GUIDELINE for ANTITHROMBOTIC REVERSAL

This document is intended as a guideline only and should not replace sound clinical judgment
For questions, please call contact antithrombosis via TigerConnect

- **Antithrombotic reversal (of anticoagulants and antiplatelets) should be limited to clinical situations (e.g. life-threatening bleed, need for urgent/emergent surgery) where immediate need of reversal outweighs risk of thrombosis (either from reversal agent itself or normalization of coagulation in a patient with underlying thromboembolic risk) and only once supportive measures have been maximized.**
- **Whenever possible, antithrombotics should be resumed in a safe, timely manner through shared decision making to avoid thromboembolic complications.**

ANTICOAGULANT	REVERSAL AGENT(S)	COMMENTS
DIRECT THROMBIN INHIBITORS (DTIs) ***PO:*** – Dabigatran (Pradaxa®) Half-life 12-17 hours in normal renal function	**Idarucizumab (Praxbind®) – *only used for reversal of dabigatran (Pradaxa®)*** Restrictions: patients confirmed to have recent dabigatran use who: – Require anticoagulant reversal for life-threatening hemorrhage OR – Require urgent/emergent invasive procedure within next 8 hours Dose: 5 gram Administration: Infuse *two* 2.5 gram/50 mL vials undiluted over 5-10 minutes each, consecutively – Line should be flushed with NS prior to infusion – Second vial should be infused within 15 minutes of first vial Onset: Immediate **Kcentra®- 4 Factor PCC** **May be considered for dabigatran reversal if idarucizumab not available** Dose: 1500 units x 1 (optional rescue dose of 1500 units available if hemostasis not achieved) Administration: Send Kcentra Kit for bedside reconstitution and administer via IV push over 5 minutes – Use within 4 hours of reconstitution Onset: <30 minutes Caution: thrombotic risk *Kcentra contains trace amounts of heparin (to mitigate thrombotic potential) and should not be used in bleeding patients with active or recent (last 100 days) heparin-induced thrombocytopenia (HIT). In this instance, please contact pharmacy to discuss possible use of the alternative procoagulant FEIBA for reversal.*	Use of PCC/idarucizumab: – **REQUIRES ATTENDING APPROVAL** – Document attending name in the order comments Additional options: – If dabigatran ingested within 1 hour, consider activated charcoal. – Mechanical methods, such as dialysis, may be considered as a last resort Laboratory measurement: – A normal thrombin time (<17 seconds) rules out clinically relevant dabigatran effect – **Do not use INR to guide management**
IV: – Argatroban – Bivalirudin (Angiomax®) Half-life 10-90 minutes	**IV DTIs:** – Short half-life and discontinuation of IV DTIs are primary means of attenuating bleed. – Support with crystalloid and blood products to facilitate rapid renal clearance of drug. – IV DTIs should be discontinued immediately upon bleeding discovery and rarely require other means of reversal.	
FACTOR XA INHIBITORS – Fondaparinux (Arixtra®) Half-life 17-21 hours¥ – Rivaroxaban (Xarelto®) Half-life 5-9 hours¥ – Apixaban (Eliquis®) Half-life 8-15 hours¥ – Edoxaban (Savaysa ®) Half-life 10-14 hours¥ ¥In normal renal function	**Kcentra®-4 Factor PCC** Dose: 1500 units x 1 (optional rescue dose of 1500 units available if hemostasis not achieved) Administration: Send Kcentra Kit for bedside reconstitution and administer via IV push over 5 minutes – Use within 4 hours of reconstitution Onset: <30 minutes Caution: thrombotic risk *Kcentra contains trace amounts of heparin (to mitigate thrombotic potential) and should not be used in bleeding patients with active or recent (last 100 days) heparin-induced thrombocytopenia (HIT). In this instance, please contact pharmacy to discuss possible use of the alternative procoagulant FEIBA for reversal.* ***NOTE: Andexanet alfa is currenty NON-FORMULARY at UNMH***	Use of PCC: – **REQUIRES ATTENDING APPROVAL** – Document attending name in the order comments Additional option: –If rivaroxaban, apixaban or edoxaban ingested within 1 hour, consider activated charcoal –NOT DIALYZABLE Laboratory measurement: – An undetectable standard UFH/LMWH anti-Factor Xa level (<0.04 IU/ml) rules out presence of drug effect – **Do not use INR to guide management**

