Intracranial hemorrhage: Reversal of anticoagulant, antiplatelet and thrombolytic agents

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Cases to use these guidelines in

Non traumatic / spontaneous intracranial hemorrhages and intraventricular hemorrhages

Subdural hemorrhages without underlying significant parenchymal traumatic brain injury

Indications of reversal

- All intracranial hemorrhages are presumed life and limb threatening. All ICH should be considered for reversal unless coexistent conditions of reversing place patient at higher risk of reversal
- Patient undergoing neurosurgical procedures (EVD or craniotomy)
- Salvageability of an ICH patient is a clinical decision based on location, medical and neurosurgical options available for the bleed. Patient undergoing active comfort care is the only patient deemed non-salveageable in context of reversal of ICH.

Use caution in reversing ICH in presence of these conditions. PLEASE CONSULT NEUROCRITICAL CARE ATTENDING ON CALL in the following situations

- thrombosis (cerebral venous sinus thrombus ,PE, extensive DVTs)
- ischemia requiring anticoagulation
- heart valves
- HIT (K centra contraindicated)
- DIC
- Amicar or Novoseven is indicated

Warfarin

INR known 1.4- 5	Vit K 10 mg IV	plus	FEIBA 500 units IV once
INR >5	Vit K 10 mg IV	plus	FEIBA 1000 units IV once
INR unknown Draw PT/INR	Vit K 10 mg IV	plus	FEIBA 500 units IV once

Pre FEIBA INR >1.4 -5 — no additional FEIBA necessary

Pre FEIBA INR >5 — additional FEIBA 500 units IV once

Repeat INR 15-60 min after infusion complete - if INR >1.4- repeat Vit K 10 mg IV once . Consider additional FEIBA 500 units IV once

Repeat INR every 6 hours until 2 consecutive values show <1.4

Direct oral anticoagulants

Do not use lab testing to make a decision for reversal. Consider reversal if last dose within 3-5 half lives or longer in context of liver or renal failure

Rivaroxaban / Apixaban / Edoxaban	consider activated charcoal if dose taken within 2 hours Kcentra 50 units /kg once
Dabigatran-	Praxbind 5 mg IV once. Check Thrombin time. If still high consult hematology for repeat dose. If rebleeding after praxbind and/or concern for residual dabigatran – consult renal for **DIALYSIS** since Praxbind =dabigatran complex is cleared by kidneys vs consult hematology for redosing. Praxbiond reverses dabigatran within minutes. Shortfalls- rebound anticoagulation due to redistribution of dabigatran from extravascular to intravascular space and formation of antibodies to praxbind.

If time elapsed since last dose is > 5 elimination half lives – may not reverse

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Parenteral anticoagulants

Heparin IV	IV protamine 1 mg for 100 units of heparin the patient received during previous 3 hours Reduce dose by half if 30-60 minutes have elapsed since heparin given. Max protamine dose 50 mg . Administer Protamine slowly @ no more than 5mg/min or 50 mg over 10 min. Watch for hypotension. Repeat aPTT (> 30) or ACT (>180 secs) . If high may repeat 0.5 mg per 100 unit heparin given. Do not give more than 50 mg total. If protamine is contraindicated – NOVOSEVEN recombinant Favor VIIa 90 mcg/kg
Enoxaparin	Check Heparin Assay (Anti-Factor Xa levels) . Do not wait for results if life or limb threatening bleed or need for NSG procedure. Administer Protamine slowly 50 mg over 10 min. Watch for hypotension. Do not give more than 50 mg total. <8 hours since last dose with normal renal function- IV protamine 1 mg for every 1 mg of enoxaparin administered. 8-24 hours since last dose with normal renal function IV protamine 0.5 mg for every 1 mg of enoxaparin administered 8-24 hours since last dose with IMPAIRED renal function IV protamine 1 mg for every 1 mg of enoxaparin administered. >24 hours since last dose with IMPAIRED renal function IV protamine 0.5 mg for every 1 mg of enoxaparin administered If protamine is contraindicated – NOVOSEVEN recombinant Favor VIIa 90 mcg/kg
Fondaparinaux	FEIBA 20 units /kg for therapeutic doses. Dialysis increases clearance by ~20%. If FEIBA is contraindicated – NOVOSEVEN recombinant Favor VIIa 90 mcg/kg.
Argatroban	Stop infusion. Supportive care. Dialyzable to low extent ~20% over 4 hours If severe hepatic impairment consider expert consultation. Dialyzable to low extent ~20% over 4 hours
Bivalirudin	Renal consult for dialysis for critical bleeding. Dialyzable to low extent ~25% over 4hrs Half life is only 25 minutes with normal renal function, t1/2 increases to ~1h with crcl<30, hours

