

Reversal of Anticoagulants at UCDMC

Introduction:

Bleeding complications are a common concern with the use of anticoagulant agents. In selected situations, reversing or neutralizing the effects of an anticoagulant may be desired. For acute ingestions of an oral anticoagulant, activated charcoal may be a consideration, however risk for aspiration need to be evaluated.

Table 1: Considerations and suggested approaches for reversing the effects of an anticoagulant.

Goal depends on the urgency to reverse effect and patient's ability to eliminate the effects of an anticoagulant within the desired time period

Rationale or Time Frame for Establishing Hemostasis	Approach
Emergent / Urgent: Minutes to hours (Including patients with ICH on oral anticoagulation)	<ul style="list-style-type: none"> • Hold anticoagulants and consider giving a specific antidote and/or a pro-coagulant agent (see Tables 2 and 3; Appendix 1 and 2) • Topical hemostatic agents (e.g. thrombin gel) may be used in selected situations. • Consider laboratory analysis for baseline values and if necessary to modify the therapy. • <i>Therapy may be initiated prior to lab results being posted.</i>
Semi-Urgent: Hours	<ul style="list-style-type: none"> • Hold anticoagulants and consider giving a specific antidote and/or a pro-coagulant agent (see tables 2 and 3; appendix 1) if expedited reversal of effects is necessary. • Topical hemostatic agents (e.g. thrombin gel) may be used in selected situations. • Consider laboratory analysis for baseline values and if necessary to modify the therapy. Therapy may be initiated prior to results being posted.
Non-Urgent: Hours to days	<ul style="list-style-type: none"> • Hold the anticoagulant. Consider additional laboratory analysis and reassess bleeding risks.
Reduce the therapeutic target <i>(usually related to changes in risk acceptance)</i>	<ul style="list-style-type: none"> • Revision of the anticoagulation approach. • A temporary hold may be considered depending on how rapid a reduction is desired considering the current level of anticoagulation. • This usually does not involve administration of an antidote or pro-coagulant.

Table 2: Selected Reversal Agents

Reversal Agent	Mechanism	Kinetics	Description/Dose	Rebound of anticoagulant effect after “reversal”
Activated PCC (aPCC)	Replaces coagulation factors lowered by warfarin. Does not neutralize the new oral anticoagulants	Onset: ~ 5 -15 minutes Duration of effect: 8 – 12 hours	FEIBA™ (currently the only available aPCC): contains clotting factors - II, IX, and X and VII (FVII primarily in an activated form). FEIBA™ may be the first option for eminent life threatening bleed in patients taking rivaroxaban, apixaban, edoxaban, or dabigatran. Per UCDMC P and T committee, FEIBA is preferred over non-activated PCC for DOAC reversal. (See Table 3 for dosing). Although data is limited to case reports/experiences with the use of concentrated clotting factors such as FEIBA to indirectly reverse the effects of LWMH and fondaparinux, it may be an option in eminent life threatening bleeding when other modalities have not been successful.	~ 12 hr
Fresh Frozen Plasma (FFP)	Replaces coagulation factors lowered by warfarin. Contains all coagulant factors, including II, VII, IX, and X but in diluted inactive form compared to other options.	Onset: ~ 1-4 hours depending on dose and magnitude of anticoagulation Duration of effect: Less than or equal to 6 hours.	5-20 ml/kg IV (~ 10ml/min) provides partial warfarin reversal. Does not influence INR values after 12 hours when combined with Vitamin K versus Vitamin K alone. Use should be reserved for selected situations where an immediate partial reversal of warfarin is desired and concurrent prothrombin complex concentrate (PCC) is not being administered. A rebound in the INR may be observed after the administration as the effects of the anticoagulant are commonly longer than FFP. Supplemental parenteral calcium may be necessary to reverse citrate effects.	~4-6 hr
Idarucizumab	Antibody that directly neutralizes the effects of Dabigatran and has no effect on other anticoagulants	Onset: Immediate. Duration: Provides full reversal up to at least 24 hours in most patients	5gm’s IV once as a bolus over 5 minutes per vial. (Available as 2.5gm in 50ml – dose is 2 vials) If very high Dabigatran levels are present (e.g. over 800-1000ng/ml), may need additional drug for full reversal.	Unclear, but could occur if high concentrations of dabigatran are present (e.g. overdose)

