Anticoagulant Reversal Recommendations (Adults)
(Oral anticoagulants, Parenteral anticoagulants, Fibrinolytics)
Updated August 2022

General Principles:

Bleeding management - Consider fluid resuscitation and consult organ-specific specialist as deemed necessary by attending provider.

The following document has additional information for consideration.
Expert Consensus Decision Pathway 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. Journal of the American College of Cardiology Volume 76, Issue 5, 4 August 2020, Pages 594-622

Labs:

Coagulation Studies – Given a patient's current clinical condition and necessity for urgent anticoagulation reversal, consider the safety of timely and appropriate coagulation studies resulting in actionable patient management interventions. If a result of "no clot" is reported, this means that the PT/INR, aPTT or other coagulation study could not be interpreted. Carefully consider if it is safe to recollect a specimen. If not, consider reversal.

Drugs:

Alteplase (tPA, Activase®)
Apixaban (Eliquis®)
Argatroban
Bivalirudin (Angiomax®)
Dabigatran (Pradaxa®)
Edoxaban (Savaysa®) – non formulary
Enoxaparin (Lovenox®)
Fondaparinux (Arixtra®)
Heparin
Rivaroxaban (Xarelto®)
Tenecteplase (Tnkase)
Warfarin (Coumadin®, Jantoven®)

Topics:

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ORAL AGENTS

Apixaban (Eliquis®), Rivaroxaban (Xarelto)

Andexanet alfa has been removed from the WVU Medicine formulary.

Situation	Recommendation
Acute Overdose	• Activated charcoal may be considered (no data available at this time) • Consider giving activated charcoal 1-2 hours post-overdose before intestinal absorption occurs
Life-threatening or uncontrolled bleeding	**Prothrombin complex concentrate (PCC)** • Prothrombin complex concentrate (PCC) - KCentra is the preferred agent. ○ KCentra – 25-50 units/kg **Dialysis** – NOT effective for drug removal

Edoxaban (Savaysa®)

Situation	Recommendation
Acute Overdose	• Activated charcoal may be considered (no data available at this time) • Consider giving activated charcoal 1-2 hours post-overdose before intestinal absorption occurs
Life-threatening or serious bleeding and/or emergent surgical intervention	• **1st Line**: Prothrombin complex concentrate (PCC) - KCentra is the preferred agent. (Profilnine if KCentra is unavailable) in consultation with Blood Bank ○ KCentra – 25-50 units/kg • **2nd Line**: Fresh frozen plasma (FFP) – 5-10 mL/kg: there are conflicting opinions on the efficacy of FFP in rivaroxaban overdose • Dialysis – NOT effective for drug removal

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Dabigatran (Pradaxa®) Bleeding Management, Acute Overdose, Reversal

Note: (Idarucizumab (Praxbind®) Restricted use: reversal of dabigatran only for emergency surgery/ urgent procedures needed within 8 hours and/or life-threatening or uncontrolled bleeding.

Situation	Recommendation
Acute Overdose	• Activated charcoal may be used in the event of an acute overdose of dabigatran if drug has been taken *within 2 hours* before intestinal absorption occurs
Life-threatening or uncontrolled bleeding or reversal for emergency surgery/urgent procedures	• Idarucizumab (Praxbind) – 5 grams given as two 2.5 gram doses as follows: Prior to administration, flush preexisting IV line with sodium chloride 0.9%. • Begin administration within 1 hour of puncturing the vial. Administer dose undiluted as an IV bolus either via syringe or as an infusion by hanging the vials. Infusion of each vial should take no longer than 5 to 10 minutes. The second vial of 2.5 g should be administered no later than 15 minutes after the end of the first 2.5 g vial.
Bleeding Management (other considerations)	• 1st line - Idarucizumab (Praxbind) – see above • 2nd line - Prothrombin complex concentrate (PCC) - Kcentra – 25-50 units/kg • 3rd line - Dialysis – approximately 60% is removed over 2-3 hours