	Notes	Effect on coagulation panel
Heparin IV		aPTT
Enoxaparin	Renally eliminated	Anti-Xa levels (controversial)
Fondaparinux	Renally eliminated	Anti-Xa levels (controversial)
Argatroban		Falsely elevates INR Monitor PTT
Bivalirudin	Renally eliminated	Falsely elevates INR, Monitor aPTT
Protamine	Administer Protamine slowly 50 mg over 10 min, no more than 5mg/minute	

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Oral antiplatelet agents

Aspirin /dipyridamole/cilostazol /clopdogrel/Prasugrel/ticlopidine /ticagreclor

Non surgical bleeds on single antiplatelet agents only.	No action OR ddAVP 0.4 mcg/kg once
Non surgical bleeds on dual antiplatelet agents	No action or ddAVP 0.4 mcg/kg ± plus platelet transfusion 1 unit
Surgical bleeds /EVD planned	ddAVP 0.4 mcg/kg once only PLUS platelet transfusion.

Platelet units
1 unit if Aspirin /dipyridamole/cilostazol.
2 units if clopdogrel/Prasugrel/ticlopidine /ticagreclor or dual agents
More than 2 units may be needed if ticagreclor

Note

- NSAIDs do not need platelets transfusion or reversal
- Presence of stents (intracranial, carotid, vertebral or coronary) should be considered when considering reversal**.** Most acute stents require dual antiplatelet in first 3 months and single antiplatelet long term

Antiplatelet Agents			
Medication	**Time to Maximum Antiplatelet Effect**	**Duration of Antiplatelet Activity**	**Notes**
Aspirin	30 minutes	At least 4 days	Antiplatelet effects begin within ½ hour of dose and persist for at least 4 days after stopping therapy. Aspirin is dialyzable (in case patient has underwent dialysis since last aspirin dose)
Aspirin/Dipyridamole (Aggrenox®)	• 30 minutes	At least 4 days	Antiplatelet effects begin within 1/2 hour of dose and persist for at least 4 days after stopping therapy. Aspirin is dialyzable (in case patient has underwent dialysis since last aspirin dose)
Clopidogrel (Plavix®)	• 2 to 5 hours with 300 to 400mg loading dose • 3 to 7 days with no loading dose	Up to 10 days	More rapid inhibition of platelet function is achieved with loading doses; antiplatelet effect lasts up to 10 days after stopping therapy
Cilostazol (Pletal®)	3 to 6 hours	48 hours	Antiplatelet effects lasts for 48 hours after chronic administration

Prasugrel (Effient®)	30 minutes after a 60mg loading dose	5 to 7 days	Antiplatelet effect lasts 5-7 days after stopping therapy.
Ticagrelor (Brilinta®)	Within 30 minutes after a 180mg loading dose	More than 2.5 days	Antiplatelet activity is reduced to 30% after 2.5 days
Ticlopidine (Ticlid®)	2 to 5 days	5 to 7 days	Antiplatelet effect lasts 5-7 days after stopping therapy.
Reference: Table adapted from Ortel. Blood. 2012 Dec 6; 120(24):4699-705. Micromedex® online database- Accessed Feb 9th, 2014			

DDAVP for the management of platelet dysfunction in Intracranial hemorrhage			
Medication	**Dosage/Administration**	**Indications**	**Mechanism of Action**
Desmopressin (DDAVP)	**0.4mcg/kg** (maximum 40mcg) in 50mL Normal Saline to be infused over 15 minutes • Tachyphylaxis with reduced efficacy and potential for increased bleeding time may occur with repeat doses • Do NOT give more than 2 doses in any 48 hour time period	• History of antiplatelet agents • Qualitative platelet dysfunction as seen with uremia/renal failure or hepatic failure • Haemophilia A or Von Willebrand's disease	DDAVP increases plasma levels of von Willebrand factor, factor VIII, and t-PA contributing to a shortened activated partial thromboplastin time (aPTT) and bleeding time. **Onset:** 30 minutes **Peak:** 1.5 to 2 hours **Duration:** 4 hours
Reference: Micromedex® online database- Accessed Feb 9th, 2014Canavese C, Salomone M, Pacitti A, et al: Reduced response of uraemic bleeding time to repeated doses of desmopressin. Lancet 1985; 1(8433):867-868.			

Platelet Function Assay-LOW QUALITY EVIDENCE

The PFA test result is dependent on platelet function, plasma von Willebrand Factor level, platelet number, and (to some extent) the hematocrit. The PFA test is initially performed with the Col/Epi membrane. If the Col/Epi closure time is prolonged (>180 seconds), the Col/ADP test is automatically performed.

