Guidelines for the Management of Anticoagulant and Anti-Platelet Agent Associated Bleeding Complications in Adults

Purpose: To be used as a common tool for all practitioners involved in the care of patients who present with bleeding problems related to use of anticoagulant and anti-platelet agents. The guidelines were developed to represent available evidence from the literature. It is recognized that there may be instances where interventions not identified in these guidelines may be indicated. **These guidelines are not meant to supersede the clinical judgment of the treating physician.** For purposes of organization, the guidelines are arranged in a linear order from initial interventions through definitive care. The clinician should recognize that treatment phases may overlap and interventions will occur concurrently.

Quick Index to Reversal Recommendations

Anticoagulant Medications

Thrombolytics

Anti-Platelet Medications

General Principles of Management of Anticoagulant-Associated Bleeding

HISA-HT

Hold further doses of anticoagulant (or anti-platelet agent)

Investigate for bleeding source

Supportive treatment:

- volume resuscitation, inotropes as needed
- optimize oxygenation

Consider ***A***ntidote (e.g. Vitamin K, protamine)

Hemostatic measures:

- Local or topical agents (fibrin glue, sealants, hemostatic agents, topical aminocaproic acid or tranexamic acid)
- Systemic hemostatic measures (intravenous tranexamic acid)
- Surgical intervention
- Interventional radiology (e.g. embolization)

Transfusion

- Packed Red Blood Cells, platelets, Fresh Frozen Plasma (FFP), cryoprecipitate as indicated
- Factor concentrates: Prothrombin Complex Concentrate (4-Factor PCC), Recombinant Factor 7a, FEIBA

Anticoagulant Reversal Agents/Procoagulants/4-Factor PCC/Anti-Fibrinolytics

Agent	Dose	Comments
Vitamin K	1-10 mg IV/PO, **not** SQ or IM	• Infusion reactions rare (anaphylaxis): administer over 30 min • Takes 6 hrs (IV) to 24 hrs (PO) to reverse warfarin • Large doses can cause warfarin resistance on resumption • Use smaller doses if mechanical heart valve (1 -2 mg)
Protamine sulfate	12.5-50 mg IV	• Full reversal of unfractionated heparin • Heparin: 1mg for every 100 units of heparin remaining • Dalteparin: 1mg for every 100 anti-Xa (10a) international units of dalteparin • Enoxaparin: 1mg for every 1mg of enoxaparin given in previous 8 hrs • Tinzaparin: 1mg for every 100 anti-Xa (10a) international units of tinzaparin • 60-80% reversal of LMWH • No reversal for fondaparinux • May require repeat dose after a few hours
Platelets	1 apheresis unit	• Raise platelet count by 10-30 x 10^9/L
Frozen Plasma (FFP)	10-30 mL/kg (1 unit = ~250ml)	• Replaces all coagulation factors, but cannot fully correct ○ Hemostasis usually requires factor levels ~30% ○ Factor IX (9) may only reach 20% • Risk of acute lung injury and circulatory overload • Large volume, takes hours to thaw and infuse, must be type specific • May need repeat dose after 6 hours

4- Factor PCC (Kcentra) – *preferred*
 	
PCC = prothrombin complex concentrates
	<u>Dosing:</u>
	INR 2-3.9: 25 units/kg (max of 2500 units) + Vitamin K 2.5mg IVPB
	
