# GUIDELINE for ANTITHROMBOTIC REVERSAL

This document is intended as a guideline only and should not replace sound clinical judgment.

## Table 1: Reversal for ANTICOAGULANT therapy

<table>
<thead>
<tr>
<th>ANTITHROMBOTIC</th>
<th>REVERSAL AGENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIRECT THROMBIN INHIBITORS (DTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV: Argatroban</td>
<td><strong>4 Factor PCC</strong></td>
<td>Off-label use of rFVIIa/PCC:</td>
</tr>
<tr>
<td>Bivalirudin (Angiomax®)</td>
<td><strong>Dose</strong>: 50 units/kg (dose cap at 100 kg to mitigate thrombotic risk)</td>
<td>- Requires attending approval</td>
</tr>
<tr>
<td>Half-life 10-90 minutes</td>
<td><strong>Administration</strong>: Place in empty IV bag and give slow IV push over 10 minutes</td>
<td>- Document attending name in the order comments</td>
</tr>
<tr>
<td>PO: Dabigatran (Prada®)</td>
<td><strong>Use within 4 hours of reconstitution</strong></td>
<td>Additional options:</td>
</tr>
<tr>
<td>Half-life 12-17 hours in normal renal function</td>
<td><strong>Onset</strong>: &lt;30 minutes</td>
<td>- If dabigatran ingested within 1 hour, consider activated charcoal.</td>
</tr>
<tr>
<td>The aPTT is currently the only readily available lab test to qualitatively measure dabigatran. Do not use PT/INR</td>
<td><strong>Caution</strong>: thrombotic risk</td>
<td>- Mechanical methods, such as dialysis, may be considered as a last resort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Additional options:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If dabigatran ingested within 1 hour, consider activated charcoal.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Recommend not giving rFVIIa and PCC together due to high risk of thrombosis unless clinical situation warrants</td>
</tr>
</tbody>
</table>

| **FACTOR XA INHIBITORS** | | |
| Fondaparinux (Arixtra®) | **4 Factor PCC** | Off-label use of rFVIIa/PCC: |
| Half-life 17-21 hours in normal renal function | **Dose**: 50 units/kg (dose cap at 100 kg to mitigate thrombotic risk) | - Requires attending approval |
| Rivaroxaban (Xarelto®) | **Administration**: Place in empty IV bag and give slow IV push over 10 minutes | - Document attending name in the order comments |
| Half-life 5-9 hours (up to 13 hours in elderly) | **Use within 4 hours of reconstitution** | Additional option: |
| Apixaban (Eliquis®) | **Onset**: <30 minutes | If rivaroxaban, apixaban or edoxaban ingested within 1 hour, consider activated charcoal. |
| Half-life 8-15 hours | **Caution**: thrombotic risk | Recommend not giving rFVIIa and PCC together due to high risk of thrombosis unless clinical situation warrants |
| Edoxaban (Savaysa®) | | |
| Half-life 10-14 hours | | |

The PT and the UFH/LMWH anti-Factor XA assay are currently the only readily available labs test to qualitatively measure rivaroxaban, apixaban or edoxaban. Do not use INR.
### Heparin

**Half-life: 1-2 hours**

<table>
<thead>
<tr>
<th>Protamine</th>
<th>Dose: 1 mg reverses 100 units of UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time since UFH</strong></td>
<td><strong>Dose per 100 units UFH over last 3h</strong></td>
</tr>
<tr>
<td>&lt;30 min</td>
<td>1 mg</td>
</tr>
<tr>
<td>30-120 min</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>&gt;120 min</td>
<td>0.25 mg</td>
</tr>
</tbody>
</table>

- Do not exceed 50mg in a single dose; high doses can have an undesirable anticoagulant effect.
- In clinical practice, give 50 mg IV x1 over 10 minutes. May redose if bleeding continues.

**Administration:** Slow IV push not to exceed 5mg/minute

**Onset:** 5-15 minutes

**Caution:** Rapid administration can cause severe hypotension and anaphylaxis.

### LMWHs (enoxaparin)

**Half-life: 2-8 hours**

<table>
<thead>
<tr>
<th>Protamine</th>
<th>Dose: 1 mg for each 1 mg of enoxaparin in last 8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If &gt;12 hrs have elapsed since LMWH administration, protamine may not be needed</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Do not exceed 50mg in a single dose; high doses can have an undesirable anticoagulant effect</strong></td>
<td></td>
</tr>
<tr>
<td><strong>In clinical practice, give 50 mg IV x1 over 10 minutes. May redose if bleeding continues.</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Administration:** Slow IV push not to exceed 5mg/minute