<table>
<tr>
<td>HEPARIN
Half-life: 1-2 hours</td>
<td colspan="2">Protamine
Dose: 1 mg reverses 100 units of IV-administered UFH
<table>
<tr><th>Time since UFH</th><th>Dose per 100 units UFH over last 3h</th></tr>
<tr><td><30 min</td><td>1 mg</td></tr>
<tr><td>30-120 min</td><td>0.5 mg</td></tr>
<tr><td>>120 min</td><td>0.25 mg</td></tr>
</table>
– Do not exceed 50mg in a single dose; high doses can have an undesirable ANTIcoagulant effect
– In clinical practice, give 50 mg IV x1 over 10 minutes
Administration: Slow IV push not to exceed 5mg/minute
Onset: 5-15 minutes
Caution: Rapid administration can cause severe hypotension and anaphylaxis</td>
<td>– Prophylactic SQ doses of UFH are not likely to cause significant hemorrhage.
– Look for other causes of hemorrhage

Laboratory measurement:
– If anti-Xa or aPTT remains elevated or if bleeding not controlled, may redose with 50 mg
– Consider FFP and other blood product support</td>
</tr>
<tr>
<td>LMWHs
(enoxaparin)
Half-life: 2-8 hours in normal renal function</td>
<td colspan="2">Protamine (Does not reverse LMWH as effectively as it does UFH)
Dose: 1 mg for each 1 mg of enoxaparin in last 8 hours
– If >12 hrs have elapsed since LMWH administration, protamine may not be needed
– Do not exceed 50mg in a single dose; high doses can have an undesirable ANTIcoagulant effect
– In clinical practice, give 50 mg IV x1 over 10 minutes.
Administration: Slow IV push not to exceed 5mg/minute
Onset: 5-15 minutes
Caution: Rapid administration can cause severe hypotension and anaphylaxis</td>
<td>Laboratory measurement:
– If anti-Xa remains elevated or if bleeding not controlled may give 2nd dose of 0.5mg protamine per 1 mg LMWH
– Consider FFP and other blood product support</td>
</tr>
<tr>
<td>WARFARIN
Half-life 36 hours</td>
<td>ACTIVE BLEEDING AT ANY INR:
▪ Hold warfarin & give Vit K 5-10mg IV (may repeat q12h based on repeat INR)

MAJOR OR LIFE THREATENING BLEED:
▪ Hold warfarin & give Vit K 10mg IV (may repeat q12h based on repeat INR) PLUS either Kcentra (preferred) or FFP

▪ Kcentra 1500 units x 1 OR
▪ FFP 10-30 mL/kg

ASYMPTOMATIC SUPRATHERAPEUTIC INR (i.e., no active bleeding)
▪ INR 5-9: Omit 1-2 warfarin doses ± 1-2.5mg PO Vit K
▪ INR > 9 (NO BLEED): Omit 1-2 warfarin doses & give 2.5-5mg PO Vit K

SURGERY REVERSAL
▪ INR > 1.5-2.5
Surgery <24 hours: 0.5-1mg IV Vit K x1 +/- 5-8mL/kg FFP
Surgery 24-96 hours: 0.5-1mg PO Vit K x1 monitor INR q12-24h
▪ INR >2.5-5
Surgery <24 hours: 1-2.5mg IV Vit K x1 +/- 5-8mL/kg FFP
Surgery 24-96 hours: 1-2.5mg PO Vit K x1 monitor INR q12-24h</td>
<td>Phytonadione (Vitamin K)
Dose: See box on left
Administration: IV- dilute in 50 ml NS and give over 30 minutes
Onset: PO=24 hours; IV=12 hours
Caution: IV - may be associated with very small risk of anaphylaxis

