GUIDELINES for LIFE-THREATENING BLEEDING requiring EMERGENT (within 1 HR) ANTICOAGULANT REVERSAL

Not intended for use prior to non-emergent surgical procedures.
Emergent reversal increases risk of thrombosis especially with FVIIa, Kcentra, Praxbind

REVERSAL PROCEDURES

Agent	DURATION OF ACTION	Arterial and venous thromboembolic complications possible for extended period post reversal. Weight the potential benefits of reversing anticoagulant against the potential risks of thromboembolic events and low efficacy.
Alteplase (tPA) (Activase®)	5-10 minutes, hepatic	**First line: 10 units cryoprecipitate** **Second line: Tranexamic acid 1 gram IVPB STAT over 20 minutes**
Apixaban (Eliquis®) *Class: Oral direct factor Xa inhibitor*	2 days CrCl / Time 50-80 / 2days 30-50 / 3days < 30 / 3days	**No antidote** FFP not effective If ingested within 3 hours, administer activated charcoal Lab: INR/PT-screen for presence; if elevated (>1.4)=drug present, if normal=drug absent Consider **PCC4 (Kcentra**) if above measures are ineffective and if death is imminent with continued bleeding **Kcentra** 50 units/kg (Max dose is 5000 units) IV at over 30 minutes
Argatroban *Class: IV Direct Thrombin Inhibitor*	2-3 hours (longer with moderate to severe hepatic impairment)	**No antidote** Turn off infusion Lab: Monitor aPTT to confirm clearance repeat q 60 minutes(A) Consider **Factor VII** 40 mcg/kg if above measures are ineffective and if death is imminent with continued bleeding.
Bivalirudin (Angiomax®) *Class: IV Direct Thrombin Inhibitor*	1.5 hours (up to 3.5 hr with CrCl less than 15 ml/min)	**No antidote** Turn off infusion Lab: Monitor aPTT or ACT to confirm clearance q 60 minutes (A) Consider **Factor VII** 40 mcg/kg if above measures are ineffective and if death is imminent with continued bleeding.
Dabigatran (Pradaxa®) *Class: Oral Direct Thrombin Inhibitor*	2 days CrCl / Time 50-80 / 2.5 days 30-50 / 3days < 30 / 5days	**Antidote: Praxbind** 5 g (2x 2.5g/50ml) IV Push ASAP Lab: Check aPTT if elevated – dabigatran may be contributing to bleed " if normal – unlikely dabigatran contributing to bleed If ingested within 2 hours, administer activated charcoal Lab: Monitor aPTT to confirm reversal FFP not effective
Enoxaparin (Lovenox®) *Class: Low Molecular Weight Heparin*	10.5-17.5 hours (Longer with CrCl less than 30 ml/m)	**Antidote: Protamine** partially reverses the anticoagulant effect of enoxaparin (60%) Time since last dose of enoxaparin / Dose of protamine for each 1 mg of enoxaparin administered 8 hours or less / 1 mg 9-12 hours / 0.5 mg Greater than 12 hours / Not likely to be useful Lab: Monitor anti Factor Xa activity to confirm reversal
Edoxaban (Savaya®) *Class: Oral direct factor Xa inhibitor*	CrCl / Time > 80 / 1 day 50-80 / 1.5 days 30-50 / 3days < 30 / 6days	**No Antidote** FFP not effective If ingested within 8 hours, administer activated charcoal Lab: INR/PT-screen for presence; if elevated (>1.4)=drug present, if normal=drug absent Administer **PCC4 (Kcentra**) if above measures are ineffective and if death is imminent with continued bleeding **Kcentra** 50 units/kg (Max dose is 5000 units) IV over 30 minutes
Fondaparinux (Arixtra®) *Class: IV indirect factor Xa inhibitor*	2-5 days (Longer with CrCl less than 50 ml/min)	**No antidote** Lab: No available coagulation labs to assess degree of anticoagulation Consider **PCC4 (Kcentra**) if above measures are ineffective and if death is imminent with continued bleeding **Kcentra** 50 units/kg (Max dose is 5000 units) IV over 30 minutes