**Onset:** 5-15 minutes

**Caution:** Rapid administration can cause severe hypotension and anaphylaxis.

### Warfarin

**Half-life 36 hours (5 days for INR normalization)**

**Supratherapeutic INR**

- INR 5-9: Omit 1-2 warfarin doses ± 1-2.5mg PO Vit K
- INR > 9 (NO BLEED): omit 1-2 warfarin doses ± 2.5-5mg PO Vit K

**Active bleeding at any INR:**

- Hold warfarin & give Vit K 5-10mg IV (may repeat q12h). **PLUS either PCC or FFP (PCC is preferred)**
- 4 Factor PCC 25 units/kg if INR >1.7 -<4*
- 4 Factor PCC 35 units/kg if INR 4-6*
- 4 Factor PCC 50 units/kg if INR > 6*
- (dose cap at 100 kg to mitigate thrombotic risk)

**OR**

- FFP 10-30 mL/kg

**Surgery reversal**

- INR > 1.5-2.5
  - Surgery <24 hours: 0.5-1mg IV Vit K x1 +/ 5-8ml/kg FFP
  - Surgery 24-96 hours: 0.5-1mg PO Vit K x1 monitor INR q12-24h

- INR > 2.5-5
  - Surgery <24 hours: 1-2.5mg IV Vit K x1 + 5-8ml/kg FFP
  - Surgery 24-96 hours: 1-2.5mg PO Vit K x1 monitor INR q12-24h

- **Phytonadione (Vitamin K)**
  - **Dose:** See box on left
  - **Administration:** IV- dilute in 50 ml NS and give over 30 minutes
  - **Onset:** PO=24 hours; IV=12 hours
  - **Caution:** IV - may be associated with very small risk of anaphylaxis

**FFP**

- **Dose:** See box on left
- **Administration:** At least 10 ml/min
- **Onset:** 2-6 hours
- **Caution:** Carries risk of infection, must be thawed and a large volume is required (often > 1 liter)

**PCC**

- **Dose:** See box on left
- **Administration:** Place in empty IV bag and give slow IV push over 10 minutes
  - Use within 4 hours of reconstitution
  - **Onset:** <30 minutes
  - **Caution:** thrombotic risk

**Off-label use of rFVIIa/PCC:**

- **Requires attending approval**
- **Document attending name in the order comments**

**Round dose to nearest whole vial**

**Repeat INR 30 minutes after end of PCC infusion.**

Although rarely needed, may consider repeat PCC dose if INR target not achieved

*Denotes that doses are NOT based on high quality evidence.

UFH = unfractionated heparin, PCC = prothrombin complex concentrates (Bebulin), FFP = fresh frozen plasma, rFVIIa = recombinant active factor VIIa (NovoSeven), DDAVP = desmopressin, SNP = slow intravenous push, LMWH = low molecular weight heparin

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Consider the following agents, along with ROTEM testing, if patient refractory to standard therapies:

**DDAVP**  
Mechanism: increases release of vWF and enhances platelet adhesion and aggregation  
**Dose:** 0.3 mcg/kg in 50 ml NS IV over 15 minutes  
**Caution:** Serial doses associated with tachyphylaxis, hyponatremia, and seizures

**Aminocaproic acid:**  
Mechanism: antifibrinolytic  
**Dose:** 4-5 gm loading dose in 250 ml NS over 15 minutes followed by infusion of 1gm/hr infusion until bleeding subsides (max 30 gm/day)  
**Caution:** May require renal adjustment

**Tranexamic acid:**  
Mechanism: antifibrinolytic  
**Dose:** 1 gm loading dose in 50 ml NS IV over 10 minutes followed by 1 gm in 250 ml NS infused over the next 8 hours  
**Caution:** May require renal adjustment

