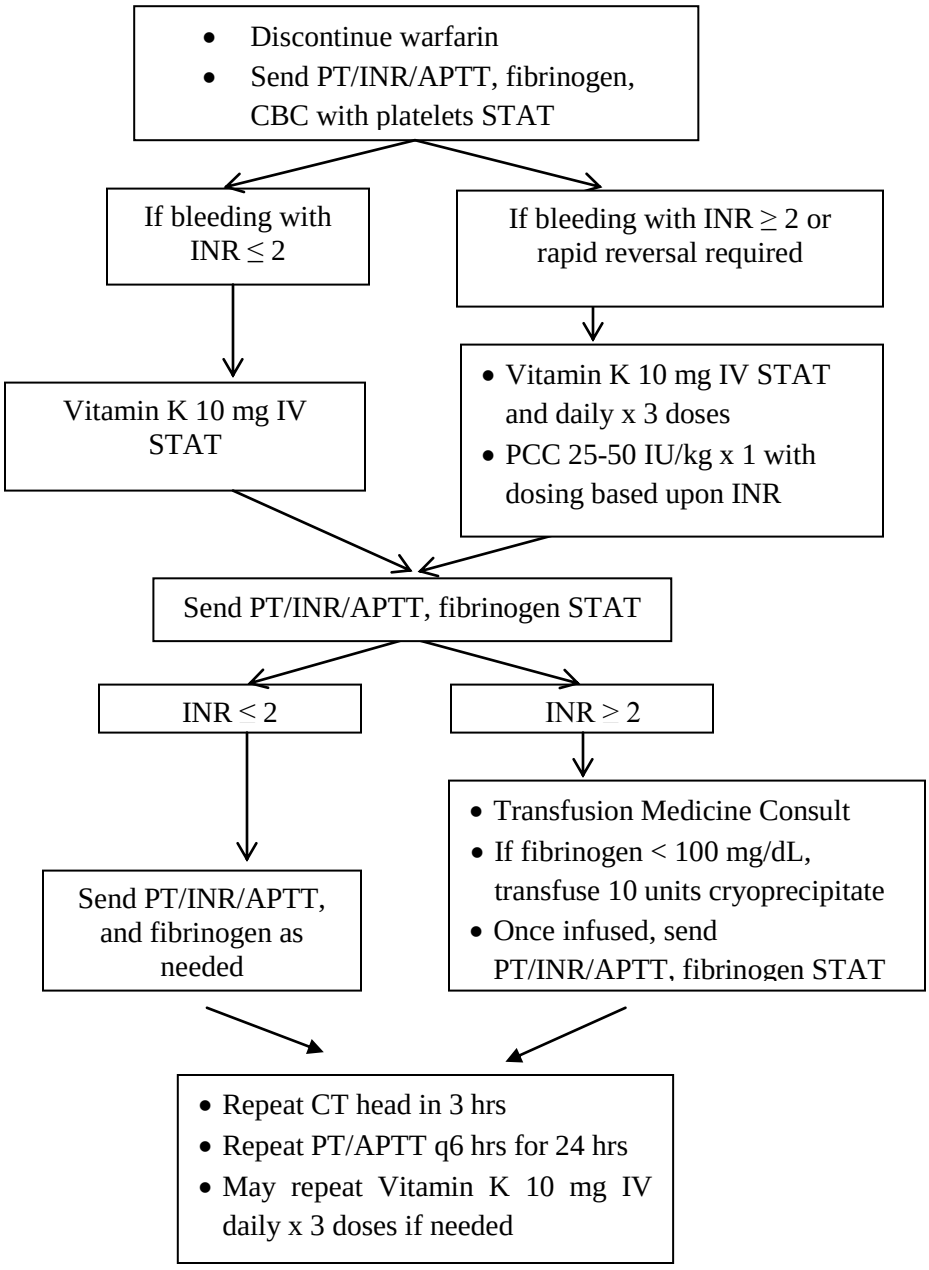
Initial Reversal of Warfarin for Intracranial Hemorrhage



1. Additional Information about Warfarin Reversal
   a. Full effect of vitamin K on warfarin reversal occurs approximately 24 hours after administration. Some effects may be seen in 6-12 hours.
   b. Doses of vitamin K greater than 10 mg are excessive and do not reverse anticoagulation more quickly. The Physician will be contacted by Pharmacy for clarification.
   c. Contact Cardiology, Hematology, or Transfusion Medicine if additional information is needed.
   d. Use the EPIC order set "Reversal of Anticoagulation" to reverse anticoagulation or manage bleeding from an anticoagulant
   e. With the exception of Emergency Department, Neurocritical care and Neurosurgery Faculty, all other requests for PCC require a Transfusion Medicine Consult.

III. REFERENCES:

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