**RESTRICTIONS Kcentra and Praxbind restricted to anesthesia, critical care, ED, neurosurgery, hematology attendings
Relative contraindications to FVII, Kcentra, Praxbind: 1) History of thrombotic or thromboembolic event in past 6 weeks such as DVT, PE, ischemic stroke, acute coronary syndrome, acute mesenteric ischemia or acute peripheral arterial ischemia 2) Known prothrombotic condition such as major surgery within 6 wks, malignancy, DIC or polytrauma 3) Hepatic disease 4) Intraparenchymal hemorrhage thought not survivable. IF ANY OF THESE CRITERIA IS MET please discuss the possibility of FFP 4 units (warfarin) instead with neurosurgery (if head bleed) or hematology or critical care intensivist (bleed from site other than head).

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REVERSAL PROCEDURE

Anticoagulant	DURATION OF ACTION	**Arterial and venous thromboembolic complications possible for extended period post reversal. Potential benefits of reversing anticoagulant should be weighed against the potential risks of thromboembolic events and low efficacy.**
Heparin *Class: Unfractionated Heparin*	3-6 hours (dose dependent)	**Antidote: Protamine** fully neutralizes heparin Time / Protamine Dose per each 100 units of heparin administered within the past time frame 0-30 minutes: 1 mg 30-60 minutes: 0.5 mg 1-2 hours: 0.375 mg 2-6 hours: 0.25 mg Lab: Monitor aPTT to confirm reversal
Rivaroxaban (Xarelto®) *Class: Oral direct factor Xa inhibitor*	1 day CrCl / Time 50-80 / 1 day 30-50 / 1day < 30 / 1.5 days	**No Antidote** FFP not effective If ingested within 8 hours, administer activated charcoal Lab: INR/PT-screen for presence; if elevated (>1.4)=drug present, if normal=drug absent Administer **PCC4 (Kcentra**) if above measures are ineffective and if death is imminent with continued bleeding **Kcentra** 50 units/kg (Max dose is 5000 units) IV over 30 minutes
Warfarin (Coumadin®) *Class: Oral Vitamin K antagonist*	2-5 days Oral vitamin K: Onset of action is 6-12 hours. Expect INR to fall within 24 to 48 hrs IV vitamin K: Onset of action is 1-2 hours. Hemorrhage usually controlled in 3-6 hours. Expect INR to fall within 12 hours.	STAT CBC, INR, PTT, Type and screen on admission Lab: Check PT/INR **Antidote:** Administer **vitamin K** 10 mg IVPB slow IV infusion over 10 minutes (1mg/min max) **CNS bleed + INR ≥ 1.4:** Administer **PCC4 (Kcentra**) • Fixed Dose Initial INR 1.4-7.5 and 100 kg or less: 1500 units over 10 minutes Initial INR > 7.5 and/or greater than 100kg: 2000 units over 15 minutes Repeat INR 1.5-5: 500 units over 10 minutes Repeat INR greater than 5: 1000 units over 15 minutes • Weight based Pre-treatment INR / 2-3.9 / 4-6 / Greater than 6 Kcentra dose / 25 units/kg / 35 units/kg / 50 units/kg Max dose / 2500 / 3500 / 5000 Infuse over / 15 min / 20 min / 30 min **ALL OTHER life-threatening bleeding + INR ≥ 1.5:** Administer Plasma. Call Transfusion Service 2-3185 to initiate "PERC protocol" *Refer to APPENDIX A: EMERGENT REVERSAL OF WARFARIN for process details* Lab: re-check PT/INR 20 minutes post Kcentra or Plasma to confirm reversal EXCEPTIONS: KCENTRA may be used for emergent warfarin reversal in an organ threatening bleed in a VOLUME RESTRICTED CLOSED SPACE (eye, pericardium) or for life threatening AIRWAY BLEED or when VOLUME (greater than 1L) of plasma needed would cause life threatening fluid overload. *Refer to APPENDIX B for Elevated INR due to Liver Disease (not on AC)*
Clopidogrel (Plavix®) Prasugrel (Effient®) Ticagrelor (Brilinta®) Aspirin *Class: Anti-platelet*	5 days	**No Antidote** **DDAVP*** (Dexmopressin) 0.3 mcg/kg IV once Administer 2 x 5 pack of **pooled random donor platelets** if patient will undergo surgery * hyponatremia (< 14%) with th potential for extreme decreases in plasma osmolality, seizures, coma, respiratory arrest, and death. Monitor for signs/symptoms of hyponatremia

