UNC HEALTH CARE GUIDELINE

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 Last Updated: June 2014

Reviewed by: Stephan Moll, MD, Abhi Mehrotra, MD, and Rhonda Cadena, MD

TABLE 1: MANAGEMENT OF WARFARIN RELATED BLEEDING EVENTS

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

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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

Mild	Delay next dose or discontinue IV direct thrombin inhibitor.
Moderate	*Consider any of the following based on bleeding severity:* • Symptomatic treatment Mechanical compression Surgical intervention • Fluid replacement and hemodynamic support • Blood product transfusion *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	*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.* 1) Administer KCentra (4-factor PCC) 50 units/kg IV (max dose 5000 units) x 1 2) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, thrombin clotting time (TCT), CBC (platelets).

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

Bleeding Severity	Management Recommendations
Mild	Delay next dose or discontinue dabigatran.
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

Bleeding Severity	Management Recommendations
Mild	Delay next dose or discontinue Factor Xa inhibitor.
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 for apixaban or rivaroxaban (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, proceed to the steps below.*
Severe or Life-threatening	*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.* 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, anti-Xa activity (send-out lab), CBC (platelets). 3) If PT prolonged, administer vitamin K 10mg IV x one dose (as there may be vitamin K deficiency present).
Table adapted from Eerenberg. Circulation. 2011 Oct 4; 124(14):1573-9	

F. Antiplatelet agents that irreversibly inhibit platelet function: aspirin, clopidrogel, 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.

Agent	Time to Maximum Antiplatelet Effect	Elimination Half-Life	Notes
Aspirin	30 min	15-30 min	Antiplatelet effects begin within one hour of dose and persist for at least 4 days after stopping therapy.
Clopidogrel (Plavix)	3-7 days	8 hours	More rapid inhibition of platelet function is achieved with loading doses; antiplatelet effect lasts up to 10 days after stopping therapy.
Prasugrel (Effient)	30 min	7 hours	Antiplatelet effect lasts 5-7 days after stopping therapy.
Ticagrelor Brilinta)	1.5 hours	7 hours	Antiplatelet effects are decreased to 30% activity after 2.5 days.
Ticlopidine (Ticlid)	1-3 hours	24-36 hours	Antiplatelet effect lasts 5-7 days after stopping therapy.
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.

Developed by: Leah Hatfield, PharmD BCPS and Sheh-Li Chen, PharmD, BCOP Last Updated: June 2014

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III. REFERENCES:

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- UNCH Blood Derivative Compendium v02014 04.
- www. Clotconnect.org

APPENDIX A: Summary of Anticoagulation Reversal Recommendations

Drug	Elimination Half-Life	Removed by Dialysis	Summary of emergent reversal for life-threatening bleeding
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 x1 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 x1 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 x1 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 x1 at 3 units/kg/min 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 x1 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 x1 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

Drug	Elimination Half-Life	Removed by Dialysis	Summary of emergent reversal for life-threatening bleeding
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 50 g) Administer KCentra® (4-factor PCC) 50 units/kg x1 at 3 units/kg/min, (max dose 5000 units) Monitor PT/INR and anti-Factor Xa activity level to confirm reversal
	INR	**Clinical Setting**	**Therapeutic Options**
Warfarin (Coumadin, Jantoven)	INR < 4.5	No bleeding	Hold warfarin until INR in therapeutic range
		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

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