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 in the ED
    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 KCentra dosing and administration information is in Appendix B
    d. 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
    e. The responsibility of the nurse:
        i. Prepare the factor product based upon package insert instructions (Appendix B)
        ii. Administer the product within one hour of preparation
        iii. Inform the ED Pharmacist/Coag pharmacist on call:
            1. Patient's name and MRN
            2. Date and time of administration
            3. Actual dose administered
    f. The responsibility of the ED pharmacist/Coag pharmacist
        i. Continuous monitoring of appropriateness of KCentra (4-factor PCC) use in the ED
        ii. Ensure patient is charged appropriately
        iii. Report to the Medication Safety Committee

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 1.25-2.5 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 5 -10 mg IV + KCentra (4-factor PCC) (stocked in Pharmacy) 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) (stocked in Pharmacy) INR 2.0-3.9: KCentra 25 units/kg x 1 (Max 2500 units) INR 4.0-6.0 or unknown: KCentra 35 units/kg x 1 (Max 3500 units) INR > 6.0: KCentra 50 units/kg x 1 (Max 5000 units) *SEE KCENTRA DOSING GUIDELINES AVAILABLE IN APPENDIX B*	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* *Witt. J Thromb Thrombolysis (2016) 41:187–205*				

* 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. Intravenous Direct 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). A Hematology/ Coagulation consult should be considered for further recommendations.*
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.* *A Hematology/Coagulation consult should be obtained after the following*: 1) Administer KCentra (4-factor PCC) 50 units/kg IV (max dose 5000 units) x 1 a. See dosing guide in Appendix B. STOCKED IN PHARMACY 2) For persistent refractory bleeding, pursue formal Heme/Coag consult. 3) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, thrombin clotting time (TCT), CBC (platelets).

E. Oral Direct Thrombin Inhibitors: Dabigatran

Idarucizumab (Praxbind®) is FDA approved to reverse the anticoagulant effects of dabigatran for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding. Additionally, 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). Obtain a Hematology/Coagulation consult for further recommendations.*
Severe or Life-threatening or emergency surgery/urgent procedures	*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. Idarucizumab (Praxbind) is used to reverse the coagulant effects of dabigatran.* *A Hematology/Coagulation consult should be obtained after the following*: 1) Administer idarucizumab (Praxbind) 5 g (2 vials) IV x 1 administered as 2 consecutive IV bolus injections (2.5 g each) or as 2 consecutive IV infusions (2.5 g each) a. STOCKED IN ED PYXIS and PHARMACY 2) For persistent refractory bleeding, pursue formal Heme/Coag consult. 3) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, PT, aPTT, thrombin clotting time (TCT), Dabigatran level (send out), CBC.

Table adapted from

1. *Pollack.NEJM. 2015;373(6):511-20.*
2. *van Ryn. Thromb Haemost. 2010 Jun;103(6):1116-27*

F. Factor Xa Inhibitors: Apixaban, Rivaroxaban, Edoxaban, Betrixaban, Fondaparinux

Coagulation factor Xa (Andexxa®) is FDA approved to reverse the anticoagulant effects of **apixaban and rivaroxaban** for patients with life-threatening or uncontrolled bleeding. Additionally, rivaroxaban and apixaban are highly protein bound

and are not dialyzable. **At UNCMC, Andexxa® is formulary restricted for life-threatening bleeding due to intracranial hemorrhage while on apixaban or rivaroxban with approval by the Neurocritical Care Attending.** If patients require Andexxa® to manage hemorrhagic complications, a Hematology/Coagulation consult is advised.

Furthermore, there is no specific reversal agent or pharmacologic antidote for edoxaban, betrixaban, or fondaparinux. Thus, management of hemorrhagic complications is primarily supportive. 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 and obtain a Hematology/Coagulation consult for further recommendations.*
Severe or Life-threatening bleed from Edoxaban, Betrixaban, or Fondaparinux	*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 from edoxaban, betrixaban, or fondaparinux. 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.* *A Hematology/Coagulation consult should be obtained after the following*: 1) Administer KCentra (4-factor PCC) 50 units/kg IV x 1 (max dose 5000 units) a. See dosing guide in Appendix B. STOCKED IN PHARMACY 2) Emergent surgery or urgent procedure a. Administer KCentra (4-factor PCC) 50 units/kg IV x 1 (max dose 5000 units) b. See dosing guide in Appendix B. STOCKED IN PHARMACY 3) For persistent refractory bleeding, pursue formal Heme/Coag consult. 4) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, CBC, PT, aPTT, corresponding anticoagulant drug level (e.g. edoxaban level, fonadaparinux level, or betrixaban level) as send out lab. 5) If PT prolonged, administer vitamin K 10mg IV x one dose (as there may be vitamin K deficiency present).

