Deaconess ANTICOAGULANT AND ANTIPLATELET MEDICATION REVERSAL

1: Identify the medication 2: Stop the medication 3: Confirm time of last dose

Emergent—Life-threatening bleeding. Immediate action needed:
Hold anticoagulants and consider giving a specific antidote and/or a pro-coagulant agent (see table below) Consider laboratory analysis for baseline values and if necessary to modify the therapy. Therapy may be initiated prior to lab results being posted

Urgent—Non-life-threatening bleeding. Potential intervention within 6-12 hours:
Hold anticoagulants and consider giving a specific antidote and/or a pro-coagulant agent (see table below) Consider laboratory analysis for baseline values and if necessary to modify the therapy.

Non-Urgent—Non-bleeding patient. 12–24 hours or greater:
Hold the anticoagulant. Consider additional laboratory analysis and reassess bleeding risks.

Drug: Agent Type	Monitor	Half-life (t1/2)	Reversal Recommendation	Administration/Miscellaneous
Vitamin K antagonist: warfarin (Coumadin); Coagulation factors II, VII, IX, X; anticoagulant proteins C, S	Monitor PT/INR	20–60 hrs	Determine risk (emergent, urgent, non-urgent for appropriate intervention) • **Non-Urgent:** Hold the anticoagulant. Consider additional laboratory analysis and reassess bleeding risks. Consider Vitamin K 2.5 to 5 mg PO x 1 based on INR. • **Urgent:** Phytonadione (Vitamin K) 10 mg IV over 30 minutes – *Vitamin K ALONE can significantly reverse the INR within 6–8 hours and should be considered as a sole agent if no intervention is needed until that time.* • **Emergent:** PCC 4 factor (Kcentra) 1500 units IV PLUS Vitamin K 10 mg IV over 30 minutes – Dose may be repeated (max 5000 units)	• FFP: plasma can be used if 4FPCC is unavailable. – FFP may require 2 or more adult doses for total reversal and may exceed 6 hours o single adult plasma dose = 10-15ml/kg • If INR remains elevated post single dose and/or the patient is still experiencing uncontrolled bleeding, redosing of PCC can be considered. Max dose is 5000 units. Redosing of Vitamin K is rarely indicated, but may be given after 12 hours of original dose.
Anticoagulant: Heparin (UFH); binds to antithrombin; inactivates Xa; inactivates IIa; indirect thrombin inhibitor	aPTT; Monitor platelet count	90 minutes	• 1mg protamine/100 units of IV heparin infused over 10 mins; max dose = 50mg protamine repeating to calculated amount	• IV slowly -over 10 mins • Beware anaphylactoid reaction; >50mg/dose
Anticoagulant: enoxaparin (Lovenox; LMWH); binds to antithrombin; inactivates Xa	aPTT; Monitor platelet count	7–12 hrs ~ upon renal function	• Activity 60% neutralized by protamine; ≤ 8hrs; give 1mg protamine/1mg enoxaparin. Last dose > 8hrs—give 0.5mg protamine/1mg enoxaparin • Second dose needed: 0.5mg protamine/1mg of enoxaparin 2–4 hrs after the first. Max dose of 50mg protamine.	• See UFH
Anticoagulant: fondaparinux (Arixtra); binds to antithrombin; inactivates Xa; a heparinoid.	Monitor platelet count; thrombocytopenia is rare.	17–21 hours	• None • *(None of the following products has been shown to reduce bleeding in these pts; however, there is no direct antidote for fondaparinux)*	• Supportive care; blood components • 4F-PCC (Balfaxar contains heparin) 2000 units. A repeat dose of 500-2000 units can be considered if needed for ongoing signs of bleeding or hemodynamic instability
Thrombolytic: tenecteplase	Monitor neurologic exam; PT and aPTT, fibrinogen, platelet count.	~5 min	• TXA 1gm IV bolus over 10 mins followed by 1gm gtt over 8 hours • 1 Cryoprecipitate dose *(1 adult dose = 5 pooled units)* • Platelets *(single adult dose = 1 unit)*	• If TXA contraindicated: use Amicar (contact pharmacy for dosing) • Keep fibrinogen ≥ 150 mg/dl
Factor Xa inhibitor: oral 1) Rivaroxaban (Xarelto) 2) Apixaban (Eliquis) 3) Edoxaban (Savaysa) 4) Betrixaban (Bevyxxa)	PT/INR (if normal, less likely that drug is contributing to ongoing bleeding)	1) 5–9 hrs and elderly 11–13 hrs 2) 8-15 hrs 3) 9-11 hrs 4) 19-25 hrs	• **Vitamin K is NOT effective** • Supportive care • 4F-PCC (Balfaxar contains heparin) 2000 units. A repeat dose of 500-2000 units can be considered if needed for ongoing signs of bleeding or hemodynamic instability	• If initial interventions do not control bleeding: – Consider plasma (adult dose = 15 ml/kg)
Oral platelet inhibitors: 1) Clopidogrel (Plavix-P2Y_{12}) 2) Prasugrel (Effient-P2Y_{12}) 3) Ticagrelor (Brilinta-P2Y_{12}) 4) Vorapaxar (Zontivity-Par1)	Monitor bleeding, Hct, Monitor platelet function (VerifyNow: plt function test)	1) ~ 6 hrs 2) ~ 7 hrs 3) ~ 7 hrs 4) ~ 8 **days**	• Platelets • *Start with single unit (single unit= 1 adult dose)* • *Utility of platelet transfusion in critical bleeding patients remains under investigation.* • DDAVP (caution: fluid overload) 0.4 mcg/kg IV x 1. Max dose of 20 mcg.	• Platelet count > 50 for major surgery/100k for neurosurgical/ophthalmic. • DDAVP 0.4 mcg/kg in 50 ml NS over 15–30 mins. • Platelet transfusions have not been shown to improve clinical outcomes; however, the recommendations provided are based on the most recent neuro/critical care guidelines.
Direct thrombin inhibitor: (oral) dabigatran (Pradaxa)	APTT: (if normal, less likely that drug is contributing to ongoing bleeding)	(t1/2=12–17 hours but much longer with renal impairment)	• Idarucizumab 5g, provided as two separate vials each containing 2.5g/50ml; give one after the other. Limited data supports administration of an additional 5g of idarucizumab (Praxbind)	

