FLAGLER HOSPITAL PROTOCOL – REVERSAL OF ANTICOAGULATION IN PATIENTS WITH LIFE THREATENING BLEEDING

Reversal of anticoagulation is desirable and may improve outcome in patients with serious or life-threatening bleeding and in patients in need for an urgent invasive procedure or surgery who remain actively anticoagulated (1, 2).

OBJECTIVE:

To provide an optimal strategy for reversing anticoagulants in patients with serious or life-threatening bleeding or need an urgent invasive procedure or surgery.

SCREENING:

All patients admitted to the hospital who are receiving anticoagulants and are suspected to be bleeding or are in need for an urgent invasive procedure or operation will be eligible for reversal pursuant to the protocol outlined below.

As with any protocol, this protocol serves to provide evidence-based, comprehensive recommendations to guide our multidisciplinary team in patient care, with the expectation that expert practitioners will modify and customize as necessary the present protocol to meet individual patient needs. This Protocol is not intended to replace the physician's judgment; it is intended to provide guidance to the physician for the group of patients described in this Protocol.

DIAGNOSIS AND INTERVENTIONS:

Indications for use antidotes **(1, 2)**

- Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage.

- Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome.

- Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed clearance or overdose.

- Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance.

- Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or

vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery.

Potential indication for use

- Need for urgent surgery or intervention in patients with acute renal failure

Antidotes should not be used

- Elective surgery
- Gastrointestinal bleeds that respond to supportive measures
- High drug levels or excessive anticoagulation without associated bleeding
- Need for surgery or intervention that can be delayed long enough to permit drug clearance

Reversal of anticoagulation

All anticoagulant and antiplatelet drugs should be discontinued and anticoagulant effect should be reversed immediately as follows (see summary in table 1 modified from reference 1):

1. *Warfarin:*

If INR is greater than or equal to 1.4, provide 10 mg of IV vitamin K STAT infused over 30 minutes plus 4-factor Prothrombin complex concentrate (Kcentra) IV STAT per pharmacy protocol.

i. When the INR is between 1.4 and 1.9, the lowest marketed dose of 4F-PCC should be used (25 units/Kg to a maximum of 2500 units).

If Kcentra is contraindicated, provide 15 to 30 ml/kg of fresh frozen plasma (FFP) IV STAT.

PT/INR should be repeated within 15 to 60 minutes after infusion of 4F-PCC or FFP then PT/INR every 6 hours for 36 hours; then as needed. The goal INR is less than 1.4.

If the repeat INR is still elevated greater than 1.4 after initial reversal, repeat doses of Vitamin K 10 mg IV can be administered every 12 hours and consider FFP administration. Further corrections will be attempted with FFP. Repeat doses of KCentra are not recommended

For some patients who are neurologically intact with small radiographic hematomas and mild elevation in INR (e.g., INR < 2), conservative management may be reasonable, though the risks and benefits of Warfarin reversal should be discussed.

In cases of ICH associated with cerebral venous thrombosis, reversal of Warfarin is not recommended

In cases of ICH concurrent with symptomatic or life-threatening thrombosis, heparin-induced thrombocytopenia or DIC, reversal of Warfarin should be individualized after assessing risk and benefits.

2. *Unfractionated Heparin:*

If aPTT is greater than 40 and heparin infused over proceeding 2-3 hours, provide protamine sulfate IV STAT 1mg for every 100 units of heparin given, up to 50mg. PTT should be repeated at 1 hour after protamine and then every 4 hours x 3. Repeat protamine dosing is not recommended.

3. *Enoxaparin:*

If the known last dose is within 8 hours, provide protamine sulfate 1 mg per milligram of enoxaparin IV STAT (maximum 50 grams). If the known last dose is 8 to 24 hours prior and aPTT is greater than 37, consider protamine sulfate 0.5 mg per milligram of enoxaparin IV STAT (maximum 50 grams). Protamine sulfate only partially reverses the anti-factor Xa activity of low molecular-weight heparin.

4. *Direct oral anticoagulants (DOAC).*

Reversal should be guided primarily by severity of bleeding, timing of last dose, renal function and age and not by laboratory testing (1, 2).

KCentra can be associated with risk of serious or fatal thrombotic events associated with its use. Therefore the use of Kcentra for reversal can only be recommended in patients with life-threatening bleeding or undergoing an emergent procedure.

Factor Xa Inhibitors – Apixaban (Eliquis), Edoxaban (Savaysa) or Rivaroxaban (Xarelto):
If the known last dose occurred within 3–5 terminal half-lives of drug exposure or in the context of renal or liver failure: Consider 50 units/Kg Kcentra IV STAT or 15 to 30 ml/kg of FFP IV STAT.

Direct thrombin inhibitors – Dabigatran (Pradaxa):
If the known last dose occurred within 3–5 terminal half-lives of drug exposure or the patient has renal failure: provide idarucizumab 5 grams IV STAT(given in two 2.5 gram doses administered 15 minutes apart). Consider hemodialysis or idarucizumab redosing for refractory bleeding after initial administration.
Argatroban:
If aPTT is > 40 and argatroban has been infused over the previous 2 to 3 hours, consider 50 units/Kg Kcentra IV STAT or 15 to 30 ml/kg of FFP IV STAT.

Half-lives in healthy subjects (likely longer in the elderly and with poor renal function):

1. Dabigatran: 12-14 hours
2. Rivaroxaban: 5-9 hours
3. Apixaban: 9-14 hours
4. Edoxaban: 10-14 hours

For patients presenting within 2 h of ingestion of a DOAC and are intubated with enteral access and/or those at low risk of aspiration, activated charcoal (50 g) will be administered.

