**Anticoagulation Reversal: Unfractionated Heparin (UFH) and Low Molecular Weight Heparin (LMWH)**

- **Patient with life-threatening or major bleeding while on UFH/LMWH**
  - Life-threatening or major bleeding may include:
    - Intracranial hemorrhage
    - GI hemorrhage requiring intervention
    - Retropharyngeal or retroperitoneal bleeding
    - Emergent surgery
    - Ruptured hollow viscus
    - Intraocular bleed compromising vision
    - Cardiac tamponade

- **Discontinue UFH/LMWH**
- **Consider indication for anticoagulation when considering interventions for bleeding**
- **Fluid replacement and hemodynamic support**
  - Consider PRBC

### UFH

<table>
<thead>
<tr>
<th>If UFH was given as:</th>
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<tr>
<td>IV bolus within:</td>
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<tr>
<td>&lt; 30 mins: 1 mg protamine*/ 100 units UFH</td>
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<tr>
<td>30-60 mins: 0.5 mg protamine*/ 100 units UFH</td>
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<tr>
<td>1-3 hrs: 0.25 mg protamine*/ 100 units UFH</td>
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<tr>
<td><strong>Maximum protamine dose:</strong> 50mg</td>
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<tr>
<td><strong>Continuous infusion:</strong> 1 mg protamine*/ 100 units UFH infused over the last 3 hrs</td>
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<tr>
<td><strong>Subcutaneous:</strong> 1 mg protamine*/100 units UFH given in the last 12 hrs</td>
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<tr>
<td>Give 25 mg as a bolus over at least 5 mins followed by an infusion of the remainder of the dose over 8 hrs</td>
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<tr>
<td>Check aPTT and/or activated clotting time (ACT) 5–15 mins after protamine administration.</td>
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<tr>
<td>If aPTT/ACT remains elevated with active bleeding, consider additional, lower dose of protamine.</td>
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### LMWH

<table>
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<tr>
<th>If LMWH given:</th>
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<tr>
<td>≤ 8 hrs ago: 1 mg protamine* per 1 mg enoxaparin (or 100 anti-Xa Units of other LMWH e.g. dalteparin)</td>
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<tr>
<td>8-12 hrs ago: 0.5 mg protamine* per 1 mg enoxaparin</td>
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<tr>
<td>≥ 12 hrs ago: protamine administration may not be advisable; factors such as dose and renal function should be considered. A reduced dose of protamine may also be considered.</td>
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<tr>
<td><strong>Maximum protamine dose:</strong> 50mg</td>
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<tr>
<td>Check aPTT level 2–4 hrs after first protamine dose</td>
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<tr>
<td>For normal treatment doses of LMWH, it is unlikely that aPTT will be elevated</td>
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<tr>
<td>If bleeding continues, may repeat with reduced dose 0.25-0.5 mg protamine* per 1 mg enoxaparin (or 100 anti-Xa units of other LMWH).</td>
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<tr>
<td>Since LMWHs are not fully reversed by protamine, some case reports have used Recombinant Factor VIIa (FVIIa) in life-threatening bleeding.</td>
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<tr>
<td>Safety for this indication is unknown and there is concern for the risk of thrombotic events. FVIIa is generally not recommended in cases of intracerebral hemorrhage</td>
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<tr>
<td>Hematology consultation should be considered prior to using FVIIa</td>
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<tr>
<td>There is no established dose of FVIIa but low doses (1–2 mg) are advised</td>
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</tbody>
</table>

### Protamine Sulfate:

- Protamine neutralizes anti-factor IIa activity of LMWH but not anti-factor Xa activity
- Protamine does not reverse fondaparinux
- Increased risk of hypersensitivity reaction among (may consider premedication with corticosteroid/antihistamine if time permits):
  - Vasectomized or sterile males
  - Patients with fish (not shellfish) allergy
  - Patients who use protamine-containing insulin (NPH or NPH-containing combinations)
- Protamine test dose: protamine prescribing information does not include a recommendation for a test dose, nor do standard references.
  - Some authors recommend that a small intravenous dose of protamine (5–10 mg) be given to test the sensitivity in potentially allergic patients.
  - Slow administration (max 5 mg/min) to minimize adverse reactions. **Max single dose= 50 mg in any 10 min period.** Doses ≤ 25 mg may be given as IV push over at least 5 mins. Doses > 25 mg should be given as IV piggyback over at least 10 mins.

*Slow administration (max 5 mg/min) to minimize adverse reactions. Max single dose= 50 mg in any 10 min period. Doses ≤ 25 mg may be given as IV push over at least 5 mins. Doses > 25 mg should be given as IV piggyback over at least 10 mins.*
References


Guideline Authors

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- Antolin Flores, MD

Guideline Approved


Disclaimer: Clinical practice guidelines and algorithms at The Ohio State University Wexner Medical Center (OSUWMC) are standards that are intended to provide general guidance to clinicians. Patient choice and clinician judgment must remain central to the selection of diagnostic tests and therapy. OSUWMC’s guidelines and algorithms are reviewed periodically for consistency with new evidence; however, new developments may not be represented.

OSUWMC Tools

- Dabigatran (Pradaxa®) Reversal Treatment for Bleeding Events
- Rivaroxaban (Xarelto®), Apixaban (Eliquis®), Edoxaban (Savaysa®): Factor Xa Inhibitors-Reversal Treatment for Bleeding
- Warfarin: Management of Elevated INR and Reversal

Quality Measures

- Rate of hypersensitivity reactions to protamine
- Rate of premedication use prior to protamine administration
- Dose of protamine administered and frequency of repeat doses
- Frequency of Recombinant Factor VIIa administration for LMWH reversal
- Thrombotic events:
  - Pulmonary embolism (PE)
  - Deep vein thrombosis (DVT)
  - Myocardial infarction (MI)
  - Stroke

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