

Anticoagulant reversal for intracranial hemorrhage (ICH) and other life threatening bleeds

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SUMMARY TABLE-please see respective sections for further details – Reviewed May 2015

<u>Anticoagulant</u>	<u>Reversal</u>	<u>Comments/Alternatives</u>
<u>Warfarin</u>	Vitamin K 10 mg IV over 15-30 min AND Prothrombin Complex Concentrates (PCC) 25 units/kg if INR 1.7-4, 35 units/kg if INR 4-6, or 50 units/kg if INR>6)	1.)FFP is not recommended with use of PCC unless otherwise indicated
<u>Unfractionated heparin (UFH)</u>	1mg Protamine IV for each 100 units of UFH. Infusion should not exceed 5mg/minute due to risk of anaphylaxis. Maximum single dose of Protamine is 50 mg, but may be repeated	Need to consider timing and total amount of UFH administered over the last 3 hours in calculation (see subsection below.) Increased risk of hypersensitivity reaction/anaphylaxis in patients with a fish allergy or prior protamine exposure

<p>Low molecular weight heparin(LMWH)</p>	<p>Enoxaparin - 1 mg protamine IV for each 1 mg of enoxaparin administered in the last 8 hours</p> <p>Dalteparin or Tinzaparin - 1 mg protamine IV for each 100 units of dalteparin or tinzaparin administered in last 8 hours</p> <p>For either regimen, may consider Factor VIIa 50-90 mcg/kg IV for life threatening intractable bleed**</p>	<p>Protamine only partially reverses the activity of LMWH.</p> <p>Note differences in dosing between enoxaparin and other LMWHs</p> <p>May administer 0.5 mg protamine for every 1 mg enoxaparin (or 100 units of dalteparin) if LMWH dose administered 8-12 hours prior</p> <p>Round Factor VIIa dose to nearest 1 mg.</p>
<p><u>Fondaparinux (Arixtra®)</u></p>	<p>Prothrombin Complex Concentrates (PCC) 50 units/kg IV**</p>	<p>Factor VIIa 45-90 mcg/kg or FEIBA 50 units/kg may be tried if no clinical response to PCC.</p> <p>May repeat Factor VII in 2 hours if bleeding recurs</p> <p>Round Factor VIIa dose to nearest 1 mg.</p>
<p><u>Rivaroxaban</u></p>	<p>Prothrombin Complex Concentrates (PCC) 50 units/kg IV**</p>	<p>Factor VIIa 45-90 mcg/kg or FEIBA 50 units/kg may be tried if no clinical response to PCC.</p> <p>Round Factor VIIa dose to nearest 1 mg</p> <p>Note: If anti-Xa level is undetectable there is likely no anticoagulant effect and “reversal” is not necessary</p>

<p><u>Apixiaban</u></p>	<p>Prothrombin Complex Concentrates (PCC) 50 units/kg IV**</p>	<p>Factor VIIa 45-90 mcg/kg or FEIBA 50 units/kg may be tried if no clinical response to PCC.</p> <p>Round Factor VIIa dose to nearest 1 mg</p> <p>Note: If anti-Xa level is undetectable there is likely no anticoagulant effect and “reversal” is not necessary</p>
<p><u>Dabigatran</u></p>	<p>Activated oral charcoal if ingestion occurred within 2 hours</p> <p>Idarucizumab 5 gm IV once</p>	<p>Consider HD, especially if renal impairment</p> <p>If no clinical response to idarucizumab, consider Prothrombin Complex Concentrates (PCC) 50 units/kg**</p> <p>Note: If thrombin time and aPTT are normal there is likely no anticoagulant effect and “reversal” is not necessary</p>
<p><u>Alteplase</u></p>	<p>Cryoprecipitate 0.1 units/kg IV if fibrinogen <100 mg/dL</p>	<p>If bleeding is refractory or life threatening consider Aminocaproic acid (Amicar®) 1 g per 10 kg IV</p>
<p><u>Enteric Coated Aspirin</u></p>	<p>1 unit single donor platelet</p>	<p>May consider repeat 1 single donor unit if PFA-100 (orderable in EPIC) is not normalized</p> <p>Consider DDAVP IV or Factor VIIa** IV if refractory bleeding</p>