Protamine	Negates the effect of heparin and combines chemically with heparin molecules to form an inactive salt. Partially reverses the effects of LMWH	Onset: ~ 5 minutes Duration is irreversible and dose dependent. Rebound of anticoagulation risk with subcutaneous heparin or LWMH doses.	<p>See IV infusion guidelines [Link].</p> <p>- For IV Heparin: 1mg protamine per 100 units of heparin, (max dose 50 mg) at a rate not to exceed 5 mg per minute.</p> <p>If the infusion has been held:</p> <ul style="list-style-type: none"> • Greater than 60 min, administer 0.5 mg protamine/100 units of heparin. • Greater than 2 hrs, administer 0.25 mg protamine/100 units heparin <p><i>Because the half-life of IV heparin is relatively short (~60 to 90 min) with effects dissipating rapidly after stopping the IV infusion, consider calculating the dose of protamine sulfate from the amount of heparin administered within the preceding few hours. e.g. From a continuous IV infusion of heparin at 1,250 units/hour, approximately 30 mg of protamine sulfate would be used.</i></p> <p><i>After an IV bolus and bleeding (or high risk): (1mg/100 units UFH if aPTT at goal, 1.5mg/100 units if the aPTT is elevated. Infuse at 5 mg/min)</i></p> <p>Can repeat aPTT shortly after administration. If still elevated secondary to heparin, can consider additional protamine.</p> <p>Higher doses may be used after selected procedures (e.g. cardiopulmonary bypass).</p> <ul style="list-style-type: none"> • If aPTT remains elevated, repeat administration of protamine • Caution as hypotension, flash pulmonary edema and allergic reactions may occur with rapid administration. 	Rebound heparin effect may be seen if heparin or LMWH has been given SC or large IV doses of heparin are given in cardiopulmonary bypass. Additional protamine may be indicated 2-4 hours after initial dose.
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<p>Prothrombin Complex Concentrates (PCC)</p>	<p>Replaces coagulation factors lowered by warfarin. Contains coagulant factors, including II, VII, IX, and X, in concentrations 25 times that of FFP. Requires activation of factors in vivo. Does not directly neutralize the activity of new oral anticoagulants</p>	<p>Onset: ~ 5-15 minutes Duration of effect: 12-24 hours used with Vitamin K</p>	<ul style="list-style-type: none"> • Doses of 12.5-50 International units/kg IV (Max infusion rate 2ml/min) have been explored to reverse the effects of warfarin. Differences between available products exist. • PCC4 (KCentra™): clotting factors II, VII, IX and X • PCC3: not recommended for anticoagulation reversal at UCDMC <p>Kcentra™ may be an option for eminent life threatening bleed due to rivaroxaban, apixaban, edoxaban, or dabigatran. See Table 3 for dosing. <u><i>Kcentra™ does contain heparin and may not be option in patients who are sensitive to heparin or have a recent diagnosis of heparin-induced thrombocytopenia.</i></u></p> <p>To prevent treatment delays in major bleeding, the INR can be drawn and then 1,000 units PCC4 administered. Depending on the INR and clinical assessment of the bleeding, the balance of the dose based on the INR result can be administered.</p> <p>Call the Anticoagulation, CPCS Service, or ED Pharmacist for assistance.</p>	<p>~12 to 24 hr</p>
<p>Recombinant activated Factor Seven (rFVIIa)</p>	<p>Non-specific pro-coagulant. Delivers rFVIIa, which activates extrinsic clotting pathway resulting in thrombin formation. Does not directly neutralize the activity of new oral anticoagulants</p>	<p>Onset: ~5-10 minutes Duration of effect 4-6 hours, used with FFP and Vitamin K in patients with elevated INR due to warfarin. Infuse over 3-5 minutes.</p>	<p>See related guidelines for situational use in non-anticoagulated patients (trauma, CT surgery services and in the cardiac catheterization lab). No dose ranging trials are available in this setting. Low doses of 1mg IV have normalized the INR for warfarin patients and reduced the ACT for bivalirudin patients within 15 minutes. Call the Anticoagulation, CPCS Service, or ED Pharmacist for approval outside established guidelines.</p>	<p>6-12 hr</p>

