UNFRACTIONATED HEPARIN, LOW MOLECULAR WEIGHT HEPARIN AND FONDAPARINUX

OBJECTIVE:
To aid practitioners in prescribing unfractionated heparin (UFH), low molecular weight heparins (LMWH) and fondaparinux to patients.

MECHANISM OF ACTION:
UFH and LMWH act as anticoagulants by forming complexes with and substantially increasing the activity of antithrombin (AT). The AT-UFH or AT-LMWH complexes catalyze the inhibition of several activated blood coagulation factors: especially thrombin (factor IIa) and factor Xa, as well as factors IXa, Xla and XIIa. This ultimately reduces the formation of thrombin and fibrin.

LMWH are derived by chemical or enzymatic depolymerization of UFH. These smaller molecules retain the ability to inactivate Factor Xa but have substantially reduced inhibitory activity against thrombin (Factor IIa). LMWHs have more predictable pharmacokinetic properties compared with UFH; this allows LMWHs to be administered in fixed doses based on patient weight, without the need for dose adjustment based on laboratory monitoring.

Fondaparinux is a synthetic and specific inhibitor of activated factor X (Xa). Its mechanism of action is also the potentiation of antithrombin. AT-fondaparinux complexes selectively inhibit factor Xa. Neutralization of factor Xa reduces the formation of thrombin and fibrin. Fondaparinux does not inactivate thrombin.

USES FOR UFH AND LMWH:
1. Prevention and treatment of venous thromboembolism (VTE)
2. Treatment of superficial venous thrombosis (SVT) depending on extent and most proximal location of SVT (see Guide: Superficial Phlebitis / Superficial Vein Thrombosis)
3. Acute coronary syndromes
   - Unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)
   - ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolitics, percutaneous coronary intervention (PCI), or no form of reperfusion therapy.
4. During and/or after certain cardiovascular procedures including coronary artery bypass surgery and peripheral arterial surgery
5. During hemodialysis to prevent clotting of the dialysis circuit
6. Bridging during temporary warfarin interruption in high risk and some intermediate risk patients (see Guide: Warfarin: Perioperative Management)
7. Anterior wall myocardial infarction (MI)
8. Intracardiac thrombus
9. Systemic arterial embolism
10. Selected stroke syndromes
11. Cervical artery dissection

USES FOR FONDAPARINUX:

1. Prevention and treatment of VTE
2. Treatment of SVT depending on extent and most proximal location of SVT (see Guide: Superficial Phlebitis / Superficial Vein Thrombosis)
3. Acute coronary syndromes:
   - Unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)
   - ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or no form of reperfusion therapy.
   - Note: In patients undergoing any percutaneous coronary intervention (PCI), the use of fondaparinux as the sole anticoagulant is not recommended because of an increased risk of guiding catheter thrombosis. An effective anti-thrombin regimen such as UFH should be used as an adjunct to PCI.
4. Prevention and treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT)

DOSESING OF UFH:

Intravenous (IV) UFH must be adjusted to maintain a therapeutic activated partial thromboplastin time (aPTT). See below for details.

- **VTE prophylaxis**: 5,000 U subcutaneously (SC) q8h or q12h.
- **Acute VTE treatment**: IV bolus 5,000 U (or 80 U/kg) followed by a rate of 20 U/kg/hour adjusted to maintain a therapeutic aPTT.
- **Acute VTE treatment for non-hospitalized patients**: initial dose of 333 U/kg SC followed by 250 U/kg SC q12h.
- **Acute coronary syndromes** (intermediate and high-risk unstable angina, non-ST segment elevation MI): IV bolus 60-70 U/kg (maximum 5,000 U) followed by 12-15 U/kg/hour (maximum 1,000 U/hour) adjusted to maintain a therapeutic aPTT.
- **ST segment elevation MI patients who have received a fibrinolytic agent (t-PA or TNK)**: IV bolus 60 U/kg (maximum 4,000 U) followed by a rate of 12 U/kg/hour (maximum 1,000 U per hour) adjusted to maintain a therapeutic aPTT.

DOSESING OF LMWH:

Dosing of LMWH depends on the drug used. In Canada, the four commonly used LMWHs are dalteparin (Fragmin®), enoxaparin (Lovenox®), nadroparin (Fraxiparine®), and tinzaparin (Innohep®).