	INR 4-6: 35 units/kg (max of 3500 units) + Vitamin K 5mg IVPB
	
	INR>6: 50 units/kg (max of 5000 units) + Vitamin K 10mg IVPB
	
	<u>Rate of infusion</u>:
	0.12 ml/kg/min (~ 3 units/kg/min) up to max of 8.4 ml/min (~ 210 units/min)
		• Approved for rapid reversal of warfarin in bleeding patients.
		• Must be given with IV Vitamin K concurrently when used for warfarin reversal.
		• Do NOT give repeat dose.
		• Risk of thrombosis is low.
		• Contraindicated in active HIT with thrombosis. **CAUTION: contains small amount of heparin so DO NOT use if patient allergic to heparin**
		• 4-Factor Content: 500 units of Factor IX contains:
		  • Factor II (2): 380-800 units
		  • Factor VII (7): 200-500 units
		  • Factor X (10): 500-1020 units
		  • Protein C and S
		  • Heparin
		• Dose is based on patient's weight and pre-dose INR
		• Measure INR prior to treatment close to the time of dosing (Pharmacy must verify INR before dispensing) – stored in pharmacy
		• Correction of Vitamin K antagonist- impairment of hemostasis is reached at the latest 30 min after the injection and will persist for ~ 6-8 hrs. However, the effect of vitamin K (if given simultaneously) is usually achieved within 4-6 hrs. Thus, repeat treatment with human 4-Factor PCC is NOT usually required when vitamin K has been given. Monitoring of INR during treatment is mandatory.

Idarucizumab (Praxbind)	5 grams IV (2.5 grams/50 ml x 2 doses)	• Infuse each 2.5 grams/50 ml premixed vial – each vial to be administered over 5-10 min
FEIBA (not currently stocked at Lapeer) – anti-inhibitor coagulant complex	50 units/kg	• Small volume infusion (20-50mls), Max rate: 2 units/kg/min • No clinical trials for this off-label use • High dose (100 units/kg) & repeat doses within 12 hours should be avoided

The following may ONLY to be used at the direction of Hematology, Trauma, or Intensivists		
Aminocaproic acid (Amicar)	4-5 grams over one hour	• Loading dose 4-5 grams over one hour. • Followed by 1 gram/hr IV infusion for ~ 8 hrs or until bleeding is controlled (max of 30 grams/day)
Tranexamic Acid	10-30 mg/kg	• Loading dose: 1 gram over 10min followed by maintenance dose of 1 gram over next 8 hrs (125 mg/hr)
Desmopressin (DDAVP)	0.3-0.4 mcg/kg	• Infuse over 30 minutes in 50 ml saline
Recombinant Factor 7 a (NovoSeven)	15-30 mcg/kg Trauma dose: 100-200 mcg/kg x 1 dose	• Infusion of small volume over 10-20 minutes (may require multiple small infusions to make total dose) • Rapid INR correction due to warfarin, but may not correct bleeding because only restores Factor 7a. • Unknown value in correcting bleeding with direct thrombin inhibitors, anti-Xa (10a) inhibitors, clopidogrel and related drugs • **Risk of thrombosis 5-10% with higher doses** • Studies fail to show mortality benefit • If patient still bleeding, may consider dose increase to 30-60 mcg/kg, if dose is to be repeated. • May need repeat dose after 2 hours

Definitions Used for Reversal Situations

Non-urgent: **Reversal is elective (procedures > 12-24 hours)**
Urgent (without bleeding): **Reversal needed within hours (6-12 hours)**
Emergent(with bleeding): **Emergency Reversal (< 6 hours)**

Reversal of Warfarin (Coumadin) **		
Non-Urgent	Urgent (No Major Bleeding)	Emergent (Major bleeding or surgery for life threatening condition within 6 hours)
• Stop warfarin 5 days prior to procedure • Check INR 1-2 days prior • If INR greater than 1.9 administer Vitamin K 1.25-2.5 mg PO • For supra-therapeutic INR, consider Vitamin K 5-10 mg PO • Consult cardiology if patient has mechanical heart valve (high risk of thrombosis)	• Stop warfarin • If procedure can be delayed 6-24 hours, vitamin K 1.25-10 mg PO or low-dose vitamin K 1-2.5 mg IV • Higher doses of vitamin K 5-10 mg IV may be needed depending on initial INR results and post-reversal INR which is checked 24 hrs after dose • Higher doses of vitamin K may increase need to and duration of bridging therapy (e.g. enoxaparin, IV heparin) if warfarin is to be restarted • Consider 1-2 units of FFP for INR greater than 4.5. Repeat every 6-12 hours until 2 successive INR results are at desired target. • Consult cardiology if patient has mechanical heart valve (high risk of thrombosis)	• Stop warfarin • HISA-HT • Give Vitamin K and/or FFP – or Kcentra if pt not a candidate for FFP or life-threatening bleed • High dose vitamin K 5-10 mg IV; repeat every 12 hours as needed • Higher doses of vitamin K may increase need to and duration of bridging therapy (e.g. enoxaparin, IV heparin) if warfarin is to be restarted • Consider 2-4 units of FFP depending on urgency of situation; recheck INR in 8 hrs • 4-Factor PCC (Kcentra). **USE DOSING PROTOCOL PER PHARMACY (page 4-5)** • Do not repeat dose of Kcentra. • Consult cardiology if patient has mechanical heart valve (high risk of thrombosis)

