Title: Anticoagulation Reversal Guidelines	Document #: 932 Version: 3
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Policy Statement/Purpose:

To provide guidelines for the reversal of anticoagulation or management of bleeding associated with anticoagulants. The following procedures/guidelines have been approved by the SCHS Pharmacy and Therapeutics committee to promote safe and effective use of anticoagulants and reversal agents.

Definitions: *(Definitions of acronyms or specialized terminology)*

FFP = fresh frozen plasma
INR = international normalized ratio
CBC = complete blood count
aPTT = activated partial thromboplastin time
PT = prothrombin time
BMP = basic metabolic panel

Major bleeding: non-life threatening bleeding associated with a drop in hemoglobin of 2g/dL or more, or requiring transfusion of 2 or more units of packed red blood cells.
Life threatening bleeding: bleeding into a critical organ (e.g. intracranial, intraspinal, retroperitoneal, intramuscular with compartment syndrome), hemoglobin drop >5g/dL, bleeding associated with hypotension requiring use of intravenous inotropic agents, bleeding requiring reversal in < 2 hours or necessitating emergent surgical intervention.
Emergent surgery/intervention: surgery that must be performed immediately, and for which a delay could result in death or permanent disability.

Instructions:

1. **LABORATORY EVALUATION**
   a. The following labs should be drawn STAT and repeated as clinically indicated to help identify the presence or absence of anticoagulation
      CBC PT/INR
      aPTT BMP

2. **REVERSAL OF ANTICOAGULATION - VITAMIN K ANTAGONISTS (WARFARIN)** [1,2,3]
   (t1/2 = 36 hours, five days for complete reversal)
   a. **Major/life threatening bleeding or for emergent intracranial intervention**
      i. Give vitamin k (phytonadione) 10mg IV over 60 minutes
      ii. Give KCentra (four factor prothrombin complex concentrate). Administer IV, not to exceed an infusion rate of 8ml/min (~200units/min). Dosing weight = actual body weight. Max dosing weight = 100kg. Round to nearest vial size.

INR*	Dose of KCentra**
2-3.9	25 units/kg (max dose 2500 units)
4-6	35 units/kg (max dose 3500 units)
>6	50 units/kg (max dose 5000 units)

*INR 1.3-1.9 may consider 25 units/kg for life threatening bleeding
**May consider lower dose of 12 units/kg if desired by physician

      iii. Consider platelet administration in the setting of thrombocytopenia or in the setting of concomitant antiplatelet therapy (eg, ASA, clopidogrel)
      iv. Monitoring:
         1. Check INR 30 minutes after completing administration

2. If repeat INR is >1.5 consider repeating dose

Considerations:
Inclusion: INR > 1.5 requiring immediate intervention where conventional therapy (i.e. FFP, vitamin K) has failed to normalize INR, is contraindicated, or more rapid reversal of coagulopathy is necessary Assess for risk factors for thrombosis or thromboembolic event (i.e prior ischemic stroke, CAD, PE, etc) and conduct risk vs benefit prior to PCC (KCentra) administration Contraindications to KCentra: known anaphylactic or severe systemic reactions to KCentra, disseminated intravascular coagulation, patients with known heparin-induced thrombocytopenia (KCentra contains heparin)

b. Without significant bleeding who need NON-URGENT REVERSAL

Pts who can wait up to 24 hours before going to surgery including those with elevated INR without clinically significant bleeding

INR value	Reversal within 12 hours	Reversal within 24 hours
INR ≥ 1.5 but ≤ 1.9	Vitamin K 2.5mg IV	Vitamin K 1mg IV or 2.5mg PO
INR > 1.9 but ≤ 3	Vitamin K 2.5mg IV	Vitamin K 1-2mg IV or 2.5-5mg PO
INR > 3 but ≤ 5 No significant bleeding	Vitamin K 5mg IV	Vitamin K 2-3mg IV or 5mg PO
INR > 5 but < 9 No significant bleeding.	Vitamin K 5mg IV	Vitamin K 5mg IV or 10mg PO
	Recheck INR in 6 hours. If INR still elevated may repeat vitamin k doses as above.	Recheck INR in 12 hours. If INR still elevated may repeat vitamin k doses as above.

