PURPOSE:

This guideline is intended to provide a reference for EMS practitioners on for the reversal of existing anticoagulation in patients exhibiting uncontrollable hemorrhage or requiring urgent procedure/surgery. Decision about the need for reversal and medication used will be made be sending or accepting providers. This protocol serves as a resource for EMS supporting such treatments

This protocol is extracted from the Aspirus System Reversal of Anticoagulants Guideline

POLICY:

I. **Supportive data:**
   a. 4F-PCC (KCentra®) has been approved by the FDA for reversal of anticoagulation produced by Vitamin K antagonists in conjunction with Vitamin K administration when dosed according to FDA-approved dosing.
   b. Idarucizumab (PraxBind®) has been shown in the REVERSE-Ad trial to effectively neutralize both unbound and bound dabigatran within 4 hours of administration reversing aPTT and diluted thrombin time values.
   c. Andexanet alfa (Andexxa®) has been approved by the FDA for reversal of rivaroxaban and apixaban when anticoagulation reversal is necessary due to life-threatening or uncontrolled bleeding.
   d. Limited in vitro evidence suggests that 4F-PCC may represent an option, in addition to supportive care, to mitigate hemorrhage resulting from rivaroxaban (Xarelto®), apixaban (Eliquis®), or edoxaban (Savaysa®) anticoagulation. Studies comparing hemostatic/clinical efficacy have shown fixed-dosing regimens to be similar to standard and variable-dosing strategies.

II. **Desired patient outcome:**
   a. Safely reverse anticoagulation
   b. Provide consistent and efficient management of hemorrhage related to anticoagulation

EMR/EMT/AEMT

A. Apply oxygen and manage the airway as indicated
B. Treat trauma patients as applicable per **General Trauma Management**.
C. Control hemorrhage- Consider **Protocol- Tourniquet Application**
D. Keep patient warm.
E. If patient becomes pulseless follow appropriate ARC/AHA BLS & ACLS guidelines and protocols.
F. Establish ***at least*** (2) large bore IV's. One dedicated IV shall be used only for the infusion of reversal agents. **[AEMT]**

PARAMEDIC / CRITICAL CARE PARAMEDIC / RN PROVIDER

A. Consideration shall be taken to the etiology of the hemorrhage and/or the need for an urgent surgery/procedure.
B. Medications for anticoagulation need to be obtained from sending hospital
   1. Administer medication or continue infusions per sending hospital parameters or per paramters within this protocols
C. The following conditions shall be considered highest priority for reversal of anticoagulation include:
   1. **Aortic dissection**
   2. **Major trauma with signs of active hemorrhage**
   3. **Major non-traumatic hemorrhage such as a gastrointestinal bleed or intracranial hemorrhage.**

Warfarin

I. Information
   a. Warfarin inhibits the production of Vitamin K-dependent clotting factors II, VII, IX and X. The risk of hemorrhage increases with INR values greater than 4.5.
   b. Bleeding associated with warfarin can be managed by holding doses of warfarin and administration of Vitamin K, Fresh Frozen Plasma (FFP), or 4F-PCC. The treatment is determined by the severity, location, extent of the bleed, and the initial INR value.

II. No evidence of bleeding but INR is supratherapeutic
   a. Urgent reversal needed: **4F-PCC** plus **Vitamin K** 5-10 mg IV
      a. **FFP** 10-15 mL/kg plus **Vitamin K** 5-10 mg IV is an alternative, in cases where more time is available. It may take 24 hours for hemostasis depending upon initial INR

III. Minor bleeding in patients on warfarin
   a. May consider administering 2.5 mg of **Vitamin K** orally (preferred) or 0.5 mg IV depending on INR, site of bleeding, risk of progression to more serious bleeding, and thrombotic risk; if INR remains elevated after 24 hours, may administer another dose

IV. Major or life-threatening bleeding in patients on warfarin
   a. Administer **Vitamin K** and **4F-PCC** immediately. No specific order of administration is required for optimal pharmacological effect
      a. Administer **Vitamin K** 10 mg IV because of the long half-life of warfarin and short half-life of clotting factor
      b. Administer **4F-PCC** 1500 units
         i. If patient has history of being HIT positive, but documentation was greater than 3 months ago, 4F-PCC may be given (contains Heparin)
         ii. Obtain INR 30 to 60 minutes after administration of 4F-PCC
         iii. If INR is not less than 2, give an additional 4F PCC
   b. INR greater than or equal to 2: Administer an additional **4F-PCC** 500 unit
   c. INR less than 2
      a. Evaluate for treatment with either **FFP** or **4F-PCC**
      b. Consider **4F-PCC** (scarce evidence for use) if no significant risk factors for thrombosis present.
         i. Relative risk factors:
            1. Thromboembolic event in previous 6 weeks: DVT//PE, ACS, ischemic stroke
            2. Known thrombotic disorder: malignancy, DIC, poly-trauma, HIT
            3. Non-survivable intra-parenchymal hemorrhage
         ii. Dosing: No established dosing identified for INR less than 1.5, thus consider additional administration of 4F-PCC 500 units
      c. Consider **FFP** 10-15 mL/kg (or 4 units) immediately
         i. Repeat labs upon completion
         ii. Repeat 4 units if INR remains greater than 1.7