** According to the European Union Stroke Initiative (EUSI), patients with oral anticoagulation treatment (OAT) associated ICH and an INR above 1.4 should have OAT discontinued and the INR normalized with 4-Factor PCCs or FFP in addition to intravenous infusion of vitamin K. Refer to hospital-specific Warfarin Toxicity Management Guidelines for further information.

Reversal of Heparin

Protamine sulfate is used to reverse the effects of Heparin:

- **Heparin (half life of 1-2 hrs): 1mg of protamine sulfate for every 100 units of IV heparin remaining (infused in last 2-3 hrs)**
  - Example: 20-30mg if heparin infused at 1000 units/hr
  - Check PTT in 2 hrs and consider more protamine if still prolonged

**** Half-life is longer with subcutaneous administration for all agents so may require monitoring with PTT (heparin) every 3 hrs with repeat protamine (decrease dose to 0.5mg increments though) for heparin if bleeding continues. ****

Non-Urgent	Urgent (No Major Bleeding)	Emergent (Major bleeding/surgery for life threatening condition within 6 hrs)
• Hold 4 hrs prior to procedure	• Wait 2-4 hrs if possible • Consider protamine sulfate if delay not possible for high bleeding risk procedures – will reverse 60% of activity (e.g. 1mg for every 100 units of IV heparin remaining/infused in last 2-3 hrs)	• HISA-HT • Protamine sulfate (e.g. 1mg for every 100 units of IV heparin remaining/infused in last 2-3 hrs) • No proven role for Recombinant Factor 7a or 4-factor PCC. • No role for Frozen Plasma (FFP)

Reversal of LMWH (Enoxaparin, Dalteparin, Tinzaparin) and Fondaparinux+

Protamine sulfate is used to reverse the effects of LMWH:

- **Enoxaparin (half-life of 4.5 hrs): 1mg of protamine sulfate for every 1mg of Enoxaparin given in previous 8 hrs**
- **Dalteparin (half-life of 2.2 hrs): 1mg of protamine sulfate for every 100 units of Dalteparin given in previous 8 hrs**
- **Tinzaparin (half-life of 3.9 hrs): 1mg of protamine sulfate for every 100 units of Tinzaparin given in previous 8 hrs**

**** Half-life is longer with subcutaneous administration for all agents so may require monitoring with anti-Xa (10a) level (LMWH) every 3 hrs with repeat protamine (decrease dose to 0.5mg increments though) for LMWH if bleeding continues. ****

Enoxaparin (Lovenox); Dalteparin (Fragmin); Tinzaparin (Innohep)

Non-Urgent	Urgent (No Major Bleeding)	Emergent (Major bleeding/surgery for life threatening condition within 6 hrs)

• Hold day of procedure
• Once-daily regimens
  ○ May consider ½ dose day prior to procedure
• Twice-daily regimens
  ○ Hold evening dose day prior and morning of procedure
	• Wait 12-24 hours if possible
	• Consider protamine sulfate if delay not possible for high bleeding risk procedures – will reverse 60% of activity (e.g. 1mg for every 1 mg enoxaparin given in previous 8 hrs)
		• HISA-HT
		• Protamine sulfate (e.g. 1mg for every 1 mg of enoxaparin given in previous 8 hrs)
		• No proven role for Recombinant Factor 7a or 4-Factor PCC.
		• No role for Frozen Plasma (FFP)

+Fondaparinux has no specific antidote. Consider Recombinant Factor 7a (30 µg/kg) for life-threatening bleeding (BUT NO proven benefit). **Consult with Hematology.**

