Anticoagulation Reversal Guideline for Adults

Antithrombotic reversal strategies should be limited to clinical situations (i.e. life-threatening bleeding) where the immediate need for anticoagulant reversal outweighs the risk of thrombosis (either from the reversal agent itself or normalization of coagulation in a patient with underlying thromboembolic risk).

These recommendations are meant to serve as general guidelines and should not replace clinical judgment. Always seek input from the appropriate specialists when indicated and include the patient and/or family in shared decision making when possible.

This document is not meant to guide selection of patients for reversal therapies. Please refer to appropriate national guidelines to aide decision-making regarding need for reversal, if warranted.

1. *ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants*
2. *Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine*

All indications for anticoagulation are considered, including atrial fibrillation, venous thromboembolism, prosthetic cardiac valves, and intracardiac thrombus. **Mechanical circulatory support devices, including temporary or permanent ventricular assist devices (i.e. LVADs), are excluded from this document.**

Whenever possible, anticoagulation should be resumed in a timely manner to avoid thromboembolic complications related to the underlying indication for anticoagulation. This guideline does not provide recommendations on resuming anticoagulation.

References:

- Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Experts Consensus Decisions Pathways. *J Am Coll Cardiol*. 2017 Dec 19;70(24):3042-3067.
- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46.

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Definition of Critical, Major, and Nonmajor Bleeding

NOTE:

- Risks of reversal agents can be significant (i.e. anaphylaxis, rebound thrombosis)
- Reduction in the risk of bleeding has not been proven with most reversal agents and experience with agents and dosing is limited
- Properties (i.e. half-life, duration of action) of reversal agents/antithrombotics should be considered when planning subsequent doses or sustained reversal

Assess the severity of bleeding:

1. Is the bleeding at a critical site (Table 1)?
2. Does the patient have a hemodynamically unstable bleed?
    - Mean arterial pressure (MAP) <65 mmHg (preferred measurement), or
    - Systolic blood pressure <90 mmHg, a decrease of >40 mmHg, or orthostatic blood pressure changes
    - Surrogate markers for organ perfusion (i.e. urine output) can be used
3. Is there clinically overt bleeding with a hemoglobin drop of ≥2 g/dL?

Definitions:

- **Major bleeding:** any answer YES to questions 1-3 above
- **Nonmajor bleeding:** answer NO to all 3 questions above

Table 1. Critical Site Bleeds

Type of Bleed	Includes
Intracranial hemorrhage	Intraparenchymal, subdural, epidural, subarachnoid
Other central nervous system hemorrhage	Intraocular, intra- or extra-axial spinal hemorrhage
Pericardial tamponade	
Airway	Posterior epistaxis
Hemothorax, Intra-abdominal, retroperitoneal bleeding	
Extremity bleeds	Intramuscular, intra-articular bleeds

References:

- Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Experts Consensus Decisions Pathways. *J Am Coll Cardiol*. 2017 Dec 19;70(24):3042-3067.

Vitamin K Antagonists: Warfarin (Coumadin®)

- Warfarin may be held, or reduced, with INR correction in 2-5 days for MOST patients. Cause of elevated INR should be investigated.
- Full effect of vitamin K occurs approximately 24 hours after administration. Partial effects may be seen in 6-12 hours, thus other therapies may be necessary if rapid reversal is warranted.
  - DO NOT give subcutaneously or intramuscularly due to erratic absorption
- Prothrombin Complex Concentrate (PCC) or activated PCC (aPCC) should only be used when rapid reversal is indicated (refer to the Kcentra® Ordering Decision Tree).

