# 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>DIRECT THROMBIN INHIBITORS (DTIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV:</td>
<td>Argatroban - Bivalirudin (Angiomax®)</td>
<td>Short half-life and discontinuation of DTI are primary means of attenuating bleed – support with crystalloid and blood products to facilitate rapid renal clearance of drug</td>
</tr>
<tr>
<td></td>
<td>Half-life 10-90 minutes</td>
<td></td>
</tr>
<tr>
<td>PO:</td>
<td>Dabigatran (Prada®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Half-life 12-17 hours in normal renal function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The aPTT is currently the only readily available lab test to QUALITATIVELY measure dabigatran. Do not use PT/INR</td>
<td></td>
</tr>
</tbody>
</table>

### 4 Factor PCC
- **Dose**: 50 units/kg *(dose cap at 100 kg to mitigate thrombotic risk)*
- **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

### rFVIIa
- **Dose**: 100 mcg/kg *(dose cap at 100 kg to mitigate thrombotic risk)*
- **Administration**: IV bolus over 3-5 minutes
- **Use within 3 hours of reconstitution**
- **Onset**: <30 minutes
- **Caution**: thrombotic risk

### Factor XA INHIBITORS
- Fondaparinux (Arixtra®) | |
| Half-life 17-21 hours in normal renal function | |
| Rivaroxaban (Xarelto®) | |
| Half-life 5-9 hours (up to 13 hours in elderly) | |
| Apixaban (Eliquis®) | |
| Half-life 8-15 hours | |
| 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. | |

### 4 Factor PCC
- **Dose**: 50 units/kg *(dose cap at 100 kg to mitigate thrombotic risk)*
- **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

### rFVIIa
- **Dose**: 100 mcg/kg *(dose cap at 100 kg to mitigate thrombotic risk)*
- **Administration**: IV bolus over 3-5 minutes
- **Use within 3 hours of reconstitution**
- **Onset**: <30 minutes
- **Caution**: thrombotic risk

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

<table>
<thead>
<tr>
<th>Protamine</th>
<th>Dose: 1 mg reverses 100 units of UFH</th>
<th>Dose per 100 units UFH over last 3h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since UFH</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>&lt;30 min</td>
<td>1 mg</td>
<td></td>
</tr>
<tr>
<td>30-120 min</td>
<td>0.5 mg</td>
<td></td>
</tr>
<tr>
<td>&gt;120 min</td>
<td>0.25 mg</td>
<td></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>(Does not reverse LMWH as effectively as it does UFH)</th>
<th>Dose: 1 mg for each 1 mg of enoxaparin in last 8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since LMWH</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>&lt;30 min</td>
<td>1 mg</td>
<td></td>
</tr>
<tr>
<td>30-120 min</td>
<td>0.5 mg</td>
<td></td>
</tr>
<tr>
<td>&gt;120 min</td>
<td>0.25 mg</td>
<td></td>
</tr>
</tbody>
</table>

- If >12 hrs have elapsed since LMWH administration, protamine may not be needed  
- 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

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

<table>
<thead>
<tr>
<th>SUPRATHERAPEUTIC INR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 5-9: Omit 1-2 warfarin doses ± 1-2.5mg PO Vit K</td>
<td></td>
</tr>
<tr>
<td>INR &gt; 9 (NO BLEED): omit 1-2 warfarin doses ± 2.5-5mg PO Vit K</td>
<td></td>
</tr>
</tbody>
</table>

**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 |
| Onset: <30 minutes |
| Caution: thrombotic risk |

**APPROVAL**

- On-label use of rFVIIa/PCC:  
  - Requires attending approval |
  - Document attending name in the order comments |
- **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

**UFH=unfractionated heparin, PCC = prothrombin complex concentrates (Bebulin), FFP = fresh frozen plasma, rFVIIa = 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
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><strong>DDVAP</strong></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><strong>Dose:</strong> 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> (Plavix®)</td>
<td>8 hours</td>
<td><strong>DDVAP</strong></td>
<td>May need transfusion of functioning platelets to attenuate bleeding</td>
</tr>
<tr>
<td></td>
<td>~ 5 days for platelet recovery</td>
<td><strong>Dose:</strong> 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> (Effient®)</td>
<td>7 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;7 days for platelet recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TICAGRELOR</strong> (Brilinta®)</td>
<td>~ 9 hours</td>
<td><strong>DDVAP</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 days for platelet recovery</td>
<td><strong>Dose:</strong> 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> Eptifibatide (Integrilin®) Abciximab (Reopro®) Tirofiban (Aggrastat®)</td>
<td>30-120 minutes</td>
<td><strong>DDVAP</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Dose:</strong> 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
Last reviewed and approved by: UNMH Anticoagulation Subcommittee April 2013