Reversal of Bivalirudin (Angiomax) and Argatroban		
Non-Urgent	Urgent (No Major Bleeding)	Emergent (Major bleeding or surgery for life threatening condition within 6 hours)
• Short half-life (25 min) • Cleared by the kidneys (20%) and by proteolytic cleavage • Stop drug	• Stop drug • If procedure can be delayed, delay until aPTT or Activated Clot Time (ACT) return to normal.	• HISA-HT • Stop drug (no antidote) • Drug may be removed by hemodialysis but generally not indicated due to short half-life • Consider Recombinant Factor 7a (no proven benefit though) only for life-threatening intracranial hemorrhage • Consider Frozen Plasma (FFP) to competitively antagonize thrombin inhibition – **Consult with Hematology**.

<table>
<tr><th colspan="3">Reversal of Dabigatran (Pradaxa)</th></tr>
<tr><th>Non-Urgent [a]</th><th>Urgent (No Major Bleeding)</th><th>Emergent (Major bleeding or surgery for life threatening condition within 6 hours)</th></tr>
<tr><td rowspan="3">Creatinine Clearance > 50 ml/min:
- Hold drug x 1 day prior to minor surgery
- Hold drug x 2 days prior to major surgery</td><td>Hold drug and may check PTT</td><td>Hold drug and check PTT</td></tr>
<tr><td>Treat with activated charcoal if ≤ 2 hrs since last dose [b]</td><td>Treat with activated charcoal if ≤ 2 hrs since last dose [b]</td></tr>
<tr><td>Optimize renal function with IV fluids to maintain diuresis [c]</td><td>Optimize renal function with IV fluids to maintain diuresis [c]</td></tr>
<tr><td rowspan="2">Creatinine Clearance 30-50 ml/min:
- Hold drug x 2 days prior to minor surgery
- Hold drug x 4 days prior to major surgery</td><td>If PTT is normal: unlikely that dabigatran is contributing to bleeding
- Reassess patient
- Repeat coagulation tests</td><td>If PTT is normal: unlikely that dabigatran is contributing to bleeding
- Reassess patient
- Repeat coagulation tests</td></tr>
<tr><td rowspan="3">If PTT is elevated: dabigatran may be contributing to bleeding (no antidote)
- HISA-HT
- Consider prolonged hemodialysis (> 2 hrs)
- Reassess patient
- Repeat abnormal coagulation tests</td><td rowspan="2">If PTT is elevated: dabigatran may be contributing to bleeding:
- HISA-HT
Idarucizumab (Praxbind) is antidote for dabigatran:
• Dose is 5 grams (2 x 2.5 grams/50 ml) infusion for patients who have received dabigatran in previous 36 hrs.
• Each 2.5 grams/50 ml infusion is to be administered over 5-10 min
• Restricted to hematology, neurosurgery or gastroenterology for life-threatening bleeds only
May also consider the following:
- Use prolonged hemodialysis (> 2 hrs)
- Reassess patient.
- Repeat abnormal coagulation tests.</td></tr>
<tr><td>Creatinine Clearance < 30 ml/min:
- Hold drug x 4 days prior to minor surgery
- Hold drug x 6 days prior to major surgery</td></tr>
<tr><td></td><td>May consider TEG (thromboelastography) if available to further assess bleeding risk – not done here at McLaren-Lapeer though</td></tr>
</table>

[a] May consider longer hold times for major surgery, placement of spinal or epidural catheter or mediport.

[b] Contraindicated in setting of GI bleeding .

[c] Dabigatran is primarily excreted in the urine; therefore, need adequate diuresis.

[d] 4-Factor PCC may not lower PTT.

