Unfractionated Heparin (UFH) and Low Molecular Weight Heparin (LMWH) Reversal

- 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

If UFH was given as:
- **IV bolus within**:
  - ≤ 30 mins: 1 mg protamine*/100 units UFH
  - 30-60 mins: 0.5 mg protamine*/100 units UFH
  - 1-3 hrs: 0.25 mg protamine*/100 units UFH
- **Continuous infusion**: 1 mg protamine*/100 units UFH infused over the last 3 hrs
- **Subcutaneous**: 1 mg protamine*/100 units UFH given in the last 12 hrs
  - Give 25 mg as a bolus over at least 5 mins followed by an infusion of the remainder of the dose over 8 hrs
- **Maximum protamine dose**: 50mg

- Check aPTT and/or activated clotting time (ACT) 5–15 mins after protamine administration.
- If aPTT/ACT remains elevated with active bleeding, consider additional, lower dose of protamine.

If LMWH given:
- ≤ 8 hrs ago: 1 mg protamine* per 1 mg enoxaparin (or 100 anti-Xa Units of other LMWH e.g. dalteparin)
- 8-12 hrs ago: 0.5 mg protamine* per 1 mg enoxaparin
- ≥ 12 hrs ago: protamine administration may not be advised; factors such as dose and renal function should be considered. A reduced dose of protamine may also be considered.
- **Maximum protamine dose**: 50mg

- Check aPTT level 2–4 hrs after first protamine dose
- For normal treatment doses of LMWH, it is unlikely that aPTT will be elevated
- 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).
- Since LMWHs are not fully reversed by protamine, some case reports have used Recombinant Factor VIIa (FVIIa) in life-threatening bleeding.
  - 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
  - Hematology consultation should be considered prior to using FVIIa
  - There is no established dose of FVIIa but low doses (1–2 mg) are advised

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.
References


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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