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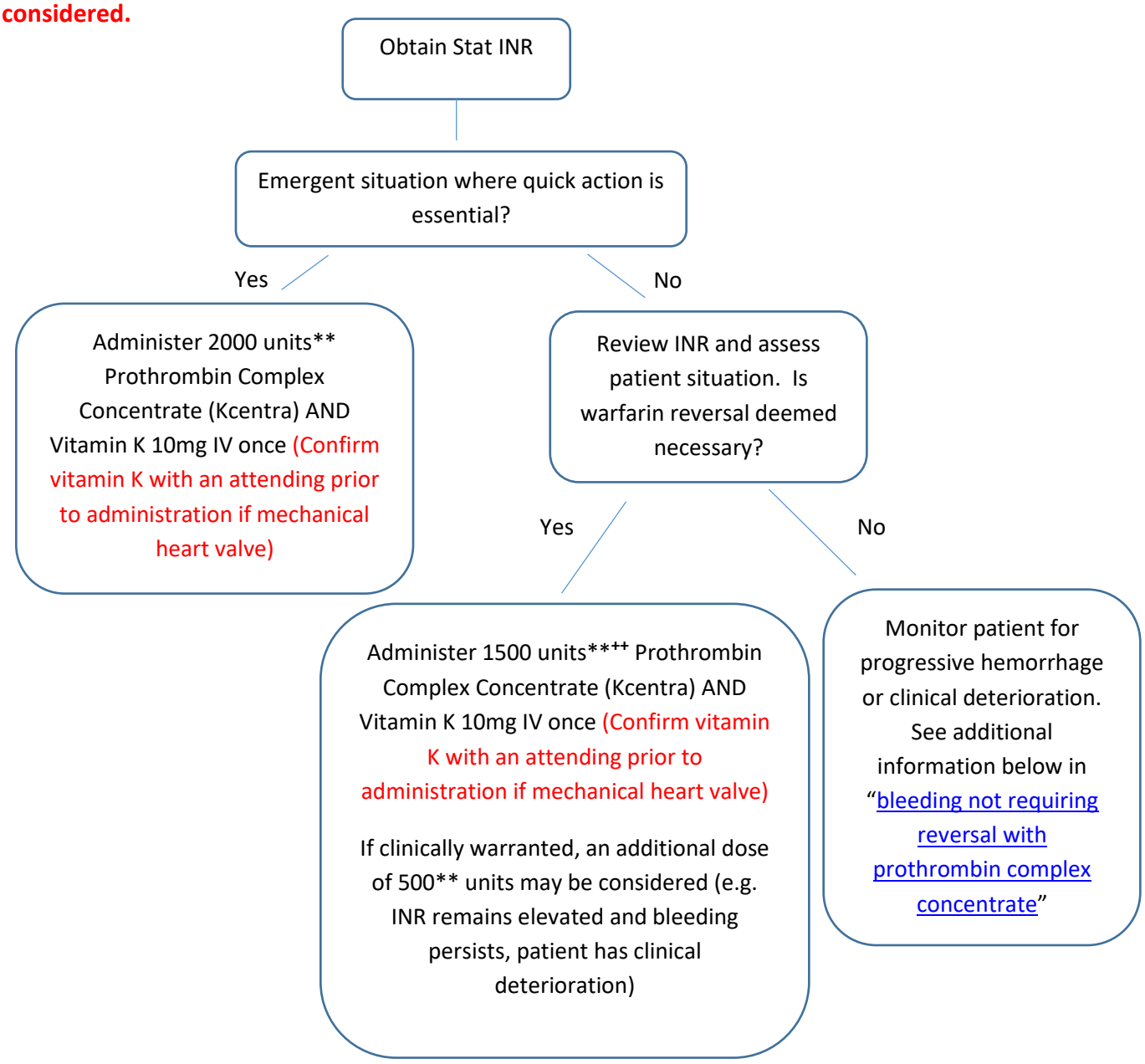
Warfarin (Coumadin® Jantoven®)

Caution: Before giving Vitamin K, the patient's risk of thrombosis should always be considered.



** Product dispensed may be within 25% variance of dose ordered based upon actual number of units within the full vial. Please update the dose given to reflect the dose dispensed.

++ Consider 1000 units if weight less than 50kg

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Clinical situations and recommendations

Mechanical heart valve patients – Avoid vitamin K unless life-threatening bleeding. Confirm with an attending provider prior to administration.