<table>
<tr><th colspan="3">Reversal of Rivaroxaban (Xarelto)</th></tr>
<tr><td>Non-Urgent [a]</td><td>Urgent (No Major Bleeding)</td><td>Emergent (Major bleeding or surgery for life threatening condition within 6 hours)</td></tr>
<tr><td rowspan="2">Creatinine Clearance > 50 ml/min:
- Hold drug x 1 day prior to minor surgery
- Hold drug x 2 days prior to major surgery</td><td>Hold drug and may check PT/INR and anti Xa level (sent out)</td><td>Hold drug and check PT/INR and anti Xa level (sent out)</td></tr>
<tr><td>Treat with activated charcoal if ≤ 2 hrs since last dose [b]</td><td>Treat with activated charcoal if ≤ 2 hrs since last dose [b]</td></tr>
<tr><td rowspan="2">Creatinine Clearance 30-50 ml/min:
- Hold drug x 1-2 days prior to minor surgery
- Hold drug x 3-4 days prior to major surgery</td><td>4-Factor PCC will be of no benefit if PT/INR or anti-Xa (10a) level is normal because there is nothing for 4-Factor PCC (Kcentra) to normalize; unlikely that rivaroxaban is contributing to bleeding
- Reassess patient
- Repeat coagulation tests</td><td>4-Factor PCC will be of no benefit if PT/INR or anti-Xa (10a) level is normal because there is nothing for 4-Factor PCC (Kcentra) to normalize; unlikely that rivaroxaban is contributing to bleeding
• Reassess patient
• Repeat coagulation tests
• Medically manage patients as if they were not on an anticoagulant.</td></tr>
<tr><td>Creatinine Clearance < 30 ml/min:
- Hold drug x 2 days prior to minor surgery
- Hold drug x 4 days prior to major surgery</td><td>If PTT is elevated: rivaroxaban may be contributing to bleeding
- HISA-HT
- No antidote available
- Reassess patient.
- Repeat abnormal coagulation tests.</td><td>If PTT is elevated: rivaroxaban may be contributing to bleeding:
• HISA-HT
• No antidote available but may consider the following: 4-Factor PCC (Kcentra) 50 units/kg
• Reassess patient.
• Repeat abnormal coagulation tests.
• Medically manage patients as if they were not on an anticoagulant.</td></tr>
</table>

[a] May consider longer hold times for major surgery, placement of spinal or epidural catheter or mediport.

[b] Contraindicated in setting of GI bleeding .

<table>
<tr><th colspan="3">Reversal of Apixaban (Eliquis)</th></tr>
<tr><td>Non-Urgent [a]</td><td>Urgent (No Major Bleeding)</td><td>Emergent (Major bleeding or surgery for life threatening condition within 6 hours)</td></tr>
<tr><td rowspan="2">Creatinine Clearance > 50 ml/min:
- Hold drug x 1 day prior to minor surgery
- Hold drug x 2 days prior to major surgery</td><td>Hold drug and may check PT/INR and anti Xa level (sent out)</td><td>Hold drug and check PT/INR and anti Xa level (sent out)</td></tr>
<tr><td>Treat with activated charcoal if ≤ 2 hrs since last dose [b]</td><td>Treat with activated charcoal if ≤ 2 hrs since last dose [b]</td></tr>
<tr><td rowspan="2">Creatinine Clearance 30-50 ml/min:
- Hold drug x 1-2 days prior to minor surgery
- Hold drug x 3-4 days prior to major surgery</td><td>4-Factor PCC will be of no benefit if PT/INR or anti-Xa (10a) level is normal because there is nothing for 4-Factor PCC (Kcentra) to normalize; unlikely that apixaban is contributing to bleeding
- Reassess patient
- Repeat coagulation tests</td><td>4-Factor PCC will be of no benefit if PT/INR or anti-Xa (10a) level is normal because there is nothing for 4-Factor PCC (Kcentra) to normalize ;unlikely that apixaban is contributing to bleeding
• Reassess patient
• Repeat coagulation tests
• Medically manage patients as if they were not on an anticoagulant.</td></tr>
<tr><td>Creatinine Clearance < 30 ml/min:
- Hold drug x 2 days prior to minor surgery
- Hold drug x 4 days prior to major surgery</td><td rowspan="2">If PTT is elevated: apixaban may be contributing to bleeding
- HISA-HT
- No antidote available
- Reassess patient.
- Repeat abnormal coagulation tests.</td><td rowspan="2">If PTT is elevated: apixaban may be contributing to bleeding:
• HISA-HT
• No antidote available but may consider the following: 4-Factor PCC (Kcentra) 50 units/kg
• Reassess patient.
• Repeat abnormal coagulation tests.
• Medically manage patients as if they were not on an anticoagulant.</td></tr>
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</table>

[a] May consider longer hold times for major surgery, placement of spinal or epidural catheter or mediport.