Subcutaneous or intramuscular vitamin k administration is not recommended for reversal

c. Elevated INR WITHOUT bleeding and WITHOUT planned intervention

High dose phytonadione (vitamin k) may result in prolonged warfarin resistance for up to a week or more. Prolonged resistance to warfarin may place patients at risk of thrombosis and may require several days of alternate therapy (e.g. heparin, LMWH). Use of low dose vitamin k can return INR to therapeutic range without producing prolonged resistance.

INR value	Warfarin Dose	Vitamin K	Comments
INR 3.1-4.4	Reduce or omit next dose	None	Resume warfarin at reduced dose when INR reaches therapeutic range
INR 4.5-10	Stop	None	Resume warfarin at reduced dose when INR reaches therapeutic range
INR >10 Low bleeding risk	Stop	Give 1.25-2.5mg PO or 0.5-1mg IV	Resume warfarin at reduced dose when INR reaches therapeutic range

INR >10 High bleeding risk*	Stop	Give 2.5-5mg PO or IV	Resume warfarin at reduced dose when INR reaches therapeutic range

*modified Outpatient Bleeding Risk Index (mOBRI): age ≥65, history of stroke, GI bleed in the past 2 weeks, and at least one of the following: recent myocardial infarction, hematocrit level <30%, creatinine >1.5mg.dL, or diabetes mellitus. One point for each of the four risk factors (high risk defined as ≥ 3 points).

3. **REVERSAL OF ANTICOAGULATION - DIRECT THROMBIN INHIBITORS**[4,5]
   a. **Major/life threatening bleeding or for emergent intracranial intervention**
      i. For **argatroban** or **bilvalrudin** (t1/2 = 25-51 minutes)
         1. turn off the infusion
      ii. For **dabigatran** (Pradaxa) (t1/2 = 12-24 hours, depending on renal function)
         1. Give 5g idarucizumab (Praxbind). Administer each 2.5g/50ml vial undiluted via slow IV push over 5 minutes, no more than 15 minutes apart). Do not administer any other infusion in the same IV line.
         2. Monitoring:
            a. Baseline aPTT
            b. Repeat aPTT after completion of idarucizumb, consider ongoing aPTT monitoring (Q12h) to ensure no re-elevation of aPTT occurs

Considerations:
The aPTT may be a qualitative indicator of anticoagulation status. If the aPTT is less than 50 seconds (i.e. 1.5x control), then minimal drug may be present

4. **REVERSAL OF ANTICOAGUALTION - FACTOR XA INHIBITORS** [6,7,8]
   a. **Major/life threatening bleeding or for emergent intracranial intervention**
      i. For **apixaban** (Eliquis), **rivaroxaban** (Xarelto), or edoxaban (Savaysa) (t1/2 = 6-12 hours, depending on renal function)
         1. Give Kcentra* (four factor prothrombin complex concentrate) 50 units/kg. Administer IV over 15-30 minutes, not to exceed an infusion rate of 8ml/min (~200unit/min). Dosing weight = actual body weight. Max dosing weight = 100kg *Recommendations are based on anecdotal reports and theory in the absence of randomized trials
         2. Monitoring: for re-elevation of coagulation parameters; signs/symptoms of clinically relevant bleeding and thromboembolic events.
      ii. For **fondaparinux** (Arixtra) (t1/2 = 17-21hrs)
         1. Give recombinant factor VIIa 90mcg/kg IVx1, Administer slow IV bolus over 2 to 5 minutes.
         2. May also give fresh frozen plasma 15mL/kg
         3. Monitoring: for re-elevation of coagulation parameters; signs/symptoms of clinically relevant bleeding and thromboembolic events. Reversal of anticoagulation should correct without intervention in approximately 2-5 days for MOST patients. Duration may be longer for those with renal impairment.