Severe or Life-threatening bleed from Apixaban or Rivaroxaban	*Consider any of the strategies outlined above based on bleeding severity. Andexxa® is a specific reversal agent that is FDA approved for only apixaban or rivaroxaban severe or life-threatening bleeding.* ***Due to limited evidence in other populations, UNCMC will formulary restrict Andexxa® to the reversal of apixaban or rivaroxaban related intracranial hemorrhage at the discretion and approval by the Neurocritical Care Attendings*** 1) Intracranial Hemorrhage a. Andexxa® per Neurocritical Care Attending i) Andexxa® is not recommended for the reversal of anticoagulant effects of apixaban or rivaroxaban for patients going to emergent surgery or urgent procedure ii) Andexxa® is not recommended to be given in addition to 4-factor PCC (KCentra®) due to limited evidence b. See dosing guide in Appendix B based on drug, dose, and timing of last dose. STOCKED IN PHARMACY *For apixaban or rivaroxaban related severe or life-threatening bleeds that is NOT intracranial hemorrhage, the strategy below may be considered based on currently available evidence. Therefore, the pharmacologic interventions below may be considered, but are not required in the management of Factor Xa inhibitor-related bleeding. A Hematology/Coagulation consult should be obtained after the following*: 2) Life-threatening or severe bleeding OTHER THAN intracranial hemorrhage a. Administer KCentra (4-factor PCC) 50 units/kg IV x 1 (max dose 5000 units) b. See dosing guide in Appendix B. STOCKED IN PHARMACY 3) Emergent surgery or urgent procedure a. Administer KCentra (4-factor PCC) 50 units/kg IV x 1 (max dose 5000 units) b. See dosing guide in Appendix B. STOCKED IN PHARMACY 4) For persistent refractory bleeding, pursue formal Heme/Coag consult. 5) To investigate potential causes of the bleeding event, obtain the following: serum creatinine, CBC, PT, aPTT, corresponding anticoagulant drug level (e.g. apixaban level or rivaroxaban level) as send out lab. 6) 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

G. 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. DDAVP is likely not a safe option, as it can lead to arterial vasospasm.
    g. Hematology/Coagulation Consult Service may be consulted if a multi-disciplinary risk versus benefit evaluation is required.

III. REFERENCES:

1. Antithrombotic therapy and prevention of thrombosis 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. CHEST. 2012;141 (2_suppl).
2. Bijsterveld NR et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. Circulation. 2002;106:2550-2554.
3. Burnette AE et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis. 2016; 41:206–232
4. Dager WE et al. Reversal of elevated INR and bleeding with low-dose recombinant activated factor VII in patients receiving warfarin. Pharmacotherapy. 2006;26(8):1091-8.
5. Eerenberg ES et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. Circulation. 2011;124: 1573-1579.
6. Holland L et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic INR due to warfarin overdose. Transfusion. 2009; 49(6):1171-1177
7. Levi M et al. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med 2010; 363:1791-800.
8. Makris M et al Guideline on the management of bleeding in patients on antithrombotic agents. British Journal of Hematology. 2012;160(1):35-46.
9. Nishijima DK et al. The efficacy of factor VIIa in emergency department patients with warfarin use and traumatic intracranial hemorrhage. Acad Emerg Med. 2010;17(3):244-51.
10. Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. Blood. 2012 Dec 6;120(24):4699-705.
11. Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015;373(6):511-20.
12. Van Ryn J et al. Dabigatran etexilate-a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103(6):1116-1127
13. UNCH Blood Derivative Compendium v02012 06 21.
14. Vavra KA et a. Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. Ann Pharmacother. 2010; 44:718-26.
15. www. Clotconnect.org
16. Product Information: PRAXBIND intravenous injection, idarucizumab intravenous injection. Boehringer Ingelheim Pharmaceuticals (per FDA), Ridgefield, CT, 2015.
17. Witt D et al. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. J Thromb Thrombolysis 2016; 41:187–205.
18. Siegal DM, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015 Dec 17;373(25):2413-24
19. Connolly SJ, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Eng J Med 2016 Sep 22;375(12):1131-41

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 Andexxa® (dosing in Appendix B) for intracranial hemorrhage • 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 (send-out lab) 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)
Betrixaban (Bevyxxa)	19 to 27 hours	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 (send-out lab) to confirm reversal
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) • Consider idarucizumab (Praxbind) 5 g IV x 1 administered as 2 consecutive IV bolus injections (2.5 g each) or as 2 consecutive IV infusion (2.5 g each)
Edoxaban (Savaysa)	10 to 14 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 (send-out lab) 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 PTA: • For each 1 mg of enoxaparin, administer 1 mg of protamine • If last dose was 8-12 hours PTA: • For each 1 mg of enoxaparin, administer 0.5 mg protamine • If last dose was >12 hours PTA: • 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 (send-out lab) 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) • Administer Andexxa® (dosing in Appendix B) for intracranial hemorrhage • Monitor PT/INR and anti-Factor Xa activity level (send-out labs) 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
		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 1.25-2.5 mg PO*
		Rapid reversal required	Hold warfarin Give vitamin K 2.5-5 mg IV
	Any INR	Non-life threatening major bleed or surgery/procedure requiring emergent warfarin reversal	Hold warfarin Give vitamin K 5-10 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

APPENDIX B: Dosing for factor Xa reversal agents

KCentra® (4-factor PCC)	For INR 2-3.9 (25 units/kg)	For INR 4-6 or unknown (35 units/kg)	For INR > 6.0 or DOAC therapy (50 units/kg)
30-49 kg	1000 units	1500 units	2000 units
50-69 kg	1500 units	2000 units	3000 units
70-89 kg	2000 units	3000 units	4000 units
≥90 kg	2500 units	3500 units	5000 units

1. ROUND ALL DOSES TO THE NEAREST WHOLE NUMBER OF VIALS
2. The number of units in each vial is displayed on the side of the product's packaging

Andexxa® (coagulation factor Xa) Dosing			
FXa Inhibitor	**Last Dose**	**Timing of FXa inhibitor last dose**	
		< 8 hours or unknown	**8-18 hours**
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg or unknown	High dose	
Rivaroxaban	≤ 10 mg	Low dose	
	> 10 mg or unknown	High dose	

1. **Low dose:** 400 mg IV bolus over 30 minutes followed by 480 mg over 2 hours (4 mg/min)
2. **High dose:** 800 mg IV bolus over 30 minutes followed by 960 mg over 2 hours (8 mg/min)