[b] Contraindicated in setting of GI bleeding .

<table>
<tr><th colspan="3">Reversal of Edoxaban (Savaysa)</th></tr>
<tr><td>Non-Urgent [a]</td><td>Urgent (No Major Bleeding)</td><td>Emergent (Major bleeding or surgery for life threatening condition within 6 hours)</td></tr>
<tr><td rowspan="2">Creatinine Clearance > 50 ml/min:
- Hold drug x 1 day prior to minor surgery
- Hold drug x 2 days prior to major surgery</td><td>Hold drug and may check PT/INR and anti Xa level (sent out)</td><td>Hold drug and check PT/INR and anti Xa level (sent out)</td></tr>
<tr><td>Treat with activated charcoal if ≤ 2 hrs since last dose [b]</td><td>Treat with activated charcoal if ≤ 2 hrs since last dose [b]</td></tr>
<tr><td rowspan="2">Creatinine Clearance 30-50 ml/min:
- Hold drug x 1-2 days prior to minor surgery
- Hold drug x 3-4 days prior to major surgery</td><td>4-Factor PCC will be of no benefit if PT/INR or anti-Xa (10a) level is normal because there is nothing for 4-Factor PCC (Kcentra) to normalize; unlikely that edoxaban is contributing to bleeding
- Reassess patient
- Repeat coagulation tests</td><td>4-Factor PCC will be of no benefit if PT/INR or anti-Xa (10a) level is normal because there is nothing for 4-Factor PCC (Kcentra) to normalize ;unlikely that edoxaban is contributing to bleeding
• Reassess patient
• Repeat coagulation tests
• Medically manage patients as if they were not on an anticoagulant.</td></tr>
<tr><td rowspan="2">Creatinine Clearance < 30 ml/min:
- Hold drug x 2 days prior to minor surgery
- Hold drug x 4 days prior to major surgery</td><td rowspan="2">If PTT is elevated: edoxaban may be contributing to bleeding
- HISA-HT
- No antidote available
- Reassess patient.
- Repeat abnormal coagulation tests.</td><td rowspan="2">If PTT is elevated: edoxaban may be contributing to bleeding:
• HISA-HT
• No antidote available but may consider the following: 4-Factor PCC (Kcentra) 50 units/kg
• Reassess patient.
• Repeat abnormal coagulation tests.
• Medically manage patients as if they were not on an anticoagulant.</td></tr>
<tr><td></td></tr>
</table>

[a] May consider longer hold times for major surgery, placement of spinal or epidural catheter or mediport.

[b] Contraindicated in setting of GI bleeding .

Reversal of Alteplase (Activase)		
General Considerations	Spontaneous ICH – Immediate Measures	Emergent (Major bleeding or surgery for life threatening condition within 6 hours)

• No definitive antidote available
• Stop infusion of thrombolytics
• Consider Intracranial Hemorrhage (ICH) if patient has any of the following (during infusion or up to 24 hours after alteplase infusion):
  ○ New acute severe headache
  ○ Sudden increase in blood pressure
  ○ Decrease in mentation
  ○ Greater than 3 point worsening on the NIH Stroke Scale
• Obtain STAT head CT (or alternative imaging if other location is suspected)
• If hemorrhage confirmed on CT:
  ○ Send STAT labs: CBC, Fibrinogen, Platelets, PT, PTT, INR, D-dimer, Type & Cross
  ○ Repeat fibrinogen level every 6 hours
	• Administer cryoprecipitate 10 units
	• Revise blood pressure parameters
	• Check fibrinogen levels after infusion of cryoprecipitate
	  ○ If fibrinogen level < 150 mg/dl: consider additional dosing with cryoprecipitate
	  ○ If cryoprecipitate cannot be given: consider aminocaproic acid (Amicar) or tranexamic acid
	