Dabigatran (Pradaxa®)

I. Information
   1. Dabigatran is an oral direct thrombin inhibitor.
   2. Anticoagulation is a result of inhibiting Factor II (thrombin), not a **depletion** of clotting factors.
   3. A prolonged aPTT may indicate the patient has taken dabigatran but it does not indicate the level of coagulation. The half-life is 12-17 hours in patients with normal renal function and drug levels are decreased by 75% within 24 hours of stopping dabigatran.

II. Life-threatening bleeding or urgent/emergent reversal desired
   1. If last dose was taken within 2 hours consider activated charcoal 50g
   2. Administer **Idarucizumab** 2.5 grams IV every 15 minutes x 2 doses.
      a. Effective at normalizing aPTT and diluted thrombin time.
      b. May take up to 11 hours to stop hemorrhage
   3. FFP is not indicated for treatment of bleeding related to dabigatran, **UNLESS** the patient

has received at least 4 units of packet red blood cells (PRBC) and INR is prolonged, or as part of the massive transfusion protocol.

Factor Xa inhibitors (Apixaban (Eliquis®) Edoxaban (Savaysa®), and Rivaroxaban (Xarelto®)

I. Information
    1. These agents, similar to dabigatran, cause anticoagulation via inhibition of factor Xa not via depletion of clotting factors like warfarin.
    2. Anticoagulation Forum guidance suggests administration of a reversal agent only if bleeding is life-threatening, into a critical organ, or is not controlled with maximal supportive measures.
    3. Apixaban and Rivaroxaban have a half-life of 12 hours and 5-9 hours respectively, in patients with normal renal function. The effect of these agents is significantly diminished within 48 of the last dose.

II. Minor-moderate bleeding: If dose is administered within 2 hours consider activated charcoal 50g

III. Life threatening bleeding (excluding hemorrhagic stroke)
    1. If dose administered within 2 hours consider activated charcoal 50g
    2. **4F-PCC** 2,000 units
        a. Consider additional 2000 units if patient has not had a positive clinical response to initial therapy

IV. Life-threatening bleeding with hemorrhagic stroke
    1. Preferred: Administer **andexanet alfa**. There is insufficient evidence about the risk and benefits to strongly favor either andexanet alfa or 4F-PCC.
        a. **Andexanet alfa** 400 mg IV bolus, followed by 4 mg/min continuous IV infusion for up to 120 minutes for patients taking rivaroxaban 10 mg or apixaban 5 mg, within less than 8 hours or unknown time.; either apixaban or rivaroxaban, any dose, at least 8 hours ago.
        b. **Andexanet alfa** 800 mg IV bolus followed by 8 mg/min continuous infusion for up to 120 minutes for patients taking rivaroxaban >10 mg or apixaban >5 mg, within **less than 8 hours** or **unknown time.**
        c. For patients taking edoxaban: Recommended dose of **andexanet alfa** 800 mg IV bolus, followed by 8 mg/min continuous infusion for up to 120 minutes.
    2. Alternative: **4F-PCC** 2,000 units
        a. Consider additional 2000 units if patient has not had a positive clinical response to initial therapy

V. Urgent/emergent reversal for high-risk invasive procedures
    1. 4F-PCC at a dose of 2000 units may be considered

Parenteral direct thrombin inhibitors:

i. Information
    1. Bivalirudin (Angiomax®) is a bivalent direct thrombin inhibitor. There is no specific antidote or reversal agent currently available. The half-life is 25 minutes in patients with normal renal function but is prolonged in patients with renal dysfunction.
    2. Argatroban is a small molecule direct thrombin inhibitor. The serum half-life is 45 minutes. Renal function does not affect half-life.
    3. Bivalirudin and argatroban are not antagonized, and neither are an inhibitor substrate for Idarucizumab (PraxBind®); there is no evidence to support concomitant use for these anticoagulants.

ii. Management of bleeding:
    1. Moderate bleeding is primarily supported with fluid management and blood product transfusion.
        a. Some guidelines suggest FFP if supportive care does not restore hemostasis
    2. Severe, or life-threatening bleeding: There are no specific reversal agents that have been demonstrated to successfully reverse bivalirudin or argatroban or to treat related bleeding
        a. There is not enough data at this time to recommend either rFVIIa, or 4F-PCC as a reversal agent

b. Low dose **Recombinent Factor VIIa** in cardiac surgical cases 1-2 mg or 30 mcg/kg for bleeding associated with bivalirudin have been reported as being effective

Fondaparinux (Arixtra®)

i. Information
    1. Fondaparinux (Arixtra®): is a parenteral factor Xa inhibitor with a long serum half-life, ranging from 17-21 hours, and prolonged in patients with renal dysfunction.

ii. Treatment
    1. There is no specific antidote or pharmacologic reversal agent available.
    2. Consider supportive care.
    3. For severe, or life-threatening bleeding resistant to usual management, consider **Recombinent Factor VIIa** as a single dose of 90 mcg/kg.