Pharmacokinetics/Dynamics

Agent	Mechanism	Onset	Duration of Action	Notes
Antithrombotic Agent				
Warfarin (Coumadin®)	Inhibits factors VII, IX, X, II, proteins C and S	--	2-5 days	
Reversal Agents				
Fresh Frozen Plasma (FFP)	Contains factors VII, IX, X, II (diluted), fibrinogen, proteins C and S	1-4 hours	≤6 hours	• Inherent INR of 1.6 • Large administration of volume (200 mL per unit)
Vitamin K (phytonadione)	Cofactor for hepatic production of factors VII, IX, X, II	6-10 hours (PO) 1-2 hours (IV)	24-48 hours (PO) 12-14 hours (IV)	• PO is preferred for patients with nonmajor bleeding • IV should be ordered only if patient has major bleeding, or needs an emergent procedure (≤6 hours) • Duration depends on INR and dose administered
PCC (Kcentra®)	Contains factors, including VII, IX, X, II (at a concentration 25x FFP)	5-15 minutes	6-8 hours	• Contains heparin – contraindicated in patients with HIT • May need to be approved by Blood Bank pathologist (see Operational Standard 2.3 – Pharmacy Clotting Factor Distribution) ○ Refer to Kcentra® Ordering Decision Tree • Contraindicated in disseminated intravascular coagulation (DIC) due to high risk of thrombosis
aPCC (FEIBA®)	Contains factors VIIa (activated), IX, X and II	15-30 minutes	8-12 hours	• Consider use in patients with HIT • Higher thrombotic risk due to activated factor VII • May need to be approved by Blood Bank pathologist (see Operational Standard 2.3 – Pharmacy Clotting Factor Distribution)

Management of Warfarin-Related Bleeding

INR/Clinical Scenario	Bleeding	Intervention	Monitoring
INR supratherapeutic but <4.5	No	Lower or omit next dose	Recheck INR the next day
INR 4.5-10.0	No	Lower or omit next dose	Recheck INR the next day
INR >10.0	No	PO vitamin K 2.5-5mg (IV if unable to tolerate PO)	Recheck INR the next day
Nonmajor bleeding (NOT requiring hospitalization, surgical/procedural intervention, or transfusion)	Yes	Supportive measures Consider continuing warfarin provided appropriate indication	--
Nonmajor bleeding (requiring hospitalization, surgical/procedural intervention, or transfusion)	Yes	Supportive measures Consider 2.5-5 mg PO/IV vitamin K	Recheck INR the next day after vitamin K administered
Major bleeding or emergent surgery/procedure requiring reversal (≤6 hours)	Yes	10 mg IV vitamin K <u>Kcentra® (use actual body weight):</u> **INR <1.4:** Not recommended **INR 1.4-2.0:** Use clinical judgment **INR 2.0-3.9:** 25 units/kg (2500 units max) **INR 4.0-6.0:** 35 units/kg (3500 units max) **INR >6.0:** 50 units/kg (5000 units max) FEIBA® should be given if the patient has a history of HIT (same dosing as Kcentra®) Alternatively, consider giving FFP 10-15 mL/kg in addition to vitamin K in lieu of Kcentra®/FEIBA® If INR ≥1.4 within first 24-48 hours after reversal, consider additional 5-10 mg IV vitamin K	Recheck INR 30 minutes after Kcentra®/FEIBA® given, then q6 hours for 24-48 hours Recheck INR the next day after vitamin K administered

References:

- Kcentra® [package insert], CSL Behring, 2013
- FEIBA® [package insert], Shire, 2013
- Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Experts Consensus Decisions Pathways. *J Am Coll Cardiol*. 2017 Dec 19;70(24):3042-3067.
- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46.
- Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians. *Chest*. 2012 Feb;141(2 Suppl):e152S-e184S.