Vitamin K	<p>Leads to production of functional coagulation factors II, VII, IX, and X (depleted by warfarin). Cofactor for hepatic production of Factors II, VII, IX and X.</p> <p>Only works on warfarin, does not neutralize the activity of other anticoagulants.</p>	<p>Onset</p> <ul style="list-style-type: none"> • PO 12-24 hr • IV 4-12 hr • SC and IM <i>not</i> recommended <p>Duration dependent on warfarin intensity, INR rebound occurring in days</p>	<p>See IV infusion guidelines. Can be given IV or PO. The IV form can be given PO for smaller doses. (Appendix 1 for dosing) Call the anticoagulation service for advice on dosing. IV: Infuse immediately at maximum rate of 1mg/min.</p> <p>IV Vitamin K</p> <ul style="list-style-type: none"> - ICH: 10mg IV Vitamin K - Low doses (e.g. 0.25mg – 1mg) are effective in causing partial reversal at 24-48 hours. This can be considered for partial reversal of a very high INR - IV doses \geq 2mg will have similar degree of INR drop at 24-48 hours. The higher the dose, the longer the duration of reversal. <p>PO Vitamin K</p> <ul style="list-style-type: none"> - Higher home doses of warfarin may require higher doses of Vitamin K to achieve certain reduction in INR. <p>Bridging therapy</p> <ul style="list-style-type: none"> - Lower Vitamin K doses correlates with shorter duration of bridging therapy. <p>Adding FFP with Vitamin K</p> <ul style="list-style-type: none"> - Minimal additional effect on the INR measured greater or equal to 12 hours later. 	Dose dependent
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Table 3: Drug Reversal Considerations

Anticoagulant	Elimination route and half-life (normal/healthy patients)	Laboratory assays to consider	Pharmacologic Reversal Agents to Consider	Comment
Apixaban	Hepatic/Renal 9-14 hours	Chromogenic anti-factor Xa calibrated for apixaban, INR ^a	KCentra™, FEIBA™	<p>FEIBA™ is preferred for major or life threatening bleeding with doses ranging 8-25 units/kg. Call Anticoagulation Service, CPCS, or ED Pharmacist for assistance with dosing.</p> <p>Data on the agent and dose to reverse the effects of apixaban has not been established.¥ Not dialyzable.</p> <ul style="list-style-type: none"> • <u>Minor bleeding</u>, monitor and re-check labs • <u>Major bleeding</u>: FEIBA™ low dose (8 units/kg); Second Option: may consider KCentra™ if clinically necessary • <u>Emergent life threatening bleed</u>: FEIBA™ 8units/kg to 25-50 units/kg. Second Option: KCentra™ 25-50 units/kg
Argatroban	Hepatic ~60-90 min	aPTT ACT in selected cardiac procedures		Effective means to reverse argatroban has not been established. Currently not used at UCDMC.
Bivalirudin	Enzymatic ~25-45 minutes	aPTT ACT in selected cardiac procedures	rFVIIa, Partially dialyzed	In a few cardiothoracic surgery cases at UCDMC, low dose rFVIIa (e.g. 1-2 mg) was able to drop ACT's and slow bleeding within the surgical field. In hypothermia, a decline in enzymatic elimination may occur resulting in higher laboratory values. As long as the temperature is very low, the infusion rate may be reduced or held until the patient is warmed.