REFERENCE LIST

1. Desmurs-Clavel H, Huchon C, Chatard B, et al. Reversal of the inhibitory effect of fondaparinux on thrombin generation by rFVIIa, aPCC and PCC. Thromb Res. 2009; 123: 796-8.
2. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood. 2008; 111: 4871-4979.
3. Zahir H, Brown KS, Vandell AG, et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. Circulation 2015; 131: 82-90.
4. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011; 124: 1573-1579.
5. Newman WC, Zhang X, et al. Administration of 4-factor prothrombin complex concentrate as an antidote for intracranial bleeding in patients taking direct factor Xa inhibitors. World Neurosurg 2015; 84: 1956-1961.
6. Ghadimi K, Levy JH, Welsby IJ. Prothrombin Complex concentrates for bleeding in the perioperative setting. Anesth Analg. 2017; 122: 1287-1300.
7. Awad NI, Cocchio C. Activated prothrombin complex concentrates for the reversal of anticoagulant-associated coagulopathy. Pharmacy and Therapeutics 2013; 38: 696-701.
8. Raval AN, Cigarroa JE, Chung MK, et al. Management of patients on non-Vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: a scientific statement from the American Heart Association. Circulation.2017; 135: e604-e633.
9. Klein L, Peters J, Miner J, Gorlin J. Evaluation of fixed dose 4-factor prothrombin complex concentrate for emergent warfarin reversal. Am J Emerg Med. 2015; 33: 1213-1218.
10. Dentali F, Marchesl C, Pierfranceschi MG, et al. Safety of prothrombin complex concentrate for rapid anticoagulation reversal of Vitamin K anticoagulation: A meta-analysis. Thromb Haemost 2011; 106: 429-438.
11. Varga C, Al-Touri S, Papadoukakis S, et al. The effectiveness and safety of fixed low dose prothrombin complex concentrates in patients requiring urgent reversal of warfarin. Transfusion 2013; 53:1451-1458.
12. Khorsand N, Veeger NJGM, Muller M, et al. Fixed versus variable dose of prothrombin complex concentrate for counteracting Vitamin K antagonist therapy. Transfusion Medicine 2011; 21: 116-123.
13. van Aart L, Eijkhout HW, Jan S. Kamphuis JS, et al. Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: An open, prospective randomized controlled trial. Thrombosis Research. 2006; 118: 313-320.
14. Khorsand N, Veeger NJGM, et al. An observational, prospective, two-cohort comparison of a fixed versus variable dosing strategy of prothrombin complex concentrate to counteract Vitamin K antagonists in 240 bleeding emergencies. Haematologica 2012; 97: 1501-1506.
15. Khorsand N, Kooistra HAM, van Hest RM. A systematic review of prothrombin complex concentrate dosing strategies to reverse Vitamin K antagonist therapy. Thrombosis Research 2015; 135: 9-19.
16. Frontera JA, Lewin JJ, Rabenstein AA et al. Guidelines for reversal of antithrombotics in intracranial hemorrhage. Neurocrit Care 2016; 24: 6-46.
17. Yaghi S et al. Treatment and outcome of hemorrhagic transformation after intravenous altepase in acute ischemic stroke. Stroke 2017; 48: e343-e361.
18. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC,Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM,Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49:eXXX–eXXX. doi: 10.1161/STR.0000000000000158.

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