Unfractionated Heparin and Low Molecular Weight Heparins

- Pharmacologic effects may correct without intervention for MOST patients
  - 4-6 hours for unfractionated heparin (UFH)
  - 12-24 hours for low molecular weight heparins (i.e. enoxaparin), longer if renal impairment is present
- Complete neutralization of UFH (within 5 minutes), however neutralization is incomplete for enoxaparin (~60%)
- Protamine can cause hypotension, bradycardia, pulmonary vasoconstriction, and anaphylactoid reactions (must be given <5 mg/min)
- DO NOT use FFP for reversal of heparins

Pharmacokinetics/Dynamics

Agent	Mechanism	Onset	Duration of Action	Notes
Antithrombotic Agents				
UFH	Inhibits thrombin and some factor Xa	--	4-6 hours	
Enoxaparin (Lovenox®)	Inhibits factor Xa and thrombin	--	12-24 hours	• Duration may be longer in those with acute kidney injury or chronic renal disease
Dalteparin (Fragmin®)	Inhibits factor Xa and thrombin	--	>12 hours	• Duration may be longer in those with acute kidney injury or chronic renal disease
Reversal Agent				
Protamine	Binds heparin molecule to form inactive salt	5 minutes	2 hours	• Consider pre-medicating with corticosteroids and antihistamines in those with prior exposure to protamine or fish allergy (potential for anaphylactoid reactions)

Management of Heparin-Related Bleeding

<table>
<tr><th>Type of Bleeding</th><th>Agent</th><th>Intervention</th><th>Monitoring</th></tr>
<tr><td>Nonmajor bleeding</td><td>UFH/LMWH</td><td colspan="3">• Consider continuing agent and use supportive measures
• Withhold therapy if clinically warranted
• Reversal not indicated</td><td></td></tr>
<tr><td rowspan="4">Major Bleeding</td><td>UFH (continuous infusion)</td><td colspan="3">• Stop infusion
• 1 mg protamine per 100 units UFH administered in the past 2-3 hours (max dose = 50 mg)
• Consider additional dose of 0.5 mg protamine per 100 units UFH administered in the past 2-3 hours if aPTT is still supratherapeutic</td><td>Check aPTT in 15 minutes and redose if needed[1]</td></tr>
<tr><td rowspan="3">LMWH (therapeutic dosing)</td><td colspan="3">• Stop agent</td><td rowspan="3">Consider checking anti-Xa (if available) 15-30 minutes and redose if needed</td></tr>
<tr><td>Dose given <8 hours prior:</td><td>Dose given 8-12 hours prior:</td><td>Dose given >12 hours prior:</td></tr>
<tr><td>1 mg protamine per 1 mg LMWH (max dose = 50 mg)</td><td>0.5 mg protamine per 1 mg LMWH (max dose = 50 mg)</td><td>Unlikely useful to administer protamine</td></tr>
<tr><td colspan="3">• Consider additional dose of 0.5 mg protamine per 1 mg LMWH if bleeding persists 2-4 hours after protamine administration OR renal dysfunction receiving daily administration</td></tr>
<tr><td>UFH/LMWH (prophylaxis)</td><td colspan="3">Reversal not generally recommended</td><td></td></tr>
</table>

[1]Consult Perfusion Medicine where available if Activated Clotting Time (ACT) is needed

References:

- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46.

Direct Oral Anticoagulants: Dabigatran (Pradaxa®)

Pharmacokinetics/Dynamics

Agent	Mechanism	Onset	Duration of Action	Notes
Antithrombotic Agent				
Dabigatran (Pradaxa®)	Inhibits thrombin	--	CrCl >50 mL/min: 1-2 days CrCl <50 mL/min: 3-5 days	• Duration may be longer in those with acute kidney injury or chronic renal disease
Reversal Agents				
Idarucizumab (Praxbind®)	Binds to both thrombin-bound and free dabigatran with higher affinity than thrombin	Minutes	At least 24 hours	• If refractory bleeding occurs, may consider redosing • Rebound not seen at 24 hours after dose (no need to redose after 24 hours)
PCC (Kcentra®)	Contains factors, including VII, IX, X, II (at a concentration 25x FFP)	5-15 minutes	6-8 hours	• Contains heparin – contraindicated in patients with HIT • May need to be approved by Blood Bank pathologist (see Operational Standard 2.3 – Pharmacy Clotting Factor Distribution) ○ Refer to Kcentra® Ordering Decision Tree • Contraindicated in disseminated intravascular coagulation (DIC) due to high risk of thrombosis
aPCC (FEIBA®)	Contains factors VIIa (activated), IX, X and II	15-30 minutes	8-12 hours	• Consider use in patients with HIT • Higher thrombotic risk due to activated factor VII • May need to be by Blood Bank pathologist (see Operational Standard 2.3 – Pharmacy Clotting Factor Distribution)