<u>Clopidogrel</u>	2 units of single donor platelets	Consider repeating 2 units Q12 hours until the PFA-100 and Verify Now (Plavix inhibition <20% or PRU over 240) assays are normal. Both tests are orderable in EPIC Consider DDAVP iv or Factor VIIa** IV if refractory bleeding
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* Please note these recommendations only apply to life-threatening situations where emergent reversal of anticoagulation is deemed necessary by the treating service. Most of the data comes from cases of ICH and applicability to other situations is less well studied. Adult Hematology consultation should be considered.

Examples of life threatening traumatic hemorrhage may include penetrating injury to head, neck and torso, severe blunt trauma requiring PRBC transfusion, base deficit >6, lactic acid >3, severe hypotension with SBP<90, obvious external hemorrhage from the scalp, face, neck, torso, extremities.

**Per P&T committee guidelines adult hematology consult required for approval

Guidelines for Urgent Reversal of Warfarin related Anticoagulation in patients with Intracranial Hemorrhage or Life Threatening Bleeding

Evidence of Acute Intracranial Hemorrhage on non-contrast brain CT requiring Emergent Surgical Intervention or Associated with Neurological Instability or Decline as well as other non-ICH life-threatening bleeding where emergent reversal deemed necessary. Indicated if INR Greater than 1.7

1. Vitamin K 10 mg IV (10mg/25ml NS over 15-30 minutes)
2. Prothrombin Complex Concentrate (PCC) 25-50units/kg IV over 10-15 min (dose dependent upon INR)
 - a. INR 1.7-4 – Dose 25 units/kg (max dosing weight 100 kg, max dose 2500 units)
 - b. INR 4.1-6 – Dose 35 units/kg (max dosing weight 100 kg, max dose 3500 units)
 - c. INR >6 – Dose 50 units/kg (max dosing weight 100 kg, max dose 5000 units)
3. FFP is not needed with PCC

-KCentra[®] is a 4 factor (II, VII, IX, X) non-activated prothrombin complex concentrate (PCC) and may carry an increased thrombogenic risk.

-KCentra[®] and other prothrombin complex concentrates (PCCs) are contraindicated in Disseminated Intravascular Coagulation (DIC)

-Patients on warfarin usually have an underlying prothrombotic state and PCCs may exacerbate this condition.

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Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A guideline for Healthcare Professionals From the American Heart/Stroke Association. Stroke 2010, 41:2108-2129

Proposal for Reversal of anti-Xa inhibitors

Unfractionated Heparin (UFH) – half life 60-90 minutes

1.) Stop the infusion—the half life of IV heparin is only 60-90 minutes. If bleeding is not life threatening no further therapy may be necessary

2.) If further therapy is necessary, **protamine sulfate** is the treatment of choice

a. infusion should not exceed 5mg/minute due to risk of bronchoconstriction, hypotension, and anaphylaxis

b. approximately 1mg of Protamine sulfate will neutralize 100 units of UFH

c. Maximum dose is 50 mg per 10 minutes, but may be repeated

d. A higher incidence of severe allergic reaction including anaphylaxis may exist with prior protamine exposure or exposure to protamine containing products (ex NPH insulin) or history of fish allergy

3.) There is no role for FFP in the reversal of UH

4.) For bleeding following a single bolus:

a. Immediately following a bolus - Dose 1mg protamine IV for every 100 units UFH

b. 30 min to 1 hour after a bolus – Dose 0.5 mg protamine IV for every 100 units UFH.

c. >2 hours after a bolus – Dose 0.25-0.375 mg protamine IV for every 100 units UFH

5.) For bleeding during a Continuous Infusion (CI);

a. Dose (1 mg protamine per 100 units UFH) should be given iv to neutralize all UFH given within the last hour + one half the dose of heparin given during the preceding hour + one-quarter of the dose of heparin given in the hour prior to that

b. Ex. 1000 unit UFH infusion/hr

Amount of UH to neutralize is 1000 Units + 500 Units + 250 Units = 1750 units UFH
Protamine dose (1mg/100 Units UFH) =17.5 mg iv protamine