Enoxaparin (Lovenox)

i. Enoxaparin is a low molecular weight heparin with a 3.8:1 ratio of FXa to FIIa activity.
    i. **Protamine** may be used to partially reverse the effects of enoxaparin FXa activity
    ii. If last dose administered:
        1. Less than 8 hours: 1 mg **protamine** per 1 mg of enoxaparin (50 mg maximum)
        2. 8-12 hours: 0.5 mg **protamine** per 1 mg of enoxaparin (50 mg maximum)
        3. More than 12 hours: Protamine administration may not be required
            a. Patients with renal insufficiency (CrCl less than 30 mL/min) may benefit from treatment past 12 hours.
    iii. Bleeding that persists after initial treatment may require a repeat dose of 0.5 mg **protamine** per 1 mg of enoxaparin (maximum dose of 50 mg)

Heparin

i. Unfractionated Heparin (UFH) in the presence of anti-thrombin III, binds both FIIa and FXa.
ii. For nonurgent reversal, discontinuation of UFH may suffice because its serum half-life of heparin is 60-90 minutes, thus the effects are usually significantly reduced in 3-4 hours.
iii. Urgent Reversal
    1. Administer **protamine** 1 mg to neutralize 100 units of UFH
        a. Continuous infusion UFH: Use the total heparin delivered in the previous 3 hours to calculate the total amount of UFH to reverse.
            i. Administer protamine at 5 mg/min to decrease hypotension and bradycardia.
        b. Subcutaneous UFH: Only reverse the amount received in the previous 3 hours.
            i. Administer 25 mg at 5 mg/min then remainder as infusion over 8 hours.
        c. Maximum single dose of protamine is 50 mg.
iv. Fish allergy or previous exposure to protamine may increase risk of hypersensitivity reactions. Consider pretreatment with the following:
    1. **Hydrocortisone** 50-100 mg IV once
    2. **Diphenhydramine** 50 mg IV/PO once

Resources

Pharmacokinetic/Pharmacodynamic Data for Anticoagulation Agents

Anticoagulant	Type of Anticoagulant	Onset of Action	Half-life	Specific Antidote?
Warfarin (Coumadin®, Jantoven®)	Inhibits production of Vitamin K dependent clotting factors II,VII, IX, and X	Initial anticoagulation response: within 24 hours Peak response: 72-96 hours	1 week Single dose duration of action 2-5 days	Vitamin K, 4F-PCC (Kcentra®), can also give FFP
UFH (Unfractionated heparin)	Unfractionated heparin (binds both FIIa and FXa)	IV: immediate Subcutaneous: within 20-30 minutes	60-90 minutes; effects reduced in 3-4 hours	Protamine
Enoxaparin (Lovenox®)	Low molecular weight heparin (about 4:1 ratio of FXa to FIIa activity)	Peak response in 3-5 hours	7 hours	Protamine
Fondaparinux (Arixtra®)	Parenteral factor Xa inhibitor	Subcutaneous: 1-3 hours	17-21 hours; prolonged in renal dysfunction	None; consider Factor VIIa
Dabigatran (Pradaxa®)	Oral direct thrombin inhibitor (factor II)	Peak response 1-6 hours	12-17 hours with normal renal function	Idarucizumab (Praxbind®)
Apixaban (Eliquis®)	Factor Xa inhibitor	Peak response 3-4 hours	12 hours	None; may consider 4F-PCC (Kcentra®)
Rivaroxaban (Xarelto®)	Factor Xa inhibitor	Peak response 2-4 hours	5-9 hours	None; may consider 4F-PCC (Kcentra®)
Edoxaban (Savaysa®)	Factor Xa inhibitor	Peak response 1-2 hours	10-14 hours	None; may consider 4F-PCC (Kcentra®)
Argatroban	Small molecule direct thrombin inhibitor	Peak response 1-3 hours	45 minutes; renal function does not affect half life	None
Bivalirudin (Angiomax®)	Bivalent direct thrombin inhibitor	Initial response: immediate Peak response: 15 minutes (IV bolus); 2 hours (subcutaneous)	25 minutes; prolonged with renal dysfunction	None; may consider low dose rFVIIa in cardiac surgery