Management of Dabigatran-Related Bleeding

Type of Bleeding	Intervention	Monitoring

Nonmajor bleeding	• Consider continuing medication and use supportive measures
	• Stop or hold dose if clinically warranted
	• Reversal not indicated
		• aPTT
		  ○ If prolonged, suggests presence of drug
		• Thrombin time (TT)
		  ○ More sensitive to presence of drug
		  ○ Not readily available at most institutions

Major bleeding	Idarucizumab (Praxbind®) 2.5 grams x 2 consecutive doses (5 grams total) Repeat dose of 5 grams may be considered if hemostasis not achieved If idarucizumab (Praxbind®) is unavailable, give Kcentra® (or FEIBA® if history of HIT) 50 units/kg IV x 1 dose Consider activated charcoal if last known dose given within 2 hours Dialysis can be administered as last resort (can removed ~60% over 3 hours, however depends on amount of drug in plasma and likely requires prolonged session as rebound drug levels can occur when stopped)	aPTT at baseline If Kcentra® or FEIBA® given, recheck aPTT 15-30 minutes after dose is given, then q6h for 24 hours Do not recheck aPTT if idarucizumbab (Praxbind®) is given

References:

- Praxbind® [package insert], Boehringer Ingelheim, 2015
- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46.
- Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Experts Consensus Decisions Pathways. *J Am Coll Cardiol*. 2017 Dec 19;70(24):3042-3067.

Direct Oral Anticoagulants: Apixaban (Eliquis®), Betrixaban (Bevyxxa®), Edoxaban (Savaysa®), Rivaroxaban (Xarelto®)

Pharmacokinetics/Dynamics

Agent	Mechanism	Onset	Duration of Action	Notes
Antithrombotic Agents				
Apixaban (Eliquis®)	Inhibits factor Xa	--	2-4 days	• Duration may be longer in those with acute kidney injury or chronic renal disease
Betrixaban (Bevyxxa®)	Inhibits factor Xa	--	≥72 hours	• Duration may be longer in those with acute kidney injury or chronic renal disease
Edoxaban (Savaysa®)	Inhibits factor Xa	--	2-4 days	• Duration may be longer in those with acute kidney injury or chronic renal disease
Rivaroxaban (Xarelto®)	Inhibits factor Xa	--	1-3 days	• Duration may be longer in those with acute kidney injury or chronic renal disease
Reversal Agents				
Andexanet alfa (Andexxa®)	Binds and sequesters factor Xa inhibitors. Also binds and inhibits the activity of tissue factor pathway inhibitor (TFPI), which can increase tissue factor-initiated thrombin generation	Rapid	<1 hour (continuous infusion)	• Clinical trials have shown that anti-Xa activity increases to placebo levels 2 hours after completion of the infusion. However, elevation of TFPI generation is sustained above placebo for at least 22 hours after administration • FDA approved for reversal of apixaban and rivaroxaban only • Nonformulary use at Ochsner (must meet restriction criteria- see Appendix A) • Thrombotic activity most likely related to withholding anticoagulation after bleeding. Restart anticoagulation as soon as feasible
PCC (Kcentra®)	Contains factors, including VII, IX, X, II (at a concentration 25x FFP)	5-15 minutes	6-8 hours	• Contains heparin – contraindicated in patients with HIT • May need to be approved by Blood Bank pathologist (see Operational Standard 2.3 – Pharmacy Clotting Factor Distribution) ○ Refer to Kcentra® Ordering Decision Tree • Contraindicated in disseminated intravascular coagulation (DIC) due to high risk of thrombosis
aPCC (FEIBA®)	Contains factors VIIa (activated), IX, X and II	15-30 minutes	8-12 hours	• Consider use in patients with HIT • Higher thrombotic risk due to activated factor VII