Low Molecular Weight Heparins-half life typically 2-8 hours depending on agent

1.) There is no proven method to fully reverse LMWH (60-80% reversal expected)

-anti-IIa activity can be neutralized

-anti-Xa activity (most of the anticoagulant effect of LMWHs) partially neutralized

2.) 1mg of protamine iv should be given for every 1mg of enoxaparin given in the last 8 hours or for every 100 units of dalteparin or tinzaparin given over the last 8 hours (0.5 mg/1mg enoxaparin or per 100 units dalteparin or tinzaparin should be used if last dose given between 8-12 hours prior)

3.) Recombinant Factor VIIa (rVIIa) may be considered in the management of intractable bleeding based on case reports.

a. recommended dose 50-90 mcg/kg IV X1 (round dose to nearest 1 mg). May repeat in 2 hours if bleeding recurs

Fondaparinux (Arixtra)- half life 14 hours

1.) There is no specific antidote

2.) protamine is not effective for reversal

3.) Prothrombin Complex Concentrate (PCC) may be considered in the management of intractable bleeding based on case reports

a. recommended dose of PCC is 50 Units/kg (max dosing weight 100 kg, max dose 5000 units)

4.)Recombinant Factor VIIa (rVIIa) may be considered in the management of intractable bleeding based on case reports

a.recommended dose 50-90 mcg/kg IV X1 (round dose to nearest 1 mg). May repeat in 2 hours if bleeding recurs.

Rivaroxaban-half life 5-9 hours

1.)There is no specific antidote

2.)Protamine is not effective for reversal

3.)Prothrombin Complex Concentrates (PCC) may be considered in the management of intractable bleeding

a. recommended dose is 50 units/kg IV (max dosing weight 100 kg, max dose 5000 units).

b. Recombinant Factor VIIa (rVIIa) 45-90 mcg/kg or FEIBA 50 units/kg may be tried if no clinical effects noted with PCC. Round Factor VIIa dose to nearest 1 mg.

Apixiban-half- life 12 hours

1.)There is no specific antidote

2.)Protamine is not effective for reversal

3.)Prothrombin Complex Concentrates (PCC) may be considered in the management of intractable bleeding

a. recommended dose is 50 units/kg IV (max dosing weight 100 kg, max dose 5000 units).

b. Recombinant Factor VIIa (rVIIa) 45-90 mcg/kg or FEIBA 50 units/kg may be tried if no clinical effects noted with PCC. Round Factor VIIa dose to nearest 1 mg.

Oral Thrombin Inhibitor

Dabigatran-half-life 12-17 hours

- 1.) Dabigatran is a thrombin inhibitor, as opposed to rivaroxaban and apixaban which are anti-Xa inhibitors
- 2.) Idarucizumab is a monoclonal antibody fragment that binds to dabigatran and acylglucuronide metabolites to neutralize the anticoagulant effect. The dose is 5gm IV x 1.
- 3.) Prothrombin Complex Concentrates (PCC) may be considered in the management of intractable bleeding if idarucizumab is ineffective.
 - a. recommended dose is 50 units/kg IV (max dosing weight 100 kg, max dose 5000 units).

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Tissue Plasminogen Activator (rTPA)

Guidelines for Tissue Plasminogen Activator (alteplace®) Reversal in Hemorrhagic Conversion of Ischemic Stroke as well as other life-threatening bleeding.

1. No reversal necessary two hours post tPA infusion.
2. Reversal of tPA may result in thrombosis or propagation of already infarcted tissue or thrombus.
3. Reversal only needed in symptomatic hemorrhagic conversion as evidenced by neurological decline, hemodynamic stability or other organ dysfunction.