Dabigatran	Renal 14-17 hours	Chromogenic ECT calibrated for dabigatran, INR ^a /aPTT Thrombin time for presence. ^b	Idarucizumab, FEIBA™, KCentra™, Hemodialysis	<p>Idarucizumab will directly neutralize dabigatran, limiting the need for hemodialysis as a means to expedite removal of drug. Onset of hemostasis may take hours (mean 11 hours observed in bleeding patients noting that time of data collection may have influenced observations in clinical trials).</p> <p>In the setting of, a major or life threatening active bleed where idarucizumab alone may not achieve bleeding management targets, the addition of FEIBA™ at doses ranging from 8-25 units/kg or Tranexamic Acid can be considered at the discretion of the treating physician. Call Anticoagulation Service, CPCS, or ED Pharmacist for assistance with dosing.</p> <p>Data is limited relative to an effective approach for reversal and bleeding management.¥</p> <ul style="list-style-type: none"> • <u>Minor bleeding</u>: monitor and re-check labs • <u>Major bleeding</u>: Consider Idarucizumab and if hemostasis desired in an active bleeding patient within a few hours, can consider low dose FEIBA™ (approximately 8-12 units/kg). Another option with use of Idarucizumab in traumatic non-ICH bleeding is to add Tranexamic Acid. • <u>Emergent life threatening bleed</u>: Idarucizumab 5gm IV bolus plus FEIBA™ initial dose up to approximately 25 units/kg -a second dose (up to 25 units/kg) should be readily available if hemostasis targets are not achieved and patient is still unstable. Option of Tranexamic Acid 1gram IV bolus followed by 1gram infusion over 8 hours <i>instead of FEIBA</i> at physician discretion in traumatic non-ICH bleeding. Hemodialysis may be a secondary consideration in rare situations. • Doses will be rounded to nearest vial contents. • Note*: Because hemostasis may not immediately to occur with Idarucizumab alone, FEIBA™ is the institutions preferred adjunct, however Tranexmic Acid is an alternate option to FEIBA™ with use at the discretion for the attending physician. • Experience with the use of either FEIBA™ or Tranexamic Acid with Idarucizumab is very limited • Hemodialysis can remove dabigatran depending on the amount present in the plasma. Drug levels have been shown to rebound upon cessation of hemodialysis from tissue rebound, therefore, prolonged dialysis may be considered in selected situations (See appendix 3). Can consider low dose FEIBA™ just prior to catheter placement for hemodialysis.
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Edoxaban	Hepatic/Renal 10 – 14 hours	Anti-Factor Xa level has been proposed, but no known effect on outcomes.	KCentra™, FEIBA™	<p>FEIBA™ is preferred for major or life threatening bleeding with doses ranging 8-25 units/kg. Call Anticoagulation Service, CPCS, or ED Pharmacist for assistance with dosing.</p> <p>Data on the agent and dose to reverse the effects of edoxaban has not been established.¥ Not dialyzable.</p> <ul style="list-style-type: none"> • <u>Minor bleeding</u>: monitor and re-check labs • <u>Major bleeding</u>: low dose FEIBA™ (approximately 8-12 units/kg); Second Option: may consider KCentra™ if clinically necessary <p><u>Emergent life threatening bleed</u>: FEIBA™ 8 units/kg to 25-50 units/kg. Second Option: KCentra™ 25-50 units/kg</p>
Fondaparinux	Renal 7-21 hours	Anti-Factor Xa level has been proposed, but no known effect on outcomes. Not recommended at this time	FEIBA™	<p>Degree of reversal and ability to reduce bleeding is unclear. One assessment showed a greater impact with an aPCC 20 units/kg compared to rFVIIa.</p> <p>Protamine is not recommended</p> <p>If bleeding persists in an eminent life threatening event, FEIBA 8 units/kg to 25 units/kg can be considered.</p>
LMWH	Renal ~2-8 hours	Anti-Factor Xa level drawn 4 hours post dose in selected situations. Peak effect occurs at 3-5 hours post SC dose	Protamine, FEIBA™	<p>Partial reversal of effects with protamine. Degree of reversal and ability to reduce bleeding is unclear.</p> <p>Protamine dosing (maximum 50mg):</p> <p>- Enoxaparin:</p> <ul style="list-style-type: none"> • Dose within 8 hours: 1mg protamine per 1mg Enoxaparin given • Dose 8-12 hours earlier: 0.5mg protamine per 1mg enoxaparin given. <p>Dalteparin:</p> <ul style="list-style-type: none"> • Dose within 8 hours: 1mg protamine per 100 anti-Xa units • Dose administered between 12 – 24 hours: 0.5 mg protamine per 100 anti-Xa <p>If life threatening LMWH bleeding persists or significant renal impairment is present, a repeat dose of 0.5mg protamine per 100 anti-Xa units LMWH (~1mg Enoxaparin) can be considered.</p> <p>If bleeding persists in an eminent life threatening event, FEIBA 8 to 25 units/kg can be considered.</p>