5. *Antiplatelets:*

Platelet transfusion is not indicated for patient with antiplatelet-associated hemorrhage who will not undergo surgical procedure, regardless of the type of platelet inhibitor, platelet function testing, hemorrhage volume, or neurological exam.

Platelet transfusion will be considered in patients with serious or life-threatening bleeding who are taking aspirin or ADP inhibitors [clopidogrel, prasugrel, ticagrelor, and cangrelor and will undergo surgical procedure. Hematology consultation will be considered.

a. Platelet function testing will be recommended prior to platelet transfusion.
b. Platelet transfusion is not indicated in patients with documented platelet function within normal limits or documented antiplatelet resistance.
c. If platelet function testing is not readily available, empiric platelet transfusion may be reasonable.

Platelet transfusion is not indicated in patients with hemorrhage who are taking NSAID or GP IIb/IIIa inhibitors [abcixmab,eptifibatide,tirofiban] even in the context of surgical intervention.

In candidates for platelet transfusion, one single-donor apheresis unit of platelets will be given. If further transfusion is considered, platelet testing will be requested and transfusion repeated only for those with persistently abnormal platelet function tests and/or ongoing bleeding.

In patients taking aspirin or ADP receptor inhibitors with major bleeding or ICH, a single dose of desmopressin (DDAVP) of 0.4 mcg/kg IV over 30 minutes. DDAVP can be used in addition to platelet transfusion.

6. *Thrombolytic Agents:*

- **a.** In patients with serious bleeding who received a thrombolytic agent in the previous 24 h, give cryoprecipitate 10 units initial dose.
- **b.** In cases where cryoprecipitate is contraindicated or not available in a

timely manner, give an antifibrinolytic agent, tranexamic acid 10–15 mg/kg IV over 20 min or e-aminocaproic acid (amicar) 4–5 g IV over 20 min.

c. Check fibrinogen levels after administration of reversal agents. If the fibrinogen is less than 150 mg/dL, then give additional cryoprecipitate 10 units.

Management of associated coagulation abnormalities

Underlying coagulopathies should be corrected accordingly. Consider hematology consultation.

In patients with serious bleeding and thrombocytopenia (platelets less than 100,000 u/L), one single-donor apheresis unit of platelets will be given. Consider hematology consultation.

Patients with uremic platelet dysfunction or Von Willebrand syndromes may benefit with treatment with desmopressin Injectable (DDAVP): Treat with 0.3 mcg/kg DDAVP given IV over 30 minutes. Consult hematology for dosing of VWF factor concentrate.

For uncontrolled, life-threatening bleeding, consider giving an antifibrinolytic agent, tranexamic acid 10–15 mg/kg IV over 20 min or e-aminocaproic acid (Amicar) 4–5 g IV over 20 min as a last resort. Note there is a significant risk of pathologic thrombosis with Amicar.

Serious systemic hemorrhage should be treated in a similar manner. Manually compress and compressible sites of bleeding, and consult appropriate additional services to consider mechanically occluding arterial or venous sources of medically uncontrollable bleeding.

REFERENCES:

1. Frontera, JA et al: Guideline for Reversal of Antithrombotics 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.

2. Levy JH et al: When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost* 2016; 14: 623–27.

3. Nutescu EA et al: Guidelines for the Management of Spontaneous Management of bleeding and reversal strategies for oral anticoagulants: Clinical practice considerations. *Am J Health-Syst Pharm* 2013; 70: 1914-29.

Table 1. Summary of recommendations for reversal of antithrombotic agents in patients with intracranial hemorrhage

Antithrombotic	*Reversal agent*
Vitamin K antagonists	If INR ≥ 1.4: Vitamin K 10mg IV, plus 4 factor PCC (Kcentra) IV per pharmacy protocol or 4-6 units of FFP IV if Kcentra is contraindicated
Direct factor Xa inhibitors	Activated charcoal (50g) within 2 hours of ingestion 4 factor PCC (Kcentra) 50 units/kg IV or 4-6 units of FFP IV STAT
Direct Thrombin Inhibitors	For dabigatran reversal: Activated charcoal (50g) within 2h of ingestion, AND Idarucizumab 5mg IV (in two 2.5g/50mL vials) Consider hemodialysis or idarucizumab redosing for refractory bleeding after initial administration For other DTIs: 4 factor PCC 50 units/kg IV
Unfractionated heparin	Protamine 1 mg IV for every 100 units of heparin administered in the previous 2-3h (up to 50mg in a single dose)
Low-molecular weight heparins	Enoxaparin: Dosed within 8 h: Protamine 1 mg IV per 1 mg enoxaparin (up to 50 mg in a single dose) Dosed within 8-12h: protamine 0.5mg IV per 1 mg enoxaparin (up to 50mg in a single dose) Minimal utility in reversal > 12 h from dosing Dalteparin, Nadroparin and Tinzaparin: Dosed within 3-5 half-lives of LMWH: protamine 1 mg IV per 100 anti-Xa units of LMWH (up to 50mg in a single dose) OR rFVIIa 90mcg/kg IV if protamine is contraindicated
Thrombolytic agents (plasminogen activators)	Cryoprecipitate 10 units IV OR Antifibrinolytics (tranexamic acid 10-15mg/kg IV over 20 min or ε-aminocaproic acid 4-5 g IV if cryoprecipitate is contraindicated
Antiplatelet agents	DDAVP 0.4mcg/kg IV x 1 If neurosurgical intervention: Platelet transfusion (one apheresis unit)