	Additional Considerations:
	• Platelet transfusion (particularly if patient has thrombocytopenia): 1 apheresis unit *
	• Aminocaproic acid (Amicar) 5 gram IV over 1 hr
	  ○ May consider maintenance dose if bleeding continues: 1 gram/hr IV infusion up to 23 hours
	• Tranexamic acid: 10-15 mg/kg (max 2000 mg) IV over 20 minutes
	  ○ Repeat dose after 2 hours if bleeding continues: 10 mg/kg IV
		• Administer cryoprecipitate 10 units
		• Check fibrinogen levels after infusion of cryoprecipitate
		  ○ If fibrinogen level < 150 mg/dl: consider additional dosing with cryoprecipitate
		  ○ If cryoprecipitate cannot be given: consider aminocaproic acid (Amicar) or tranexamic acid
		
		Additional Considerations:
		• Platelet transfusion (particularly if patient has thrombocytopenia): 1 apheresis unit *
		• Aminocaproic acid (Amicar) 5 gram IV over 1 hr
		  ○ May consider maintenance dose if bleeding continues: 1 gram/hr IV infusion up to 23 hours
		  ○ For uncontrolled, life-threatening bleeding: may consider Aminocaproic acid 10 gram IV in 250 ml NS over 1 hour as a last resort (Note: there is a significant risk of pathologic thrombosis with Aminocaproic acid)
		• Tranexamic acid: 10-15 mg/kg (max 2000 mg) IV over 20 minutes
		  ○ Repeat dose after 2 hours if bleeding continues: 10 mg/kg IV
		• Serious systemic hemorrhage should be treated in a similar manner. Manually compress site of bleeding, and consult appropriate additional services to consider mechanically occluding arterial or venous sources of medically uncontrollable bleeding.

*** 1 apheresis unit of platelets ~ 4-6 units of platelets**

Antiplatelet Agent Reversal

*** Consult Cardiology for All Patients with Cardiac Stents ***

COX-1 Inhibitors: Aspirin, Aspirin/Dipyridamole (Aggrenox), Dipyridamole (Persantine)

P2Y12 Inhibitors: Clopidogrel (Plavix), Ticlopidine (Ticlid), Prasugrel (Effient), Ticagrelor (Brilinta)

GPIIbIIIa Inhibitors: Eptifibatide (Integrilin), Tirofiban (Aggrastat)

General Considerations

1. Cardiology Consultation *Must consider indication for use in decision to reverse.*
    a. Consult cardiology for ALL patients with coronary stents
    b. Risk of coronary stent occlusion (which can be fatal) within 3 months of bare metal stent implantation
        - Period of risk is likely longer for drug-eluting stents, perhaps up to one year.
    c. Risk of reversal in some cases may be worse than risk of bleeding.
2. Half-lives
    a. Clopidogrel, ticlopidine, dipyridamole, prasugrel, ticagrelor: 7-10 hours
    b. Low-dose aspirin (150 mg daily): 2-4.5 hours
    c. Overdose aspirin (greater than 4,000 mg): 15-30 hours
3. Reversibility of anti-platelet effect
    a. Aspirin, clopidogrel, ticlopidine, and prasugrel inhibit platelet function for lifetime of platelet. Inhibition takes 7-10 days to resolve as new platelets are generated.
    b. Ticagrelor is a reversible inhibitor, so platelet function normalizes after drug clearance. Half-life is 7-9 hours for drug and its active metabolite.
4. Circulating drug or active metabolites can inhibit transfused platelets.
5. **Platelet function testing is recommended prior to procedure**.
6. Please see separate recommendations for patients on dual antiplatelet therapy (DAPT) with bare metal (BMS) or drug-eluting stents (DES).

Reversal of Aspirin and Aspirin/Dipyridamole (Aggrenox)		
Non-Urgent	Urgent (Not Bleeding)	Emergent (Major bleeding or surgery for life threatening condition within 6 hours)
Discontinue drug 2 days prior to procedure Do NOT discontinue in patients treated for coronary or cerebrovascular disease – cardiology consult recommended for these patients.	• Laboratory testing to evaluate platelet function (e.g. Platelet factor assay)	• HISA-HT • Laboratory testing to evaluate platelet function (e.g. Platelet factor assay) • Consider platelet transfusion (1 apheresis unit *) for critical neurosurgery/eye surgery ONLY; usually not necessary • Recommend hematology consult

