

Anticoagulant Related Major Bleeding: Reversal Strategies

Life threatening bleed: bleeding into critical organ (intracranial, intra-spinal, intra-ocular, retroperitoneal, pericardial, intramuscular with compartment syndrome), hypotension SBP < 90 mmHg (refractory to fluids), reduction in hemoglobin by 2 g/dL, ≥ 2 units of PRBC or whole blood, or hemoglobin < 8 mg/gL

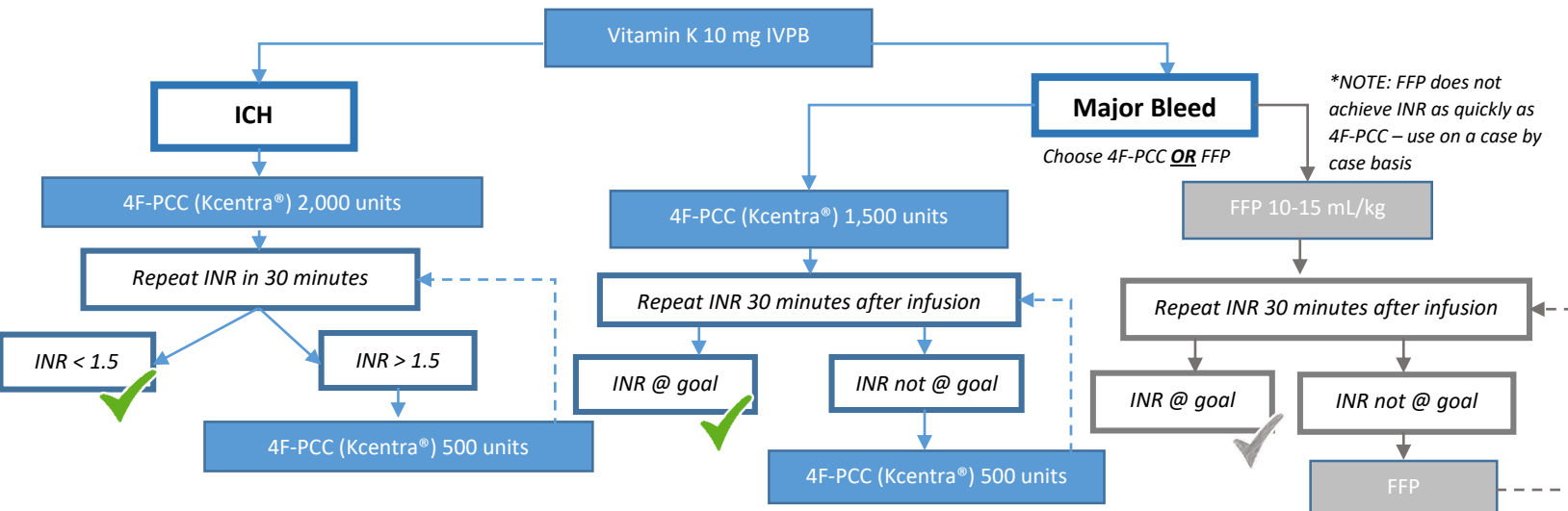
MUST WEIGH RISK AND BENEFIT TO REVERSING ANTICOAGULATION – HIGH RISK OF THROMBOEMBOLIC EVENTS OCCURRING AFTER ADMINISTRATION

Not studied in patients who have had a thromboembolic event within the previous 2 weeks (andexanet alfa) or previous 3 months (4F-PCC) - including MI, DIC, CVA, TIA, unstable angina pectoris hospitalization, or severe PVD