				• May need to be approved by Blood Bank pathologist (see Operational Standard 2.3 – Pharmacy Clotting Factor Distribution)

Management of Oral Factor Xa Inhibitor-Related Bleeding

Type of Bleeding		Intervention	Monitoring
Nonmajor bleeding		• Consider continuing medication and use supportive measures • Stop or hold dose if clinically warranted • Reversal not indicated	Anti-Xa (if available) • If prolonged, suggests presence of drug
Major bleeding	Apixaban (Eliquis®) /Rivaroxaban (Xarelto®)	Kcentra® (or FEIBA® if history of HIT) 50 units/kg IV x 1 dose (max 5000 units) If restriction criteria met, give andexanet alfa (Andexxa®). See dosing below. Consider activated charcoal if last known dose given within 2 hours	Anti-Xa at baseline (if available) If Kcentra® or FEIBA® given, recheck anti-Xa 15-30 minutes after dose is given, then q6h for 24 hours Do not recheck anti-Xa if andexanet alfa (Andexxa®) is given
	Betrixaban (Bevyxxa®)	Limited data Kcentra® (or FEIBA® if history of HIT) 50 units/kg IV x 1 dose (max 5000 units) Consider activated charcoal if last known dose given within 2 hours	
	Edoxaban (Savaysa®)	Kcentra® (or FEIBA® if history of HIT) 50 units/kg IV x 1 dose (max 5000 units) Consider activated charcoal if last known dose given within 2 hours	

Andexanet alfa (Andexxa®) Dosing

Factor Xa Inhibitor	Factor Xa Inhibitor Last Dose	Time of Last Factor Xa Dose from Andexanet alfa Infusion	
		<8 hours or Unknown	≥8 hours
Apixaban (Eliquis®)	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High dose	
Rivaroxaban (Xarelto®)	≤10 mg	Low dose	
	>10 mg or unknown	High dose	

- **Low dose:** 400 mg IVPB administered at a rate of 30 mg/min, followed within 2 min by an IV infusion of 4 mg/min for up to 120 min
- **High dose:** 800 mg IVPB administered at a rate of 30 mg/min, followed within 2 min by an IV infusion of 8 mg/min for up to 120 min

References:

- Andexxa® [package insert], Portola Pharmaceuticals, 2018
- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46.
- Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Experts Consensus Decisions Pathways. *J Am Coll Cardiol*. 2017 Dec 19;70(24):3042-3067.

Fondaparinux (Arixtra®)

Evidence supporting recommendations is limited. Please use clinical judgment and seek input from the appropriate specialists if indicated

- Pharmacologic effects may correct without intervention in 2-5 days for MOST patients (longer if renal impairment)
- Protamine and/or dialysis are not effective to reverse or remove fondaparinux

Pharmacokinetics/Dynamics

Agent	Mechanism	Onset	Duration of Action	Notes
Antithrombotic Agent				
Fondaparinux (Ariztra®)	Inhibits factor Xa	--	17-21 hours	• Duration may be longer in those with acute kidney injury or chronic renal disease
Reversal Agents				
aPCC (FEIBA®)	Contains factors VIIa (activated), IX, X and II	15-30 minutes	8-12 hours	• Higher thrombotic risk due to activated factor VII • May need to be approved by Blood Bank pathologist (see Operational Standard 2.3 – Pharmacy Clotting Factor Distribution)
Recombinant factor VIIa (rFVIIa, Novoseven®)	Selective replacement of rFVIIa (activates extrinsic clotting pathway promoting thrombin formation)	5-10 minutes	4-6 hours (rebound 6-12 hours)	• Conflicting evidence for use • Significant risk of thrombosis • May need to be approved by Blood Bank pathologist (see Operational Standard 2.3 – Pharmacy Clotting Factor Distribution)