Obtain stat CBC, PT/PTT, platelets, fibrinogen, D-dimer

If fibrinogen <100 mg/dL administer Cryoprecipitate 0.10 units/kg IV

Repeat fibrinogen in 1 hour, if less than 100 mg/dL repeat Cryoprecipitate dose IV

If bleeding is life threatening or emergent neurosurgical procedure required then consider

Aminocaproic Acid (Amicar®) 1g/10kg IV in 250cc NS over 1 hour

Reversal of antiplatelet agents

Emergent Reversal of Antiplatelet Agents in the Setting of Intracranial Hemorrhage or life-threatening bleeding

Protocol:

Intracranial Hemorrhage or life-threatening bleeding & Aspirin (alone)

No baseline laboratory studies required (do not wait for labs to order platelets)

Transfuse 1 unit single donor platelets as soon as possible after diagnosis of ICH or life threatening bleeding in a patient on aspirin monotherapy (81 or 325 mg)

Post transfusion CBC to check platelet count, and PFA-100 (platelet function assay)

Both DDAVP 0.3 mcg/kg and rFVIIa 30-90 mcg/kg have been suggested by some authors but we do **not** recommend these agents due to the lack of supportive evidence as well as the risks of hyponatremia (DDAVP) and high cost (rFVIIa)

Intracranial Hemorrhage or life-threatening bleeding & Clopidogrel (Plavix®) (either Clopidogrel alone or dual ASA & Clopidogrel)

No baseline laboratory studies required (do not wait for labs to order platelets)

Transfuse 2 units single donor platelets as soon as possible after diagnosis of ICH or life-threatening bleeding in a patient on Clopidogrel or dual antiplatelet therapy

Post transfusion check CBC (platelet count), PFA-100 (platelet function assay), and the Accumetrics Verify Now Assay (P2Y12 Assay) both orderable in EPIC

If Verify Now assay is abnormal (Plavix inhibition >20% or PRU under 240) after platelet transfusion, continue transfusion at a rate of 2 units single donor platelets every 12 hours until PFA-100 and Verify Now assays normalize, up to 48 hours

Both DDAVP 0.3 mcg/kg and rFVIIa 30-90 mcg/kg have been suggested by some authors but we do **not** recommend these agents due to the lack of supportive evidence as well as the risks of hyponatremia (DDAVP) and high cost (rFVIIa)

Discussion

Patients on antiplatelet therapy (aspirin, Clopidogrel, or both) may present with intracranial hemorrhage or life-threatening bleeding. Currently, national guidelines do not exist for the rapid reversal of these agents, but antiplatelet therapy is associated with a significant increase in morbidity and mortality in the settings of spontaneous ICH and traumatic ICH. This document is meant to include all forms of intracranial blood products.

Both aspirin and Clopidogrel irreversibly inhibit platelet function, although through different mechanisms. Neither drug has a specific antidote. In several observational studies on intracranial hemorrhage, antiplatelet therapy was associated with an increased risk of in-hospital death and poor outcome. Additionally, some recent studies have suggested that platelet transfusion is not effective in reducing hematoma size, improving outcome, or lowering in-hospital mortality. Despite this, most expert sources continue to advise “reversal” of aspirin and Clopidogrel with platelet transfusion. Many feel that the timing of transfusion is critical, with a goal of transfusing platelets within 6 hours of the onset of hemorrhage.

Our treatment algorithm is largely based on several published reviews on the topic. The mainstay of therapy is platelet transfusion in an effort to replace the dysfunctional platelets. Alternative strategies including DDAVP and rFVIIa are not recommended due to uncertain of efficacy, risks of hyponatremia, and high cost.

Recent studies in the cardiovascular surgery literature suggest that the new Accumetrics Verify Now assay of Plavix-induced platelet inhibition can “clear” patients for surgery. Previously, cardiac patients on aspirin and Plavix had to wait 7 days after cessation of both agents prior to open cardiac surgery, due to the bleeding complications. However, guidelines now state that individuals who have stopped Plavix and have a normal Verify Now assay may proceed to surgery, without waiting the full 7 days. We feel that this assay may be useful in determining if continued platelet transfusion is needed, as some authors have suggested.¹⁻⁷

References

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