Unfractionated heparin	Hepatic 1-2 hours	aPTT (may be > 150 seconds with high doses) ACT (better measure if learger doses of heparin have been given of if aPTT > 150 sec) - Low range ACT used for cardiac cath. - High range ACT used in the OR for cardiopulmonary bypass. Anti-Factor Xa level in selected situations	Protamine	For urgent situations. Effects of heparin dissipate several hours after holding. Post Cardiopulmonary bypass, an aPTT rebound may be detected up to 6 hours post the initial dose where an additional dose of protamine (~25mg) can be considered if bleeding concerns are present.
Rivaroxaban	Hepatic/Renal 5-9 hours (Elderly 11-13 hours)	Chromogenic Anti-Factor Xa calibrated for rivaroxaban, INR ^a	KCentra™, FEIBA™	<p>FEIBA™ is preferred for major or life threatening bleeding with doses ranging 8-25 units/kg. Call Anticoagulation Service, CPCS, or ED Pharmacist for assistance with dosing.</p> <p>Data on the agent and dose to reverse the effects of rivaroxaban has not been established.¥ Not dialyzable.</p> <ul style="list-style-type: none"> • <u>Minor bleeding</u>, monitor and re-check labs • <u>Major bleeding</u>: FEIBA™ low dose (approximately 8-12 units/kg); Second Option: may consider KCentra™ if clinically necessary • <u>Emergent life threatening bleed</u>: FEIBA™ 8units/kg to 25-50 units/kg. Second Option: KCentra™ 25-50 units/kg

Warfarin	Hepatic ~36-48 hours (3-7 days for the INR to normalize depending on the dose, age, drug interactions and cardiac function)	INR	Vit K, KCentra™, rFVIIa (selected situations), FFP	<p>Vitamin K doses take 12-48 hours for full effect (Appendix 1). KCentra™ dosing:</p> <p>a. Max dosing weight 100 kg</p> <p>i. INR ≥1.4 – 4: 25 units/kg (<i>actual</i> body weight)</p> <p>1. Option: Initiate with ~12.5 units/kg actual body weight can be repeated after reassessment of response</p> <p>ii. INR 4.1 – 6: 35 units/kg (<i>actual</i> body weight)</p> <p>iii. INR greater than 6: 50 units/kg (<i>actual</i> body weight)</p> <p>In a major/life threatening bleed, an initial dose of 1000 units can be given after the INR is drawn. Based on the INR result and assessment of the bleed, the balance of the dose can be administered.</p> <p>ICH: Vitamin K 10mg IV (if no suspicion for cerebral venous thrombosis). In the setting of life-threatening thrombosis, ischemia, HIT or DIC assess the risk versus benefit of giving vitamin K.</p> <p>- KCentra – Consider if INR is ≥ 1.4</p> <p>Option: rFVIIa for urgent reversal in selected settings (OR) when INR greater than 1.2: 1mg given with IV Vitamin K and FFP. Repeat INR 10-15 minutes post dose. Not to be used at same time with KCentra™ and use with caution in ICH. Call the Anticoagulation, CPCS Service, or ED Pharmacist for approval outside established guidelines for trauma, CT surgery and cardiac cath. lab, or any non-urgent situations.</p> <p>See Appendix 2 for coagulopathic patients <i>on warfarin</i> requiring emergent neurosurgical intervention.</p>
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FEIBA® is current formulary activated prothrombin complex concentrate (aPCC) product.