FFP
Dose: See box on left
Administration: At least 10 ml/min
Onset: 2-6 hours
Caution: Carries risk of infection, must be thawed and a large volume is required (often > 1 liter)

Kcentra
Dose: 1500 units x 1 (optional rescue dose of 1500 units available if hemostasis or desired target INR not achieved)
Administration: Send Kcentra Kit for bedside reconstitution and administer via IV push over 5 minutes
– Use within 4 hours of reconstitution
Onset: <30 minutes
Caution: thrombotic risk

Kcentra contains trace amounts of heparin (to mitigate thrombotic potential) and should not be used in bleeding patients with active or recent (last 100 days) heparin-induced thrombocytopenia (HIT). In this instance, please contact pharmacy to discuss possible use of the alternative procoagulant FEIBA for reversal.</td>
<td>Use of Kcentra:
– REQUIRES ATTENDING APPROVAL

– Document attending name in the order comments

Laboratory measurement:
– Repeat INR 30 minutes after Kcentra infusion

– If INR remains elevated, may give additional 1500 units x1</td>
</tr>
</table>

ANTIPLATELET	HALF-LIFE	REVERSAL AGENT	COMMENTS
ASPIRIN	15-30 minutes 5-10 days for platelet recovery	**DDAVP** Dose: 0.3 mcg/kg IV x 1 Administration: over 15 minutes Onset: Immediate Caution: Serial doses associated with tachyphylaxis, hyponatremia, and seizures	– Short half-life and discontinuation of gpIIb-IIIa are primary means of attenuating bleed – Transfusion of functioning platelets in spontaneous intracranial hemorrhage has been associated with harm and should be generally be avoided – Mechanical methods, such as dialysis, may be considered as a last resort
CLOPIDOGREL (Plavix®)	8 hours ~ 5 days for platelet recovery		
PRASUGREL (Effient®)	7 hours ≤7 days for platelet recovery		
TICAGRELOR (Brilinta®)	~ 9 hours 3 days for platelet recovery		
Gp IIb-IIIa Eptifibatide (Integrilin®) Abciximab (Reopro®) Tirofiban (Aggrastat®)	30-120 minutes		

Consider use of antifibrinolytics for refractory bleeding

Aminocaproic acid:

Mechanism: antifibrinolytic

Dose: 4-5 gm loading dose in 250 ml NS over 15 minutes followed by infusion of 1gm/hr infusion until bleeding subsides (max 30 gm/day)