*** 1 apheresis unit of platelets ~ 4-6 units of platelets**

Reversal of P2Y12 Inhibitors (Clopidogrel, Ticlopidine, Prasugrel, Ticagrelor)		
Non-Urgent	Urgent (Not Bleeding)	Emergent (Major bleeding or surgery for life threatening condition within 6 hours)
Discontinue drug 5-10 days prior to procedure	• Laboratory testing to evaluate platelet function • Consider platelet transfusion (1 apheresis unit *) if > 40% inhibited prior to high risk bleeding procedures Recommend hematology consult • Recommend cardiology consult	• HISA-HT • Laboratory testing to evaluate platelet function • Platelet transfusion (1 apheresis unit *) if > 40% inhibited; 2 units if critical neurosurgery/eye surgery or if dual agent therapy • Recommend hematology consult • Recommend cardiology consult

*** 1 apheresis unit of platelets ~ 4-6 units of platelets**

Reversal of GP IIb/IIIa Inhibitors (Eptifibatide and Tirofiban)		
Non-Urgent	Urgent (Not Bleeding)	Emergent (Major bleeding or surgery for life threatening condition within 6 hours)
Discontinue drug; short half-lives so drug will be cleared in 2-4 hours	• Wait 2-4 hours for elimination of drug • If platelet count < 20,000/µl, consider transfusion of 1 apheresis unit * of platelets (Eptifibatide rarely associated with thrombocytopenia) • Recommend hematology consult • Recommend cardiology consult	• HISA-HT • Platelet transfusion (1 apheresis unit *) if intervention is truly emergent or serious bleeding • Recommend hematology consult • Recommend cardiology consult

*** 1 apheresis unit of platelets ~ 4-6 units of platelets**

Anticoagulant Conversion Chart		
Current Anticoagulants	Anticoagulant to be Converted to	Procedure
Warfarin (INR 2-3)	Dabigatran	Discontinue warfarin and start dabigatran when INR is less than 2.
Dabigatran	Warfarin (INR 2-3)	• CrCl greater than 50 ml/min: start warfarin 3 day before stopping dabigatran • CrCL 31-50 ml/min: start warfarin 2 days before stopping dabigatran • CrCL 15-30 ml/min: start warfarin 1 day before stopping dabigatran • CrCl less than 15 ml/min: no recommendation
LMWH, fondaparinux, IV heparin	Dabigatran	• Start dabigatran when the next dose of LMWH, fondaparinux or heparin would have been due. • Start dabigatran at same time as discontinuation of heparin infusion.
Dabigatran	LMWH, fondaparinux, IV heparin	• CrCL greater than 30 ml/min: start 12 hours after last dose of dabigatran • CrCL less than 30 ml/min: start 24 hours after last dose of dabigatran *(not fondaparinux)*
Warfarin	Rivaroxaban Apixaban Edoxaban	• Discontinue warfarin • Start rivaroxaban/apixaban/edoxaban when the INR is less than 3 to avoid periods of inadequate anticoagulation.
Rivaroxaban Apixaban Edoxaban	Warfarin	• Stop rivaroxaban/apixaban/edoxaban and start warfarin with a full anticoagulant bridging dose of LMWH or fondaparinux. • Continue both warfarin and anticoagulant bridge for a minimum of 5 days and until the INR is within the desired therapeutic range.
LMWH, fondaparinux, IV heparin	Rivaroxaban Apixaban Edoxaban	• Start rivaroxaban/apixaban/edoxaban when the next dose of LMWH, fondaparinux or heparin would have been due. • Start rivaroxaban/apixaban/edoxaban at same time as discontinued of heparin infusion.
Rivaroxaban Apixaban Edoxaban	LMWH, fondaparinux, IV heparin	• Start LMWH, fondaparinux or heparin when the next dose of rivaroxaban/apixaban/edoxaban would have been due.

Abbreviations: CrCl – creatinine clearance; INR international normalized ratio, LMWH = low-molecular-weight-heparin
Warfarin (Coumadin); Dabigatran (Pradaxa); Rivaroxaban (Xarelto); Apixaban (Eliquis); Edoxaban (Savaysa); Fondaparinux (Arixtra)

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