PFA interpretation		
cEpi closure time (collagen epinephrine membrane) Normal <180 seconds	cADP closure time (collagen adenosine diphosphate membrane) Normal <150 seconds	Clinical implication
Normal	Not performed	Excludes the presence of significant platelet function defect cADP will not be performed
Prolonged	Normal	Aspirin induced platelet dysfunction is most likely
Prolonged	Prolonged	May indicate: • Anemia (Hct<0.28) • Thrombocytopenia (PLT <100k) • Significant platelet function defect other than aspirin • Long term aspirin therapy

Glycoprotein IIb/IIIa inhibitors

Abciximab , eptifibatide , tirofiban- NCS/SCCM guidelines recommend against platelet transfusion, even in the context of neurosurgical intervention. This is due to short half-lives of listed medications as well as paucity of data supporting platelet transfusion.

Eptifibtatide dialyzable 73-83% after 1 hour

Intravenous tPA Reversal Guideline

tPA REVERSAL MUST BE REVIEWED/APPROVED BY STROKE AND ICU ATTENDING. tPA half-life is short but residual tPA within the ischemic brain may still be present and warrant reversed

If CT scan shows significant, hemorrhage causing symptomatic decline:

- Stop all further antiplatelet or anticoagulants.
- Send CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match
- Tighten target SBP goal to < 140
- Consider neurosurgery for possible surgical intervention if needed
- Consider osmotic therapy as appropriate for cerebral edema
- If patient received tPA ≤ 24 hours, consider reversal of tPA with cryoprecipitate, IV amicar, and/or platelet transfusions.
  1. Cryoprecipitate 0.15 units/kg (or 10 units) , **IF** fibrinogen < 150 mg/dL. (AHA 2018 guidelines mention 200 as cutoff but not supported by reference used) Repeat fibrinogen level 30 minutes after infusion is complete and repeat cryoprecipitate dose as necessary.
  2. Amicar (epsilon aminocaproic acid) 4-5 gram over 20 minutes (If cannot tolerate cryoprecipitate).
  3. If cryoprecipitate if contraindicated or not available then- Platelet transfusion 1 unit for platelets 100 K, ONE units for platelet. Repeat platelet count 30 minutes after infusion is complete and repeat dose as necessary.

Pharmacokinetic parameters for selected anticoagulants and antiplatelet agents

Table 2 Pharmacokinetic parameters for selected anticoagulants and antiplatelet agents [161, 423]

Medication	Mechanism of action	Elimination	Half-life	Impairment affects excretion		Dialyzable
				Renal	Hepatic	
Vitamin K antagonists						
Warfarin	Inhibits vitamin K-dependent γ-carboxylation of coagulation factors II, VII, IX, and X, reducing activity of clotting factors	Hepatic metabolism; 92 % renal elimination	20–60 h	Yes	Yes	No
Direct factor Xa inhibitors						
Rivaroxaban	Prevents factor Xa-mediated conversion of prothrombin to thrombin	66 % renal; 28 % fecal	5 h	Yes	Yes	No
Apixaban	Prevents factor Xa-mediated conversion of prothrombin to thrombin	majority fecal; 27 % renal	12 h	Yes	Yes	Minimal, area under the curve decreased by 14 % over 4 h
Edoxaban	Prevents factor Xa-mediated conversion of prothrombin to thrombin	50 % renal	10–14 h	Yes	Yes	No
Direct thrombin inhibitors						
Dabigatran	Competitive direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	>80 % renal	12–17 h 16.6 h in mild, 18.7 h in moderate, 27.5 h in severe renal failure, 34.1 h in patients on hemodialysis	Yes	No	Yes ~57 % over 4 h
Argatroban	Reversible direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	0 % renal	39–51 min	No	Yes	Yes ~20 % over 4 h
Bivalirudin	Reversible direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	20 % renal	25 min; GFR 30-59 34 min GFR 10–29, 57 min	Yes	No	Yes ~25 % over 4 h
Desirudin	Irreversible direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	40–50 % renal	2 h; With renal impairment 12 h	Yes	No	Yes
Lepirudin	Irreversible direct inhibition of thrombin (factor IIa) including thrombin-mediated platelet activation and aggregation	90 % renal	1.3 h; With renal impairment 2 days	Yes	Yes	Yes
Unfractionated Heparin, LMWHs, and Heparinoids						
Heparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa). By inactivating thrombin, heparin prevents fibrin formation.	Renal	60–90 min	No	No	No
Enoxaparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	40 % Renal	4.5 h	Yes	No	No