Management of Fondaparinux-Related Bleeding

Type of Bleeding	Intervention	Monitoring
Nonmajor bleeding	• Consider continuing medication and use supportive measures • Withhold therapy if clinically warranted • Reversal not indicated	Anti-Xa (if available)
Major bleeding	• Stop agent • **Preferred**: Consider aPCC (FEIBA®) 20 units/kg IV x 1 dose • If aPCC unavailable, may consider rVIIa 90 mcg/kg IV x 1 dose	Anti-Xa (if available)

References:

- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46.
- Demurs-Clavel H, et al. Reversal of the inhibitory effect of fondaparinux on thrombin generation by rFVIIa, aPCC, and PCC. *Thromb Res*. 2009 Mar;123(5):796-8.

Intravenous Direct Thrombin Inhibitors: Argatroban, Bivalirudin (Angiomax®)

Evidence supporting recommendations is limited. Please use clinical judgment and seek input from the appropriate specialists if indicated

- Pharmacologic effects may correct without intervention in 2-6 hours for MOST patients (longer if renal/hepatic impairment)
- Protamine and/or vitamin K are NOT useful
- Idarucizumab (Praxbind®) is NOT effective and is not FDA-approved for use in these agents

Pharmacokinetics/Dynamics

Agent	Mechanism	Onset	Duration of Action	Notes
Antithrombotic Agents				
Bivalirudin (Angiomax®)	Inhibits thrombin	--	2-6 hours	• Duration may be longer in those with acute kidney injury or chronic renal disease
Argatroban	Inhibits thrombin	--	2-4 hours	• Duration may be longer in those with acute liver injury or cirrhosis
Reversal Agent				
FFP	Contains factors VII, IX, X, II (diluted), fibrinogen, proteins C and S	1-4 hours	≤6 hours	• Large administration of volume (200 mL per unit)

Management of Intravenous Direct Thrombin Inhibitor-Related Bleeding

Type of Bleeding	Intervention	Monitoring
Nonmajor bleeding	• Consider continuing medication and use supportive measures • Stop infusion if clinically warranted • Reversal not indicated	aPTT
Major bleeding	• Stop infusion • Consider FFP 15 mL/kg (may need to repeat) • Dialysis can be considered for bivalirudin to expedite clearance	Recheck aPTT 15 minutes after FFP given, then q4 hours for 24-48 hours

References:

- Yee AJ, Kuter DJ. Successful recovery after an overdose of argatroban. *Ann Pharmacother*. 2006 Feb;40(2):336-9.
- Mann MJ, Tseng E, Ratcliffe M, et al. Use of bivalirudin, a direct thrombin inhibitor, and its reversal with modified ultrafiltration during heart transplantation in a patient with heparin-induced thrombocytopenia. *J Heart Lung Transplant*. 2005 Feb;24(2):222-5.

Thrombolytics: Alteplase (Activase®, Cathflo Activase®), Tenecteplase (TNKase®)

Evidence supporting recommendations is limited. Please use clinical judgment and seek input from the appropriate specialists if indicated

Pharmacokinetics/Dynamics

Agent	Mechanism	Onset	Duration of Action	Notes
Antithrombotic Agents				
Alteplase (tPA) (Activase®, Cathflo Activase®)	Initiates fibrinolysis by binding to fibrin in a thrombus, converting plasminogen to plasmin	--	Up to 1 hour	
Tenecteplase (TNKase®)	Initiates fibrinolysis by binding to fibrin in a thrombus, converting plasminogen to plasmin (more fibrin specific)	--	1-3 hours	
Reversal Agents				
Cryoprecipitate	Fibrinogen (15-25 mg/mL), von Willebrand factor, factors VIII and XIII	--	--	
Aminocaproic acid (Amicar®)	Binds competitively to plasminogen; blocking the binding of plasminogen to fibrin and the subsequent conversion to plasmin, resulting in fibrinolysis	1-72 hours	3-4 hours	• Risk of seizures and hypotension