KCentra® is current formulary prothrombin complex concentrate (PCC) product.

Kcentra™ contains clotting factors II, VII, IX and X. It contains heparin and use should be avoided in patients where heparin is contraindicated.

Anti-Factor Xa: chromogenic anti-factor Xa assay calibrated independently to each anti-factor Xa agent (heparin, rivaroxaban, or apixaban)

FFP: Fresh Frozen Plasma

rFVIIa: Activated recombinant factor seven

a: Increased INR values may occur in the presence of high DOAC concentrations, for which further assessments should be considered. b: The thrombin time is very sensitive to the presence of dabigatran and can be a useful measure for the presence of drug. Normal thrombin times suggest minimal dabigatran is present.

¥ No data supporting improved outcomes. A FEIBA® dose up to 50 units/kg to start may be considered in urgent life threatening situations. In settings where bleeding can be observed or assessed (e.g. changing Hgb), lower doses (e.g. 8-12 units/kg) can be initiated and additional doses given as needed since the onset of effect is within minutes. Lower doses have been used for invasive procedures such as line insertions, but must be infused immediately prior to the procedure. Suggested KCentra® dosing can range from 12.5-50 units/kg depending on urgency of situation. If time is present, consider lower doses and reevaluate need for additional dosing.

Please call Anticoagulation Service for assistance: 816-2568 (CLOT)

Appendix 1: Vitamin K dosing suggestions for an initial INR greater than or equal to 5

Patient's Current Daily Warfarin Dose	Target INR Goal	Bleeding	No Bleeding
Low Daily Dose (less than or equal to 2mg/day)	2-3 at 12 hours	0.25mg – 1.25mg IV	1-2.5mg PO
	1.5 at 12 hours	greater than or equal to 2mg IV	greater than or equal to 5mg PO
	1.5 at 24 – 48 hours	0.25 – 1.25mg IV	greater than or equal to 3mg PO
	less than 1.3 at 24 – 48 hours*	greater than or equal to 2mg IV	greater than or equal to 5mg PO
Medium Daily Dose (2.1–3.9 mg/day)	2-3 at 12 hours	0.25mg – 1.25mg IV	greater than or equal to 2mg PO
	1.5 at 12 hours	greater than or equal to 2mg IV	greater than or equal to 5mg PO
	1.5 at 24 – 48 hours	0.25 – 1.25mg IV	less than or equal to 5mgPO
	less than 1.3 at 24 – 48 hours*	greater than or equal to 2mg IV	5-10mg PO
High Daily Dose (greater than or equal to 4 mg/day)	2-3 at 12 hours	0.25mg – 1.25mg IV	greater than or equal to 2.5mg PO
	1.5 at 12 hours	greater than or equal to 2mg IV	greater than or equal to 5mg PO
	1.5 at 24 – 48 hours	0.25 – 1.25mg IV	less than or equal to 5mgPO
	less than 1.3 at 24 – 48 hours*	greater than or equal to 2mg IV	5-10mg PO

*For life threatening bleed, no concern for restarting warfarin within 1 week: 10mg IV Vit K
 In the setting of a intracranial hemorrhage, 10mg IV is recommended with the potential for a repeat dose of 10mg if the INR is still ≥ 1.4 within the first 24-48 hours of the initial dose
No Bleeding Present/Non-urgent: (Call Pharmacy for assistance)
 - INR values less than 5 to normalize INR (no bleeding): Vit K less than 2mg IV (more rapid onset desired) or less than 5mg PO. Check INR in 12 hours.
 - INR (greater or equal to 5)
 Considerations:
 - INR 5-9: Hold 1-2 doses of warfarin, consider PO Vit K if bleeding risk a clinical concern.
 - INR greater than 9: Hold 1-3 doses of warfarin depending on decline and goal INR. Low dose vitamin K IV (0.25-1.25mg), or PO Vit K if bleeding risk a clinical concern.
 PO Vitamin K may not have as much of an effect at 12 hours as IV, but will begin to show similar effects after 24 hours