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Dalteparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	Renal	2.5 h; 3.7–7.7 h with renal insufficiency	Yes	No	No
Nadroparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	Renal	3.5 h	Yes	No	No
Tinzaparin	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	Renal	3.4 h	Yes	No	No

Pharmacokinetic parameters for selected anticoagulants and antiplatelet agents

Table 2 continued

Medication	Mechanism of action	Elimination	Half-life	Impairment affects excretion		Dialyzable
				Renal	Hepatic	
Danaparoid	Binds and activates antithrombin (which blocks coagulation factors Xa and IIa)	40 % Renal	25 h; 29–35 h with renal insufficiency	Yes	No	No
Pentasaccharides						
Fondaparinux	Binds with antithrombin and potentiates inhibition of free factor Xa, preventing formation of the prothrombinase complex	50–77 % Renal	17–21 h; prolonged in elderly and in renal insufficiency	Yes	No	Yes, clearance increased by 20 %
Thrombolytics						
Alteplase	Catalyzes conversion of fibrin-bound plasminogen to plasmin. Plasmin exerts additional proteolytic effects, including cleavage of platelet GPIIIa and GP1B causing inhibition of platelet function	Hepatic	Plasma: 3–6 min; Terminal: 26–77 min	No	Yes	Unknown, unlikely
Reteplase	Catalyzes conversion of fibrin-bound plasminogen to plasmin. Plasmin exerts additional proteolytic effects including cleavage of platelet GPIIIa and GP1B causing inhibition of platelet function	Renal	Plasma: 13–16 min; Terminal: not reported	Yes	No	Unknown, unlikely
Tenecteplase	Catalyzes conversion of fibrin-bound plasminogen to plasmin. Plasmin exerts additional proteolytic effects including cleavage of platelet GPIIIa and GP1B causing inhibition of platelet function	Hepatic	Plasma: 11–24 min; Terminal: 90–138 min	No	Yes	Unknown, unlikely

Antiplatelets						
Aspirin	Irreversible cyclooxygenase-1 and 2 (COX-1 and 2) enzyme Inhibitor (inhibits thromboxane A2)	5.6–35.6 % renal	20 min	Yes	Yes	Yes
Ibuprofen	Reversible COX-1 and 2 enzyme Inhibitor	80 % renal	2–4 h	Yes	Yes	No
Naproxen	Reversible COX-1 and 2 enzyme Inhibitor	95 % renal, 3 % fecal	12 h	Yes	Yes	No
Dipyridamole	Reversible adenosine reuptake inhibitor	Fecal	10 h	No	Yes	No
Clopidogrel	Irreversible inhibition of P2Y12 ADP receptor	50 % renal, 46 % fecal	6–8 h	Yes	Yes	No
Prasugrel	Irreversible inhibition of P2Y12 ADP receptor	68 % renal, 27 % fecal	2–15 h	Yes	Yes	No
Ticagrelor	Reversible inhibition of P2Y12 ADP receptor	26 % renal, 58 % fecal	7 h Metabolite = 9 h	No	Yes	No
Ticlopidine	Irreversible inhibition of P2Y12 ADP receptor	60 % renal, 23 % fecal	12 h (increases with renal failure 4–5 days after repeated doses)	Yes	Yes	No
Cilostazol	Reversible phosphodiesterase (PDE) III inhibitor, increases cAMP, inhibits ADP induced platelet aggregation, and causes vasodilation	74 % renal, 20 % fecal	10 h	Yes	Yes	No
Anagrelide	Reversible PDE inhibitor, inhibits megakaryocyte formation	70 % renal, 18 % fecal	3 days	Yes	Yes	No
Abciximab	Irreversible Glycoprotein IIB/IIIA antagonist	Unknown, likely proteolytic degradation	Free drug = 30 min; Receptor bound drug = 24–48 h	No	No	Unknown, unlikely
Eptifibatide	Reversible Glycoprotein IIB/IIIA antagonist	71.4 % renal, 1.5 % fecal	20–40 min	Yes	No	Yes Approximately 73–83 % after 1 h
Tirofiban	Reversible Glycoprotein IIB/IIIA antagonist	65 % renal, 25 % fecal	20–45 min	Yes	No	Yes
Vorapaxar	Reversible protease-activated receptor-1 (PAR-1) thrombin receptor antagonist (effectively irreversible due to long half-life)	25 % renal, 58 % fecal	3–4 days, terminal half-life 8 days	No	No	Unknown, unlikely

References

1. 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
2. 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:e46–e99