Considerations:
A coagulation assay is not currently available in St Charles to qualitatively assess the presence of anticoagulant effect. Assess for risk factors for thrombosis or thromboembolic event (i.e prior ischemic stroke, CAD, PE, etc) and conduct risk vs benefit prior to KCentra administration Contraindications to KCentra: known anaphylactic or severe systemic reactions to KCentra, disseminated intravascular coagulation, patients with known heparin-induced thrombocytopenia (KCentra contains heparin)

5. **REVERSAL OF ANTICOAGULATION WITH HEPARIN (UFH)** [9,10, 11]
   a. **Major/life threatening bleeding or for emergent intracranial intervention**
      i. For **IV unfractionated heparin (UFH)** infusion (t1/2 = 1-2 hours)
         1. Consider protamine (see table for dosing)
         2. Monitoring: if bleeding persists and aPTT is still prolonged, may repeat in 2-3 hours (recalculate dose)

Time elapsed	Dose of protamine (mg) for every 100 units of heparin given
Immediately	1 mg
30 minutes	0.5 mg
>2 hours	0.25 – 0.375mg

      ii. For **SQ unfractionated heparin (UFH)** injection
         1. Consider protamine 1-1.5mg for every 100units of heparin in divided portions. May load with 25-50mg of protamine by slow IV push, then give remaining portion as a continuous IV infusion over 8-16 hours or the expected duration of heparin absorption. Maximum single dose of protamine = 50mg
      iii. Protamine administration considerations:
         1. Administer slow IV push over 10 minutes or via IVPB. Rapid administration may cause severe adverse effects such as hypotension and bradycardia.
         2. Maximum single dose should not exceed 50mg
         3. Consider pre-treating with corticosteroids and antihistamines in patients at risk for protamine allergy such as patients with: known fish allergy, prior protamine exposure (including protamine containing insulin), or history of vasectomy.

6. **REVERSAL OF ANTICOAGULATION WITH LOW-MOLECULAR WEIGHT HEPARIN (LMWH)** [9,10, 11]
   a. **Major/life threatening bleeding or for emergent intracranial intervention**
      i. For dalteparin (Fragmin) or enoxaparin (Lovenox) (t1/2 = ~6 hours)
         1. Consider protamine* (see table for dosing)
         2. Monitoring: if bleeding persists and the aPTT remains prolonged after 2-4 hours consider a repeat dose of 0.5mg protamine for each 1mg of enoxaparin or each 100 units of dalteparin
         3.

Time elapsed	Dose of protamine (mg) for every 1mg of enoxaparin given	Dose of protamine (mg) for every 100 units of dalteparin given
<8 hours	1 mg	1 mg
>8 hours	0.5mg	0.5mg

>12 hours	May not be required	May not be required

*This is an off-label use. Protamine only partially reverse the anticoagulant effect of LMWHs by 60-75%

7. REVERSAL OF ANTICOAGULATION WITH GP IIB/IIA AGENTS

a. <u>Major/life threatening bleeding or for emergent intracranial intervention</u>

i. For **abciximab** (Reopro) or **eptifibatide** (Integrillin)

1. Consider packed red blood cells, as well as fresh frozen plasma and platelet transfusion to increase coagulation
2. Monitoring: Monitor aPTT, INR, platelet counts and hematocrit. Severe thrombocytopenia has occurred with therapeutic use.