Appendix 2: KCentra™ (PCC4) in Neurosurgical Patients on Warfarin for EMERGENT INTRACRANIAL INTERVENTION

Situation: Coagulopathic (high INR) patients *on warfarin* requiring emergent neurosurgical intervention

The CPCS pharmacist on call (see call sheet for Clinical Pharmacology) should be paged in the presence of the attending physician in addition to notifying the central pharmacy (3-4072) of the KCentra™ request including the dose and location of the patient to whom it should be delivered. Kcentra® contains heparin, and should be avoided in patients where heparin is contraindicated.

CRITERIA

- Patients with INR greater than 1.5 requiring immediate neurosurgical invasive intervention where conventional therapy (i.e., FFP, vitamin K) has failed to normalize INR, is contraindicated, or where the urgency of the procedure would necessitate a more rapid reversal of coagulopathy. **For non-surgical intervention – see table 3.**
- Dose of KCentra™ is based off pre-dose INR (**Max dosing for actual body weight is 100 kg**)
 - **INR 1.4 – 1.9: 12.5 – 25 units/kg (*actual* body weight)**
 - **INR 2 - 4: 25 units/kg (*actual* body weight)**
 - **INR 4.1 – 6: 35 units/kg (*actual* body weight)**
 - **INR greater than 6: 50 units/kg (*actual* body weight)**
 - **To expedite effects, the INR can be drawn and 1000 units administered.** Based on the INR and bleeding assessment, the balance of the dose can be administered.
- Repeat the INR 10 - 15 minutes after completing administration
- If repeated INR is greater than 1.5, call CPCS/Anticoagulation Service or ED pharmacist for assistance.
- All warfarin patients with major or life threatening bleeds without contraindications should receive IV vitamin K concomitantly to maintain INR within desired range
- Risk factors for thrombosis or thromboembolic event (i.e., prior ischemic stroke, CAD, PE, etc) should be assessed and if present, a risk vs benefit analysis should be conducted prior to KCentra™ administration.

Appendix 3: Removal of Dabigatran by hemodialysis

Dabigatran is poorly protein bound in the plasma and able to be removed by hemodialysis. Literature regarding the optimal approach for to remove dabigatran is limited and in some cases based on limited analysis. The initial report by Strainger et al suggested 2/3 drug removal during a 2 hour dialysis session, however, only a 50mg dose was given and dialysis done before adequate tissue distribution. In a subsequent report from UC Davis (Chen et al), a rebound effect was noted and that it may take longer to remove the dabigatran. Additional reports limited to single center, case reports and series have suggested that removal and rebound may depend on the duration and to some extent the dialysis blood flow rate. In general, the longer the dialysis, the less amount of rebound observed, and that higher blood flow rates above 400 ml/min may not proportionally improve removal. Another concern is establishing dialysis access and avoiding delays in initiating dialysis in emergent situations, and Factor Eight Bypassing Agent (FEIBA) at a low dose of 8 units/kg has been given here immediately prior to insertion of the catheter here without noted complications. Given the availability of Idarucizumab, need for hemodialysis may be limited to rare situations. Call the Anticoagulation service for further assistance.

Author	Study Design	Observation
Strainger	Dabigatran 50 mg x 1 + 2 HD sessions; CKD V	Hemodialysis removed ~2/3rds Cp (plasma concentration) Arterial > Venous
Singh	N=5 (Cp 149-1200ng/ml) IHD +/- CRRT	↓ Dabigatran Cp lowered by/to 52-77% → ↑ (Rebound) to 87% within 2 hr
Wanrek	Case report	2.5 hr HD (BFR 500 mL/hr): □ TT 90 – 60 sec
Khadzhynov	Dabigatran 150mg x 3 days Cp max 156 ng/ml 4 hr HD (BF 200-400 ml/min)	- 200ml/min – 49% removal - 400 ml/min – 59% removal Redistribution: < 16%
Chen	Case Report	Dabigatran Cp ↓ from 1,100ng/ml → 18 ng/ml over 4 hr, rebound → 100ng/ml 20min
Lisenfeld	Open Label	Duration of dialysis had strongest impact on reducing Dabigatran levels.
Chiew	Case report – 9gm overdose Dabigatran Cp 1560ng/ml	CVVHF x 32 hours successfully removed dabigatran - observed extraction ration of 0.2