Antidote Reversal Dosing

Antidotes	Agents to Reverse	Dose
Phytonadione (Vitamin K)	Warfarin	Urgent reversal needed: 5-10 mg IV Non-urgent, no bleeding: 2.5 mg orally (preferred) or 0.5 mg IV *5mg oral vitamin K produces an equivalent INR reduction as 1 mg administered IV
4F-PCC (Kcentra®)	Warfarin	Major or life threatening bleeding or urgent reversal needed: • 1500 units Obtain INR 30 to 60 minutes later • If INR ≥ 2, administer additional 500 units • If INR < 2, consider additional 500 units if no significant risk factors for thrombosis present
	Edoxaban, Apixaban, or Rivaroxaban	Consider 2000 units May repeat x1 if clinical response inadequate
FFP (fresh frozen plasma)	Warfarin	10-15 mL/kg (or 4 units)
Protamine	Enoxaparin (Lovenox®)	-If last dose <8 hours ago: 1 mg protamine per 1 mg enoxaparin (max 50 mg) -If last dose 8-12 hours ago: 0.5 mg protamine per 1 mg enoxaparin (max 50 mg) *Persistent bleeding after initial treatment may require a repeat dose of 0.5 mg protamine per 1 mg enoxaparin (max 50 mg)
	Unfractionated Heparin (UFH)	-1 mg of protamine to neutralize 100 units of UFH (max single dose 50 mg) *Continuous infusion UFH: use total heparin given the past 3 hours to calculate amount of UFH to reverse (give at 5 mg/min to decrease hypotension/bradycardia) * Subcutaneous UFH: only reverse the amount given in the last 3 hours (give 25 mg at 5 mg/min then the remainder as infusion over 8 hours)
Factor VIIa (Novoseven®)	Bivalirudin	Low dose rFVIIa 1-2 mg or 30 mcg/kg for bleeding in cardiac surgical cases reported as being effective
	Fondaparinux (Arixtra®)	For severe or life threatening bleeding resistant to usual management, consider rFVIIa with single dose of 90 mcg/kg
Idarucizumab (Praxbind®)	Dabigatran (Pradaxa®)	2.5 g IV every 15 minutes x 2 doses

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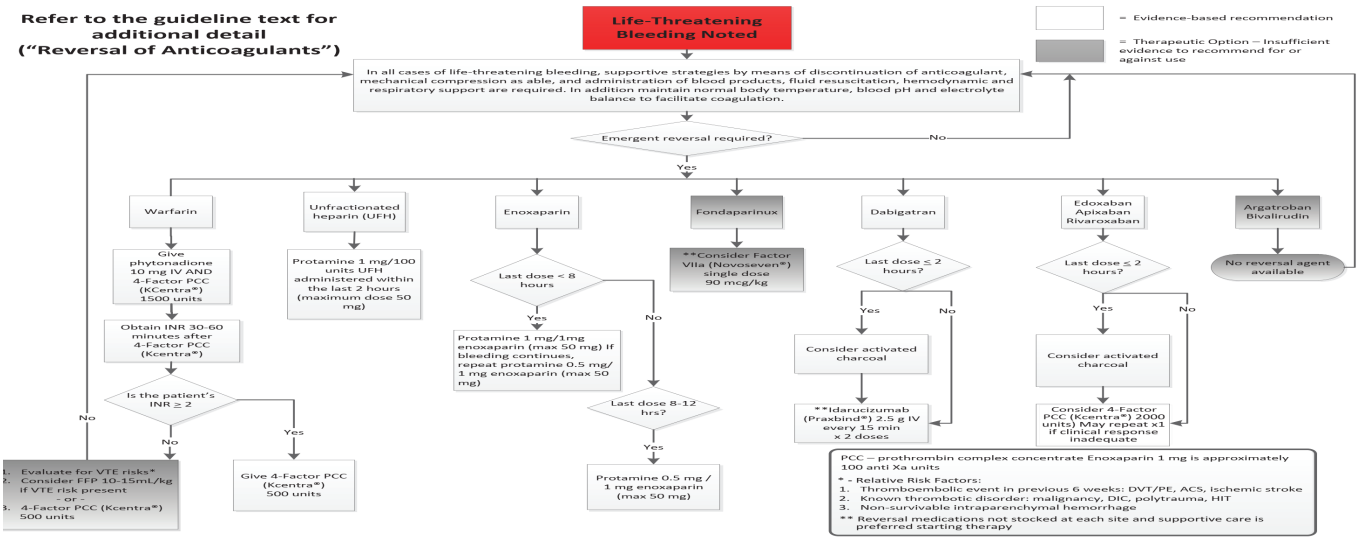

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