**Table 2: Reversal for ANTIPLATELET therapy**

<table>
<thead>
<tr>
<th></th>
<th>HALF-LIFE</th>
<th>REVERSAL AGENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASPIRIN</strong></td>
<td>15-30 minutes</td>
<td>DDAVP</td>
<td>May need transfusion of functioning platelets to attenuate bleeding</td>
</tr>
<tr>
<td></td>
<td>5-10 days for platelet recovery</td>
<td>Dose: 0.3 mcg/kg IV x 1 Administration: over 15 minutes Onset: Immediate Caution: Serial doses associated with tachyphylaxis, hyponatremia, and seizures</td>
<td></td>
</tr>
<tr>
<td><strong>CLOPIDOGREL</strong></td>
<td>8 hours ~ 5 days for platelet recovery</td>
<td>DDAVP</td>
<td>May need transfusion of functioning platelets to attenuate bleeding</td>
</tr>
<tr>
<td>(Plavix®)</td>
<td></td>
<td>Dose: 0.3 mcg/kg IV x 1 Administration: over 15 minutes Onset: Immediate Caution: Serial doses associated with tachyphylaxis, hyponatremia, and seizures</td>
<td></td>
</tr>
<tr>
<td><strong>PRASUGREL</strong></td>
<td>7 hours &lt;7 days for platelet recovery</td>
<td>DDAVP</td>
<td>May need transfusion of functioning platelets to attenuate bleeding</td>
</tr>
<tr>
<td>(Effient®)</td>
<td></td>
<td>Dose: 0.3 mcg/kg IV x 1 Administration: over 15 minutes Onset: Immediate Caution: Serial doses associated with tachyphylaxis, hyponatremia, and seizures</td>
<td></td>
</tr>
<tr>
<td><strong>TICAGRELOR</strong></td>
<td>~ 9 hours 3 days for platelet recovery</td>
<td>DDAVP</td>
<td>May need transfusion of functioning platelets to attenuate bleeding</td>
</tr>
<tr>
<td>(Brilinta®)</td>
<td></td>
<td>Dose: 0.3 mcg/kg IV x 1 Administration: over 15 minutes Onset: Immediate Caution: Serial doses associated with tachyphylaxis, hyponatremia, and seizures</td>
<td></td>
</tr>
<tr>
<td><strong>Gp Iib-IIIa</strong></td>
<td>30-120 minutes</td>
<td>DDAVP</td>
<td>May need transfusion of functioning platelets to attenuate bleeding</td>
</tr>
<tr>
<td>Eptifibatide (Integrilin®)</td>
<td></td>
<td>Dose: 0.3 mcg/kg IV x 1 Administration: over 15 minutes Onset: Immediate Caution: Serial doses associated with tachyphylaxis, hyponatremia, and seizures</td>
<td></td>
</tr>
<tr>
<td>Abciximab (Reopro®)</td>
<td></td>
<td>Dose: 0.3 mcg/kg IV x 1 Administration: over 15 minutes Onset: Immediate Caution: Serial doses associated with tachyphylaxis, hyponatremia, and seizures</td>
<td></td>
</tr>
<tr>
<td>Tirofiban (Aggrastat®)</td>
<td></td>
<td>Dose: 0.3 mcg/kg IV x 1 Administration: over 15 minutes Onset: Immediate Caution: Serial doses associated with tachyphylaxis, hyponatremia, and seizures</td>
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UFH=unfractionated heparin, PCC = prothrombin complex concentrates (Bebulin), FFP = fresh frozen plasma, rVIIa = recombinant active factor VIIa (NovoSeven), DDAVP = desmopressin, SIVP = slow intravenous push, LMWH=low molecular weight heparin  
*Denotes that doses are NOT based on high quality evidence
OVERALL MANAGEMENT OF ANTICOAGULATED BLEEDING PATIENT

Bleeding event associated with anticoagulation

Assess severity of bleed

Non-life threatening
(eg- nosebleed lasting <1 hour; small amount of blood in stool; bleeding in oral cavity)
- Hold anticoagulation
- Consider low dose IV vitamin K 1-2.5 mg
- Monitor response to interventions and ongoing coagulation parameters

Life-threatening bleed
- Intracerebral
- Gastrointestinal
- Genitourinary
- Intraperitoneal
- Retroperitoneal
- Bleeding into extremity with risk of compartment syndrome

Discontinue all anticoagulant therapy

Assessment and continual re-assessment
- Vital signs
- Coagulation parameters

Give antidote if one exists
- Vitamin K
- Protamine
- Platelets (for patients recently on anti-platelet therapy)

Identify and address source of bleed

Institute supportive strategies as needed
- Consider transfer to intensive care unit
- Intubation, fluid resuscitation, transfusion as needed
- Notify other services as needed (eg- endoscopy, radiology, surgery, OR) and have them on standby

Consider non-specific hemostatic therapies
- FFP
- PCCs
- rFVIIa
- DDAVP
- Antifibrinolytics (aminocaproic acid, tranexamic acid)

Consider methods to remove anticoagulant
- Dialysis
- Hemoperfusion
- Plasmapheresis
REFERENCES:


Originated by: Thomas Dilworth, PharmD; Allison Burnett, PharmD; Isaac Tawil, MD; David Garcia, MD
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