Management of Thrombolytic-Related Bleeding

Type of Bleeding	Intervention	Monitoring
Nonmajor bleeding	• Consider continuing medication and use supportive measures • Stop or hold dose if clinically warranted • Reversal not indicated	None
Major bleeding	**Preferred:** Cryoprecipitate 10 units (as an initial dose) if thrombolytic received in previous 24 hours If cryoprecipitate unavailable, give aminocaproic acid (Amicar®) 4-5 grams IV x 1 dose If fibrinogen <150 mg/dL, give/redose cryoprecipitate Concomitant administration of platelets is controversial	Check fibrinogen level (if available) after administration of reversal agents (goal >150 mg/dL)

References: Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46.

Antiplatelets

Evidence supporting recommendations is limited. Please use clinical judgment and seek input from the appropriate specialists if indicated

Pharmacokinetics/Dynamics of Antiplatelets

Drug	Platelet Inhibition	Return of Normal Platelet Function
Oral Antiplatelets		
Aspirin	Irreversible	7-10 days
Cangrelor (Kengreal®)	Reversible	60 minutes
Clopidogrel (Plavix®)	Irreversible	5-7 days
Prasugrel (Effient®)	Irreversible	5-7 days
Ticagrelor (Brilinta®)	Reversible	3-5 days
Cilostazol (Pletal®)	Reversible	4 days
Vorapaxar (Zontivity®)	Irreversible	>4 weeks
IV Antiplatelets		
Abciximab (ReoPro®)	Irreversible	3-7 days
Eptifibatide (Integrilin®)	Reversible	4-8 hours
Tirofiban (Aggrastat®)	Reversible	4-8 hours

Discontinuation of antiplatelet agents must be weighed against the risk of arterial thrombosis (i.e. if a patient has a bare metal or drug eluting stent placed within the past 1-3 months, respectively). Premature cessation of dual antiplatelet therapy can lead to stent thrombosis which can be potentially fatal.

Management of Antiplatelet-Related Bleeding

Type of Bleeding		Intervention	Monitoring
Nonmajor bleeding		• Consider continuing medication and use supportive measures • Stop or hold dose if clinically warranted • Reversal not indicated	Signs of bleeding
Major bleeding	Aspirin, cangrelor, clopidogrel, prasugrel, ticagrelor	• Stop medication and use supportive measures • DDAVP 0.4 mcg/kg x 1 dose • Consider platelet transfusion	Signs of bleeding
	Cilostazol, vorapaxar, abciximab, eptifibatide, tirofiban	• Stop medication and use supportive measures • Consider platelet transfusion	

References:

- Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016 Feb;24(1):6-46.

- Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. *Blood*. 2012 Dec 6;120(24):4699-705.

Appendix A. Andexanet Alfa (Andexxa®) Restriction Criteria

Use will not be supported for perioperative reversal in patients not currently experiencing a life-threatening bleed.
Approval for use is restricted to attending physicians from Neurocritical Care, or Vascular/Neurosurgery.
Andexanet alfa may be ordered for an adult patient who meets **ALL** the following criteria:

- Apixaban- or rivaroxaban-related acute life-threatening, active intracranial hemorrhage (ICH)

AND

- Must have received apixaban or rivaroxaban within the last 18 hours

AND

- Glasgow coma score equal to or greater than 7 at baseline upon admission or prior to clinical deterioration

AND

- Estimated ICH volume equal to or less than 60 mL

AND

- ICH score equal to or less than 3 (for those patients with primary ICH)

AND

- Does NOT have severe sepsis or septic shock

AND

- Has NOT received prothrombin complex concentrate products (e.g., Kcentra®) or recombinant factor VIIa (i.e., NovoSeven®) or factor eight inhibitor bypassing activity (i.e., FEIBA®) or FFP within 48 hours

AND

- Has NOT had a major thrombotic event within the past 2 weeks (including myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, or unstable angina pectoris hospitalization)

AND

- Anti-Xa (enoxaparin assay) is equal to or greater than 0.4 IU/mL