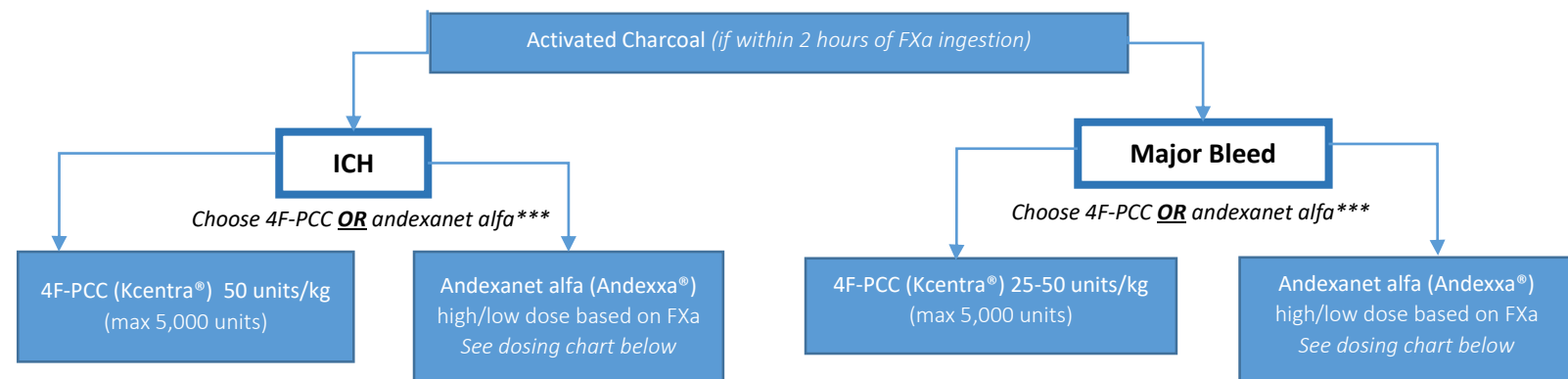
Anticoagulant	Strategies to Minimize/Reverse Anticoagulation Effect	Comments																														
Alteplase (Activase®) Tenecteplase (TNKase®)	<p>Cryoprecipitate 10 units IV over 10-30 min Indication: for life threatening bleed within 24 hours of thrombolytic therapy Check fibrinogen level after administration – if < 200 mg/dL, consider repeat dosing</p> <p>AND choose ONE of the following:</p> <ul style="list-style-type: none"> Tranexamic acid 1000 mg IV instruction Check fibrinogen levels after administration – if < 200 mg/dL, additional cryoprecipitate is recommended <p>OR</p> <ul style="list-style-type: none"> Aminocaproic Acid 5 g IV push followed by 1g/hr x 8 hours or until bleeding is controlled Check fibrinogen levels after administration – if < 200 mg/dL, additional cryoprecipitate is recommended 	<p>Cryoprecipitate will come from the blood bank</p>																														
Apixaban (Eliquis®) Rivaroxaban (Xarelto®) <i>See flowsheet on page 2</i>	<p>Activated charcoal 50 grams PO Indication: if ingested within 2 hours of administration</p> <p>AND choose ONE of the following reversal agents:</p> <ul style="list-style-type: none"> 4F-PCC (Kcentra®)*** (~\$4,800) 25 units/kg (max 2,500 units), consider 50 units/kg (max 5,000 units) in ICH or recent dose administration (ex. Within 6-12 hours) <p>OR</p> <ul style="list-style-type: none"> Andexanet alfa (Andexxa®)*** (~\$13,000-\$48,000) Dosing based on dose and time of last dose: <table border="1"> <thead> <tr> <th rowspan="2">Apixaban Dose</th> <th colspan="3">Timing of Last Dose</th> </tr> <tr> <th>< 8 hours</th> <th>8– 18 hours</th> <th>Unknown</th> </tr> </thead> <tbody> <tr> <td>≤ 5 mg</td> <td>Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min</td> <td>Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min</td> <td>Consider 4F-PCC</td> </tr> <tr> <td>> 5 mg</td> <td>High dose: 800 mg IV bolus, followed by 8mg/min up to 120 min</td> <td></td> <td></td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th rowspan="2">Rivaroxaban Dose</th> <th colspan="3">Timing of Last Dose</th> </tr> <tr> <th>< 8 hours</th> <th>8– 18 hours</th> <th>Unknown</th> </tr> </thead> <tbody> <tr> <td>≤ 10 mg</td> <td>Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min</td> <td>Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min</td> <td>Consider 4F-PCC</td> </tr> <tr> <td>> 10 mg</td> <td>High dose: 800 mg IV bolus, followed by 8mg/min up to 120 min</td> <td></td> <td></td> </tr> </tbody> </table> <p>*** Andexanet alfa is the only FDA approved FXa reversal agent but there have been no prospective head to head trials comparing it to 4F-PCC. Either are reasonable options for reversal based on clinical judgment</p>	Apixaban Dose	Timing of Last Dose			< 8 hours	8– 18 hours	Unknown	≤ 5 mg	Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min	Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min	Consider 4F-PCC	> 5 mg	High dose: 800 mg IV bolus, followed by 8mg/min up to 120 min			Rivaroxaban Dose	Timing of Last Dose			< 8 hours	8– 18 hours	Unknown	≤ 10 mg	Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min	Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min	Consider 4F-PCC	> 10 mg	High dose: 800 mg IV bolus, followed by 8mg/min up to 120 min			<p>Drug activity cannot be reliably assessed with coagulation tests, must rely on time of last dose</p> <p>Andexanet alfa is not studied in patients who require emergency surgery</p> <p>Andexanet alfa is not recommended if patient was treated with 4F-PCC due to risk of thrombosis</p> <p><i>Both 4F-PCC and andexanet alfa is restricted to the following services: ED, Neurosurgery, ICU, hematology/oncology, and cardiology</i></p>