APPENDIX A: EMERGENT REVERSAL OF WARFARIN PROCESS

STAT CBC, INR, PTT, Type and screen on admission for patient on AC with possibility of receiving blood products

Warfarin with INR >1.4 in CNS bleed: KCENTRA

1) Enter order in PowerChart: Emergent Reversal of Warfarin
   - **a.** First line: Fixed dose regimen see Warfarin for details
   - **b.** Weight based still available
2) Call pharmacy 2-5709 to facilitate order

   Caller will be asked the following information
   - Patient's name and FIN to locate order CPOE order
   - Pharmacy will confirm indication is for ICH

3) Delivered via runner from pharmacy (15-20 minutes)
4) Administer over 5-20 minutes per directions on label via a dedicated IV line
5) Vitamin K 10 mg IV is to be administered STAT to patients receiving KCENTRA
6) Re-check INR 10 minutes post infusion

Warfarin with INR>1.5* in ALL OTHER life-threatening bleeding: PLASMA

1) Initiate PERC *(Plasma for Emergent Reversal of Coumadin)* protocol via call to Transfusion Service 2-3185

   Caller will provide the following information:
   - State this is PERC protocol
   - Confirm plasma is for reversal of WARFARIN. Plasma is NOT indicated for reversal of heparin products, DOACs or antiplatelet agents.
   - Patient's name and FIN
   - Inform Transfusion Service whether or not there is time to wait for cross match results if unknown and/or thaw matched plasma if AB (20 minutes)

2) Transfusion Services will follow this algorithm:

   Blood Type on Current Specimen
   - Blood Type A, B or O: Thawed compatible plasma is routinely available. 4 units will be sent immediately via dedicated tube to ED or OR (5 minutes).
   - Blood Type AB: Transfusion Service will ask if the Clinical Service can wait 30 minutes for AB plasma to be thawed. If not, 4 units of A plasma will be sent immediately via dedicated tube to ED or OR (5 minutes)

   Blood Type on Historical Specimen (no current specimen)
   - Blood Type A or O: 4 units of A plasma will be sent immediately via dedicated tube to ED or OR (5 minutes)

- Blood Type B or AB: Transfusion Service will ask if the Clinical Service can wait 30 minutes for AB plasma to be thawed. If not, 4 units of A plasma will be sent immediately via dedicated tube to ED or OR (5 minutes)

NO historical blood type and NO current specimen

- Transfusion Service will ask if the Clinical Service can wait up to 1 hour to acquire and test current specimen. If not, 4 units of A plasma will be sent immediately via dedicated tube to ED or OR (5 minutes. The blood type will be performed and additional group compatible plasma thawed and dispensed as soon as possible

3) Dose for reversal: Generally 4 units of plasma are required for urgent reversal (10-15ml/kg). Volume of each unit is approximately 250 ml. For larger patients 6 units of plasma may be required. Additional time will be needed for the Transfusion service to thaw and issue the 5th and 6th units.
4) Rapid INR reversal requires that adequate volume of plasma (4-6 units) is transfused over 10-20 minutes
   Adequate access must be obtained (ie. Central line, multiple IV's)
5) Vitamin K 10 mg IV is to be administered STAT to patients receiving plasma
6) Transfusion Service Cooler with compatible thawed plasma arrives (30 min after phone call)
   Administer additional units needed over 5-10 minutes
   Typical dose for reversal is 10-15 ml/kg. Each unit = 250 ml. 4 units of plasma is average requirement
7) Re-check INR 10 minutes post infusion

Exceptions: KCENTRA may be used for emergent warfarin reversal in an organ threatening bleed in a VOLUME RESTRICTED CLOSED SPACE (eye, pericardium) or for life threatening AIRWAY BLEED or when VOLUME (greater than 1L) of plasma needed would cause life threatening fluid overload.

* Reversal is not required for minor elevations (1.5 or less)of the INR outside the setting of CNS hemorrhage or CNS surgery.