8. REVERSAL OF ANTICOAGULATION WITH ANTIPLATELET AGENTS

a. <u>Major/life threatening bleeding or for emergent intracranial intervention</u>

i. For **aspirin** or sustained release **aspirin+dipyridamole** – there is no reversal

ii. For **clopidogrel** (Plavix) , **prasugrel** (Effient), **ticagrelor** (Brilinta)

1. Desmopressin IVPB 0.3mcg/kg x 1
2. Prepare and transfuse 2 units of platelets

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ANTICOAGULANT REVERSAL QUICK REFERENCE TABLE

	Target of Therapy	Half-life	Duration of Effect	Monitoring Parameters	Pharmacologic Reversal	Delayed Clearance
Apixaban (Eliquis)	Factor X	6-12 hrs	2 – 4 days	PT	Limited: KCentra 50 units/kg	Renal Dysfunction
Argatroban	Thrombin	25-51 min	2 – 4 hrs	aPTT	Limited: FFP 15 mL/kg	Hepatic Dysfunction
Bivalirudin (Angiomax)	Thrombin	25-51 min	2 – 6 hrs	aPTT	Limited: FFP 15 mL/kg, Hemofiltration	Renal Dysfunction
Dabigatran (Pradaxa)	Thrombin	12 – 24 hrs	2 – 5 days	aPTT	Praxbind 5gm IVP	Renal Dysfunction
Enoxaparin (Lovenox)	Factor X and Thrombin	6 hrs	12 – 24 hrs	Factor Xa aPTT	0.5-1.0mg protamine per mg enoxaparin	Renal Dysfunction
Fondaparinux (Arixtra)	Factor X	17 – 21 hrs	2 – 5 days	Factor Xa	Factor VIIa 90 mcg/kg IV FFP 15 mL/kg	Renal Dysfunction
Heparin	Primarily Thrombin, some Factor X	1-2 hrs	4 – 6 hrs	aPTT	Protamine 1 mg per 100 units heparin max 50mg	None
Rivaroxaban (Xarelto)	Factor X	6-12 hrs	1 – 3 days	PT	Limited: KCentra 50 units/kg	Renal Dysfunction
Warfarin (Coumadin)	Vitamin K dependent clotting factors (II, VII, IX, X)	36 hrs	2 – 5 days	INR	Vitamin K 1-10mg KCentra 25-50 units/kg FFP 15ml/kg	None
Antiplatelet Agents						
Aspirin	Platelets (cyclo-oxygenase)	6 hrs	2 – 4 days	None	None	None
Clopidogrel (Plavix)	Platelets (ADP receptor)	6 hrs	5 – 7 days	None	None	None
Prasugrel (effient)	Platelets (ADP receptor)	8 hrs	5 – 9 days	None	None	None
Abciximab (Reopro)	GP IIB/IIIA Inhibitor	30 min	12 hrs	None	None Possible: KCentra FFP 15ml/kg	None
Eptifibatide (Integrillin)	GP IIB/IIIA Inhibitor	3 hrs	4 hrs	None	None Possible: KCentra FFP 15ml/kg	Renal Dysfunction
Some patients may be non-responders to antiplatelet therapy: consider platelet function assay testing if you suspect a non-responder.						

WARFARIN REVERSAL RECOMMENDATIONS BY CLINICAL SCENARIO

	Major Bleeding or Procedure/Surgery needed in 6 hours or less	Procedure/Surgery needed in 6 – 24 hours	Procedure/Surgery needed in greater than 24 hours or INR greater than 5 without bleeding
Oral Vitamin K	None	Vitamin K 2.5-10mg	Vitamin K orally
IV Vitamin K	Vitamin K 5 – 10 mg **slow** IV x 1 over 60 mins	Vitamin K 1-5 mg **slow** IV x 1 over 60 mins	None
PCC	Administer **KCentra** based on Table 1 below	None	None
Monitoring	INR 12 – 24 hours after vitamin K was given. INR 30 minutes after blood factor or FFP administration, then every 6 hours	INR 6 – 8 hours after vitamin K given	INR 12 – 24 hours after vitamin K was given.