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Dabigatran (Pradaxa®)	<p>Activated charcoal 50 grams PO Indication: if ingested within 2 hours of administration</p> <p>Idarucizumab (Praxbind®) 5 gram IV (~\$2,100) Indication: for life threatening bleeding or emergent surgery within 48 hours of dose</p>	<p>Drug activity can be assessed with aPTT</p>																														
Enoxaparin/ LMWH (Lovenox®)	<p>Protamine Dosing based on dose and time of last dose:</p> <table border="1"> <thead> <tr> <th>Time Elapsed</th> <th>Protamine Dose</th> <th>Max dose</th> </tr> </thead> <tbody> <tr> <td>< 8 hours</td> <td>1 mg protamine for every 1 mg LMWH</td> <td>Max dose: 50 mg</td> </tr> <tr> <td>8-12 hours</td> <td>0.5 mg protamine for every 1 mg LMWH</td> <td>Max dose: 50 mg</td> </tr> <tr> <td>> 12 hours</td> <td>Not recommended</td> <td>Max dose: 50 mg</td> </tr> </tbody> </table>	Time Elapsed	Protamine Dose	Max dose	< 8 hours	1 mg protamine for every 1 mg LMWH	Max dose: 50 mg	8-12 hours	0.5 mg protamine for every 1 mg LMWH	Max dose: 50 mg	> 12 hours	Not recommended	Max dose: 50 mg	<p>Causes partial neutralization of LMWH (~60%)</p> <p>If too much is given, protamine has anticoagulant effect</p>																		
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Warfarin (Coumadin®) <i>See flowsheet on page 2</i>	<p>Vitamin K 10 mg IV over 30 minutes (in addition to 4F-PCC OR FFP) AND 4F-PCC (Kcentra®) fixed dose</p> <ul style="list-style-type: none"> Intracranial hemorrhage: 2,000 units Major bleed: 1,500 units May administer rescue dose of 4F-PCC 500 units if INR ≥ 1.5 within 30 minutes after administration. If INR still not achieved, consider FFP for factor replacement. <p>Fresh Frozen Plasma (FFP)</p> <ul style="list-style-type: none"> Dose based on presenting INR or repeat INR: INR 1.7-2 (10 mL/kg) or INR ≥ 2 (15 mL/kg) 	<p>Measure current INR and INR 30 minutes after reversal administration</p>																														

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Warfarin Reversal for Life Threatening Bleed/Emergent Surgery



FXa Inhibitor (apixaban/rivaroxaban) Reversal for Life Threatening Bleed/Emergent Surgery



Andexanet Alfa Dosing Guideline			
Dose	Timing of Last Dose		
	< 8 hours	8- 18 hours	Unknown
Apixaban ≤ 5 mg Rivaroxaban < 10 mg	Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min	Low dose: 400 mg IV bolus, followed by 4mg/min up to 120 min	Consider 4F-PCC
Apixaban > 5 mg Rivaroxaban > 10 mg	High dose: 800 mg IV bolus, followed by 8mg/min up to 120 min		

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Resources:

- Ammar AA, Ammar MA, Owusu KA, Brown SC, Kaddouh F, Elsamadicy AA, Acosta JN, Falcone GJ. Andexanet Alfa Versus 4-Factor Prothrombin Complex Concentrate for Reversal of Factor Xa Inhibitors in Intracranial Hemorrhage. *Neurocrit Care*. 2021 Aug;35(1):255-261. doi: 10.1007/s12028-020-01161-5. Epub 2021 Jan 6. PMID: 33403588.
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