Caution: May require renal adjustment

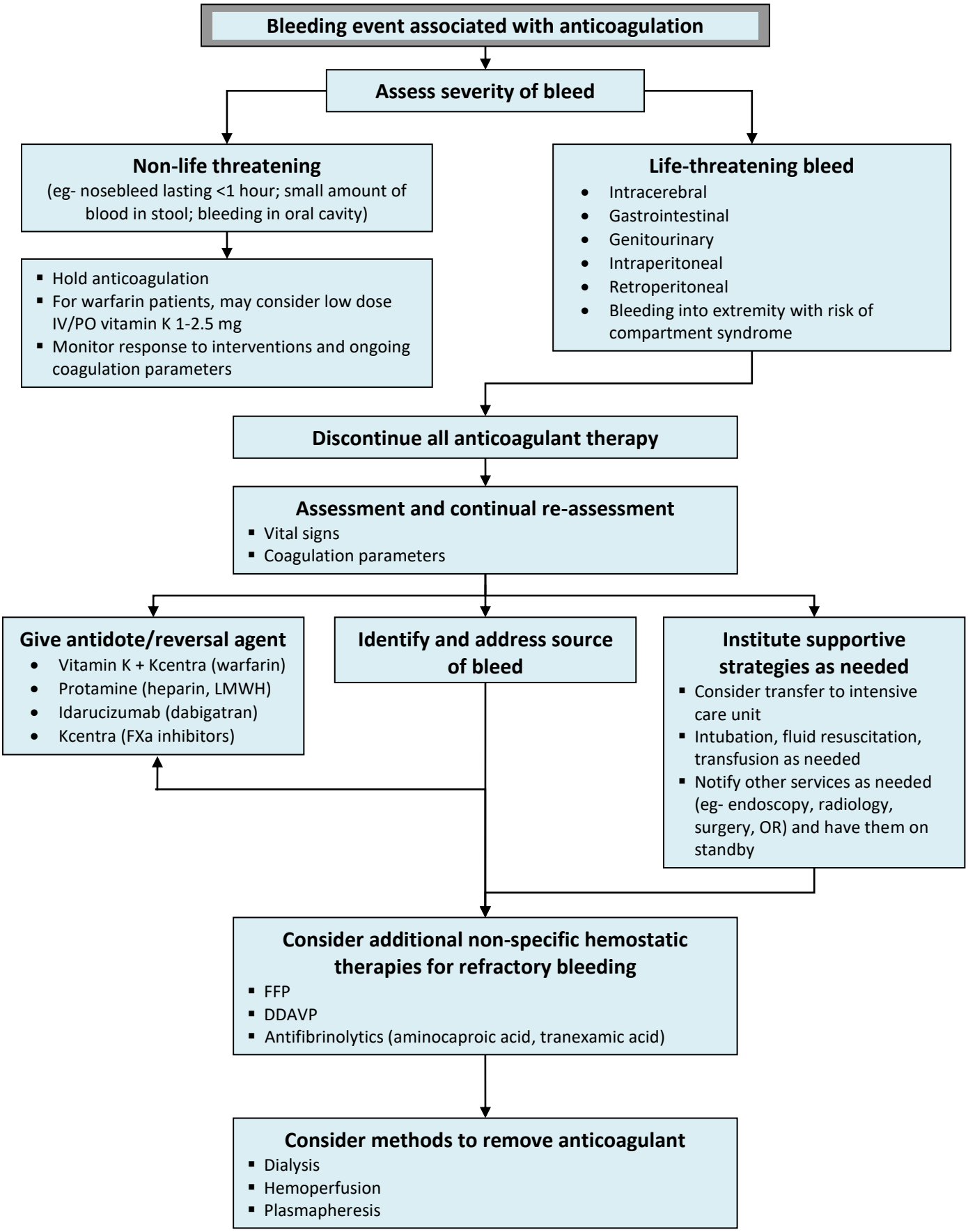
Tranexamic acid:

Mechanism: antifibrinolytic

Dose: 1 gm loading dose in 50 ml NS IV over 10 minutes followed by 1 gm in 250 ml NS infused over the next 8 hours

Caution: May require renal adjustment

OVERALL MANAGEMENT OF ANTICOAGULATED BLEEDING PATIENT



REFERENCES:

1. Garcia DA, et al. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):e24S-e43S. doi: 10.1378/chest.11-2291.
2. Tomaselli GF, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020 Aug, 76 (5) 594–622
3. Cuker A, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. Am J Hematol 2019 Jun;94(6):697-709. doi: 10.1002/ajh.25475
4. Crowther MA, Berry LR, Monagle PT, Chan AK. Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin. Br J Haematol 2002;116:178-86.
5. Li C, et al. Reversal of the anti-platelet effects of aspirin and clopidogrel. J Thromb Haemost 2012 Apr;10(4):521-8
6. Desborough MJR, et al. Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost 2017 Feb;15(2):263-272. doi: 10.1111/jth.13576
7. Baharoglu MI, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet 2016; https://doi.org/10.1016/S0140-6736(16)30392-0