**Type A plasma is compatible with 80-85% of the population. Risk of hemolysis (from anti-B) in the remaining 15-20% is rare.

Plasma is NOT indicated for the reversal of anticoagulants other than warfarin

APPENDIX B: ELEVATED INR DUE TO LIVER DISEASE

1) Chronic stable cirrhosis with elevated INR <_4: plasma is unlikely to benefit the non-bleeding patient.

2) Acute hepatitis (drug induced, shock liver etc) INR <_ 4: plasma is unlikely to benefit the non-bleeding patient.

3) Acute liver failure: Signs of sepsis with renal dysfunction, DIC, critical illness, INR > 1.6, plasma may be beneficial.

Platelets should be transfused for low or moderate bleeding risk procedures if platelet level below 50. High bleeding risk procedures warrant a discussion with Hematology.

References:

1. Kcentra (4F Prothrombin Complex Concentrate) package insert. CSL Behring GmbH, 2013
2. Dabigatran (Pradaxa) package insert. Boehringer Ingelheim Pharmaceuticals, 8/2013
3. Rivaroxaban (Xarelto) package insert. Janssen Pharmaceuticals, 8/2013
4. Apixaban (Eliquis) package insert. Bristol-Meyers Squibb. 12/2012
5. Fondaparinux (Arixtra) package insert. GlaxoSmithKline. 1/2012
6. Bivalirudin (Angiomax) package Insert. Medicines Company, 2010
7. Argatroban package insert. GlaxoSmithKline, 2012
8. Enoxaparin (Lovenox) Sanofi-Aventis, 2009
9. Protamine Sulfate package insert. AAP Pharmaceuticals. 2008.
10. Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of rF VIIa to reverse the anticoagulant effect of the pentasaccharides fondaparinux in healthy volunteers. Circulation 2002;106:2550-4.
11. Dumkow LE, Voss JR, Peters M, Jennings D. Reversal of dabigatran-induced bleedngwith a prothrombin complex concentrate and fresh frozen plasma. Am J Health-Syst Pharm 2012;69:1646-50.
12. Eerenber, E, Kamphulsen P, Sijpkens M, et al. Reversal of rivaroxaban and Dabigatran by Prothrombin Complex concentrate. Circulation. 2011;124:1573-1579.
13. Godier A, Miclot A Le bonniec B et al. Evaluation of PCC and recombinant activated factor VII to reverse rivaroxaban in a rabbit model. Anesthesiology 2012;116:94-102.
14. Mlyares MA, Davis K. Newer oral anticoagulants: A review of laborator monitoring opitons and reversal agents in the hemorrhagic patient. Am J Jealth-Syst Pharm. 2012;69:1473-84.

15. Nitzki-George D, Wozniak I, Caprini JA. Current State of Knowledge on Oral Anticoagulant Reversal Using Procoagulant Factors. Ann of Pharmaco 2013;47:841-55.

16. Nutescu, EA, Dager WE, Kalus JS, Lewin III JJ, Cipolle MD. Management of bleeding and reversal strategies for oral anticoagulants: Clinical practice considerations. Am J Health-Syst Pharm 2013;70:e82-96

17. SJMH Emergency Guideline. Emergency Reversal of Injured Anticoagulated Patient (PERC Protocol). 4/2011

18. Desmurs-Clavel H. Reversal of the inhibitory effect of fondaparinux on Thrombin generation by rFVIIa, aCCP and PCC. Thrombosis Research. 2009;123(5):796-98.

19. Elmer J. Emergency reversal of pentasaccharide anticoagulants: a systematic review of the literature. Transfusion Medicine 2011.

20. Gordon J. Anticoagulant and antiplatelet medications encountered in emergency surgery patients: a review of reversal strategies. Journal of Trauma and Acute Care Surgery 2013;75(3):475-486.

21. Frontera JA. Guideline for Reversal of Antithromboitcs in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care 2016;24:6-46.

22. Baharoglu MI. Platelet transfusion versus standard care after actue stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomized, open-label, phase 3 trial. Lancet 2016;387(10038):2605.

23. De Oliveira Manoel, AL. The critical care management of spontaneous intracranial hemorrhage: a contemporary review. Critical Care 2016;20:272.