Elevated INR, NO BLEEDING:		
INR	**Reversal Approach**	**Monitoring**
Between 3 and 10	☐ Lower warfarin dose or omit warfarin dose. ☐ If only minimally above therapeutic range, no dose reduction may be required. ☐ Resume warfarin at lower dose when INR therapeutic.	INR daily Hemoglobin/Hematocrit daily Signs/Symptoms of bleeding
GREATER than 10	☐ Hold warfarin therapy and give ***vitamin K 2.5-5mg orally*** ☐ May REPEAT vitamin K if necessary.	INR every 24 hrs after vitamin K was given or more frequently given risk of bleed. Hemoglobin/Hematocrit daily Signs/Symptoms of bleeding

Prothrombin Complex Concentrate (KCentra) Dosing Recommendations	**Pre-Treatment INR:**		
	Less than 4	**4 – 6**	**Greater than 6**
Dose of KCentra	25 units/kg	35 units/kg	50 units/kg
Maximum Dose	2500 units	3500 units	5000 units
Kcentra contains heparin and is contraindicated in patients with active heparin-induced thrombocytopenia (HIT). Max dose weight is 100kg			

Appropriate Dosing of Fresh Frozen Plasma (15 mL/kg) Patient Weight (kg)	**FFP Dose (units)**
Less than 50 or >200	Call blood bank for recommendations
50	4
60-79	5
80	6
90	7
100-119	8
120	9
130	10
140-159	11
160	12
170	13
180-199	14
200	15

TREATMENT OF SEVERE OR LIFE-THREATENING BLEEDING DUE TO:

FONDAPARINUX	**Monitoring**
☐ Factor VIIa 90 mcg/kg IV x1 ☐ FFP 15 mL/kg	Signs and symptoms of bleeding
Should correct without intervention in approximately 2 – 5 days for MOST patients. This duration may be longer in patients with renal impairment.	
DIRECT THROMBIN INHIBITORS	**Monitoring**
☐ **Argatroban**: FFP 15 mL/kg, may need to repeat if aPTT rises again ☐ **Bivalirudin:** Published experience using FFP and hemofiltration with limited success	aPTT 15 – 20 min after FFP, then every 4 hours
Should correct without intervention in approximately 2 – 6 hours for MOST patients. This duration may be longer in patients with renal impairment (bivalirudin) or hepatic impairment (argatroban). Note: Protamine and vitamin K will NOT reverse the effects of the DTIs	
DABIGATRAN	**Monitoring**
Option #1: Discontinue dabigatran ☐ If last dose was ingested less than 2 hours earlier - Charcoal (50g x 1) ☐ Creatinine clearance **greater than** 50 mL/min - anticoagulant effect of dabigatran will dissipate in 1 – 2 days ☐ Creatinine clearance **less than** 50 mL/min, anticoagulant effect of dabigatran will dissipate in 3 – 5 days	Signs and symptoms of bleeding aPTT at baseline. Consider monitoring aPTT 12-24hrs after Praxbind, if re-elevation of aPTT occurs along with clinically significant bleeding re-dose X1
Major Bleeding or need for urgent procedure/surgery **Option #2:** Direct dabigatran reversal ☐ Praxbind: 5gram dose rapid push (2- 2.5gm vials) reversal effect within minutes	
RIVAROXABAN	**Monitoring**
Option #1: Discontinue rivaroxaban ☐If last dose was ingested within 2-4 hours, charcoal may be considered (50g) ☐Creatinine clearance **greater than** 50 mL/min – anticoagulant effect of rivaroxaban will dissipate in 24-48 hours ☐Creatinine clearance **less than** 50 mL/min or in patients older than 65 years – anticoagulant effect of rivaroxaban will dissipate in 36 –72 hours	Signs and symptoms of bleeding PT and aPTT at baseline Consider monitoring PT and aPTT 15 min after administration of blood factors, and every 6 hours if needed
APIXABAN	
Option #1: Discontinue apixaban ☐Anticoagulant effect of apixaban will dissipate in 24-48 hours ☐If last dose was ingested within 2-4 hours, charcoal may be considered (50g). May repeat charcoal administration at 2 and 6 hours after ingestion (per apixaban package insert)	
Major Bleeding or need for urgent procedure or surgery **Option #2:** Attempt to reverse rivaroxaban or apixaban ☐Discontinue rivaroxaban or apixaban ☐ KCentra 50 units/kg	