Bleeding that does not require reversal with prothrombin complex concentrate – Warfarin
• Mechanical heart valve patients – Avoid vitamin K unless life-threatening or critical site bleeding. Confirm with an attending provider prior to administration.
• Consider holding a dose(s) of warfarin if clinically warranted (consider risk of worsening bleeding and risk of thrombosis)

• Institute supportive measures if needed (apply pressure and use decongestant nasal spray for nosebleeds)
• Assess for and manage comorbidities that contribute to bleeding (thrombocytopenia, uremia, liver disease)
• If INR is elevated and bleed does require hospitalization, surgical/procedural intervention, and/or transfusion, consider reversal with vitamin K
  ○ Stop Warfarin
  ○ Consider Vitamin K 2 - 5mg slow IV (over 30 minutes)
  ○ Provide supportive care and volume resuscitation

Not Bleeding – elevated INR – Warfarin
• Mechanical heart valve patients – Avoid vitamin K unless life-threatening bleeding. Confirm with an attending provider prior to administration.
• Repeat INR prior to holding doses
• Consider holding a dose(s) of warfarin if clinically warranted (consider risk of bleeding and risk of thrombosis)
• Modify bleeding risk factors (e.g. blood pressure, fall/injury precautions)
• Monitor for signs/symptoms of bleeding
• Close INR follow-up
• In general, vitamin K is not recommended in the non-bleeding patient.

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Surgery needed in a patient with elevated INR - Warfarin
• Mechanical heart valve patients – Avoid vitamin K unless life-threatening bleeding. Confirm with an attending provider prior to administration.

• If surgery is in 12 or more hours
  ○ Consider Vitamin K 2.5 – 5mg slow IV (over 30 minutes)
  ○ Recheck INR 4 hours prior to surgery.
  ➢ If indicated by INR, administer Prothrombin Complex Concentrate (PCC) 1500** units within 2 hours of surgery.

• If surgery is in less than 12 hours
  ○ Recommend Vitamin K 2.5 – 5mg slow IV (over 30 minutes)
  ○ Recheck INR 4 hours prior to surgery.
  ➢ If indicated by INR, administer Prothrombin Complex Concentrate (PCC) 1500** units within 2 hours of surgery.

** Product dispensed may be within 25% variance of dose ordered based upon actual number of units within the full vial. Please update the dose given to reflect the dose dispensed.

Overdose – Warfarin (NOT superwarfarin poisoning)
• Mechanical heart valve patients – Avoid vitamin K unless life-threatening bleeding. Confirm with an attending provider prior to administration.
• Monitor INR and manage accordingly

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PARENTERAL AGENTS

Heparin

Situation	Recommendation
Urgent Reversal of IV heparin Hemorrhage associated with UFH therapy	1 mg of protamine neutralizes approximately 100 units of unfractionated heparin ○ Calculate the amount of unfractionated heparin received in the preceding three hours. Use the following equation to guide dosing: $$Protamine\ dose = \frac{1\ x\ UFH\ in\ past\ 1\ hr}{100} + \frac{0.5\ x\ UFH\ within\ 1-2\ hr}{100} + \frac{0.25\ x\ UFH\ within\ 2-3\ hr}{100}$$ ○ Stated otherwise, use 100 % of heparin received in most recent hour, 50 % of heparin received in 2nd most recent hour, and 25 % of heparin in 3rd most recent hour ▪ Example: patient is currently receiving UFH 12 units/kg/hour with adjusted body weight of 84 kg for 6 hours • 83.3 kg x 12 units/kg/hour = 1000 units/hour ○ Most recent hour = 1000 units x 1 = 1000 units ○ 2nd most recent hour = 1000 units x 0.5 = 500 units ○ 3rd most recent hour = 1000 units x 0.25 = 250 units ○ (1000 units + 500 units + 250 units)/100 = 17.5 mg protamine ○ Outside of cardiopulmonary bypass, consider maximum dose of 50 mg ▪ Repeat dosing may be guided by aPTT, ACT, or TEG ○ Administer as slow IV push at rate not to exceed 5 mg/minute, no more than 50 mg in a 10 minute period to avoid hypotension ○ Monitor closely for protamine reaction following administration (hypotension, bradycardia, anaphylactic reaction, pulmonary edema, circulatory collapse)
Anaphylaxis to protamine – patients who have previously received protamine (including diabetic patients under treatment with protamine-containing insulin and those with fish allergy) have an approximately 1 percent risk of anaphylaxis when protamine sulfate is administered. Thrombocytopenia following protamine administration has also been reported.	