Recommendations:

1. Assess how much dabigatran is in the system to be removed: (Thrombin Time, INR and dabigatran level)
2. If there is a urgent need to start dialysis, immediately contact nephrology to facilitate
3. Consider low dose FEIBA™ (~8 units/kg) immediately prior to insertion of dialysis catheter
4. Initial hemodialysis at a tolerable blood flow rate as determined by nephrology. Can consider a lower rate after a few hours to continue removing drug rebounding into the plasma from the tissues.
5. Continue dialysis until normalization of the thrombin time or a measured dabigatran level below 40 ng/ml. This may take more than 4 hours depending on how high the initial level was.

References

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Appendix 4: Reversal of Anticoagulation during Cardiac Ablation

During cardiac ablation procedures, patients may be concurrently receiving some form of anticoagulation. The following guideline outlines approaches to reverse the effects of selected anticoagulants in the presence of a life threatening bleeding event:

Anticoagulant	Reversal agent	Dosing	Comments
Unfractionated Heparin	Protamine	Follow UCDMC Infusion guidelines	
Warfarin	Vitamin K FFP rFVIIa	See guidelines for the reversal of warfarin by vitamin K. rFVIIa: 1mg IV for life threatening bleeding events and INR above 1.3. Repeat INR 10-15 minutes post dose. If still elevated above 1.3 and life threatening bleeding is still occurring, a repeat dose can be administered. Option if time permits: PCC4 (KCentra) 25 – 50 units/kg depending on INR – see reversal guidelines	Follow UCDMC guidelines for the infusion of vitamin K. Doses of rFVIIa above 1mg require approval by the clinical pharmacology consult service (CPCS) or anticoagulation service.
LMWH	Protamine, FEIBA®*	Degree of reversal and ability to reduce bleeding is unclear. FEIBA may be an option in eminent life threatening bleeding event.	
Fondaparinux	FEIBA®*	Degree of reversal and ability to reduce bleeding is unclear.	One assessment showed a greater impact with an activated PCC (FEIBA 25 units/kg) then rFVIIa
Dabigatran	Idarucizumab FEIBA®, KCentra®	Idarucizumab 5gm IV. FEIBA®: Life threatening bleed, 25 units/kg x1 – Check TT ~10 minutes post infusion. Option is to send off a Dabigatran level. Evaluate bleeding. Option: KCentra®: 25-50 units/kg	One small assessment noted no effect by rFVIIa in reversing the effects of dabigatran.
Rivaroxaban, Apixaban or Endoxaban	FEIBA®*, KCentra®	FEIBA®** is preferred for major or life threatening bleeding with doses ranging 8-25 units/kg. KCentra®: 25-50 units/kg Evaluate response. A rivaroxaban or apixaban level can be requested.	Call the anticoagulation service, CPCS pharmacist, or ED pharmacist.

FEIBA® is current formulary activated prothrombin complex concentrate (aPCC) product.

It is the preferred agent for bleeding with the directing acting oral anticoagulants.

Initial dose 8 units/kg, but can give additional doses if bleeding does not stop.

KCentra® is current formulary prothrombin complex concentrate (PCC) product.

Kcentra™ contains clotting factors II, VII, IX and X. It contains heparin and use should be avoided in patients where heparin is contraindicated.

FFP: Fresh Frozen Plasma

rFVIIa: Activated recombinant factor seven

FEIBA® is the preferred agent for the new oral anticoagulants (DOAC).

*No data supporting improved outcomes. An FEIBA dose of 25 units/kg may be considered. Please call Anticoagulation Service for assistance: 816-2658 (CLOT)

** Call Anticoagulation Service for assistance: 816-2568 (CLOT)