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Enoxaparin (Lovenox®)

Situation	Recommendation	Administration/Monitoring
Urgent Reversal • Toxicity • Hemorrhage associated with enoxaparin therapy	• Enoxaparin administered in the previous 8 hours - Give 1 mg protamine sulfate IV per 1 mg of enoxaparin - If a second dose is needed, give 0.5 mg protamine sulfate IV per 1 mg of enoxaparin • Enoxaparin administered greater than 8 hours previously - Give 0.5 mg protamine sulfate IV per 1 mg of enoxaparin - If a second dose is needed, give 0.5 mg protamine sulfate IV per 1 mg of enoxaparin	• Outside of cardiopulmonary bypass, consider maximum dose of 50 mg ○ Repeat dosing may be guided by aPTT, ACT, or TEG • Administer as slow IV push at rate not to exceed 5 mg/minute, no more than 50 mg in a 10 minute period to avoid hypotension • Monitor closely for protamine reaction following administration (hypotension, bradycardia, anaphylactic reaction, pulmonary edema, circulatory collapse)

Fondaparinux (Arixtra®)

Antidote
• Fondaparinux is NOT inactivated by protamine • High doses of recombinant factor VIIa (90 mcg/kg) have been shown to partially normalize the prolonged aPTT, the endogenous thrombin potential, and prothrombin activation in vivo • General supportive measures should be used

Argatroban or Bivalirudin (Angiomax®)

Situation	Recommendations
Reversal of anticoagulant effects for direct thrombin inhibitors	• There are no specific antidotes for direct thrombin inhibitors • Recombinant factor VIIa can reverse the anticoagulant effect of direct thrombin inhibitors (* the usefulness of this agent in patients who are bleeding has not been established) • Hemodialysis or hemoperfusion can remove bivalirudin or argatroban

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FIBRINOLYTIC AGENTS

Alteplase (Activase®) or Tenecteplase (Tnkase®)

Antidote

• In cases of symptomatic hemorrhagic conversion in patients treated with a fibrinolytic, the following interventions may be considered depending on the clinical situation:
  ○ Cryoprecipitate, 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h)
  ▪ Obtain a fibrinogen level immediately
  ▪ Empirically transfuse with 10 U cryoprecipitate
  ▪ Continue to administer as needed to achieve a normal fibrinogen level of ≥150 mg/dL (10 U cryoprecipitate increases fibrinogen by approximately 50 mg/dL)
  ○ Platelets, 1 apheresis unit
  ▪ Platelet transfusion is recommended for the treatment of fibrinolytic-associated ICH, though benefit is unclear except in patients with thrombocytopenia (platelets <100 000/µL)
  ○ Antifibrinolytics
  ▪ Consider when blood products are contraindicated or patient/family refuses or if cryoprecipitate is not available in a timely manner
  ▪ Aminocaproic acid: 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h)
  ▪ Tranexamic acid: 1000 mg IV once infused over 10 min
  ○ Use supportive measures

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Anticoagulant Reversal and Supportive Agents -

Agent	Dose	Comments
Vitamin K	1-10 mg IV/PO, not SQ or IM	• Infusion reactions rare; administer over 20-30 minutes • Takes 6 (IV) to 24 (PO) hours to reverse warfarin • Large doses can cause warfarin resistance on resumption
Protamine sulfate	12.5-50 mg IV	• Full reversal of unfractionated heparin • 60-80% reversal of LMWH • No reversal of fondaparinux
Platelets	1 apheresis unit 5-8 whole blood units	• Raise platelet count by 30 x 10^9/L • Goal platelet count 50-100 x 10^9/L (indication dependent)
Frozen Plasma (FFP)	10-30 mL/kg (1 unit = 250 ml)	• Replaces all coagulation factors, but cannot fully correct • Hemostasis usually requires factor levels ~ 30% • Factor IX may only reach 20% • May need repeat dose after 6 hours • Large volume, takes hours to thaw and infuse
Prothrombin complex concentrates (PCC)	25-50 units/kg IV (lower doses studied)	• Rapid INR correction in warfarin patients • Small volume infusion over 10-30 minutes • Risk of thrombosis = 1.4% • Contraindicated with history of HIT • May need repeat dose after 6 hours
Recombinant factor VIIa (rFVIIa)	15-90 mcg/kg (lower doses studied)	• Rapid infusion of small volume • Rapid INR correction of warfarin, but may not correct bleeding because only restores FVIIa • Risk of thrombosis = 5-10% • May need repeat dose after 2 hours
Idarucizumab (Praxbind)		• 5 g provided as two separate vials each containing 2.5 g/50 mL idarucizumab • Rapid decrease in dabigatran plamsa concentration • Risk of thrombosis approx. 7% in clinical trial
Andexanet alfa (coagulation factor Xa (recombinant), inactivated-zhzo) (Andexxa)		• Bolus followed by infusion – high dose or low dose based upon drug, dose and time from last dose to administration of this agent • Indicated for reversal of apixaban and rivaroxaban ONLY at this time • Rapid decrease in anti-Factor Xa which may increase again after infusion ends • Risk of thrombosis approx. 18% in clinical trial

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