Note: Therapeutic dosing of LMWH is based on actual body weight and should not be capped; there is currently no established maximum dose in VTE treatment.
• **VTE prophylaxis:**
  - dalteparin: 5,000 U once daily (OD)
  - enoxaparin: 40 mg OD or 30 mg twice daily (BID)
  - nadroparin: 2,850 U OD (general surgery); 38 U/kg OD (orthopedic surgery)
  - tinzaparin: 50 - 75 U/kg OD (usually either 3500 or 4500 U OD; 3500 U OD for general surgery)

• **VTE treatment:**
  - dalteparin: 200 U/kg OD or 100 U/kg BID
  - enoxaparin: 1.5 mg/kg OD or 1 mg/kg BID
  - nadroparin: 171 U/kg OD or 86 U/kg BID
  - tinzaparin: 175 U/kg OD

• **Acute coronary syndromes:**
  - Intermediate and high-risk unstable angina, non-ST segment elevation MI:
    - enoxaparin: 1 mg/kg BID
    - dalteparin: 100 U/kg BID
    - nadroparin: 86 U/kg IV bolus, then 85 U/kg BID
  - ST segment elevation MI patients:
    - enoxaparin: <75 years – 30 mg IV x 1, then enoxaparin 1 mg/kg SC BID
      ≥75 years – 0.75 mg/kg SC BID

**DOSING OF FONDAPARINUX:**

- **VTE prophylaxis:** 2.5 mg once daily
- **VTE treatment:**
  5 mg once daily for weight <50 kg
  7.5 mg once daily for weight 50 -100 kg
  10 mg once daily for weight >100 kg
- **Acute coronary syndromes:** 2.5 mg once daily

**MONITORING OF UFH, LMWH AND FONDAPARINUX:**

- **IV UFH:** Inadequate UFH therapy in the initial 24-48 hours of treatment predisposes to recurrent VTE. The use of an UFH dosing nomogram is encouraged because it helps achieve and maintain the aPTT in the therapeutic range efficiently. aPTT reagents vary in their sensitivity to UFH; therefore, each laboratory should establish a therapeutic range locally.

  Prior to starting IV UFH, a baseline complete blood count (CBC), prothrombin time (PT)/international normalized ratio (INR) and aPTT should be done. Monitoring of the aPTT is initially required every 6 hours to guide adjustment of the infusion rate. Once a therapeutic range is achieved, then the aPTT can be checked once daily. Monitoring of the platelet count in patients receiving full-dose IV UFH is advised if the infusion will be given for ≥4 days, due to the risk of heparin-induced thrombocytopenia (HIT).
• **LMWH:** Prior to starting LMWH, a baseline complete blood count (CBC) and creatinine should be done. Laboratory monitoring is not generally required in patients receiving a LMWH. In patients receiving therapeutic LMWH with moderate to severe renal insufficiency or during pregnancy, laboratory monitoring with anti-factor Xa levels may be warranted, although target ranges are uncertain. Usual therapeutic doses of tinzaparin, without anti-factor Xa monitoring, have been used effectively and safely in patients with renal failure (down to a creatinine clearance [CrCl] of 20 mL/min).

• **Fondaparinux:** Laboratory monitoring of fondaparinux should be done in consultation with a specialist. Specific calibrators are required and a universal therapeutic target has not been established.

**Adverse Effects:**

• **Bleeding** is the most common adverse effect of UFH, LMWH and fondaparinux.

• **Heparin-induced thrombocytopenia (HIT):** Immune-mediated platelet activation has been reported in up to 5% of patients who receive UFH depending on the patient population. It may be associated with life-threatening or fatal arterial or venous thrombosis. Onset is generally between 5 and 10 days after commencing therapy, unless there has been a recent prior exposure to UFH or LMWH, in which case HIT can occur earlier. HIT occurs far less frequently in patients who are receiving LMWH. If HIT is suspected or diagnosed, all sources of heparin must be stopped, and an alternative “HIT-safe” anticoagulant such as argatroban, danaparoid, bivalirudin, fondaparinux, or a direct oral anticoagulant should generally be started. There is some evidence to support the safety of direct oral anticoagulants for treatment of HIT, but their use for this purpose is still considered off label; as is that of bivalirudin and fondaparinux.

• **Osteoporosis** is an uncommon side-effect associated with prolonged use of high doses of UFH. Three months of UFH treatment at a moderate dose (20,000 U/day) is rarely associated with clinically-significant osteoporosis.

• **Hyperkalemia** is a rare complication of UFH and is caused by aldosterone suppression.

• **Mildly increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT)** with no evidence of clinical liver dysfunction may occur in patients who receive UFH or LMWH. This does not appear to be clinically significant. Transaminase values generally return to normal within 15-30 days.

**Peri-procedure management:**

• For therapeutic IV UFH, stop heparin infusion 4-6 hours prior to a procedure; consideration should be given to re-checking the aPTT to ensure normalization.

• There is no need to stop prophylactic doses of UFH prior to most procedures; however, anesthetic guidelines and local anesthetic practices should be followed for patients receiving neuroaxial anesthesia.

• For once-daily therapeutic LMWH, stop at least 24 hours prior to procedure depending on renal function, risk of bleeding, and indication for anticoagulation. For twice-daily LMWH, stop at least 12 hours prior to the procedure. For patients receiving neuroaxial anesthesia, anesthetic guidelines and local anesthetic practices should be followed.
• There is no need to stop prophylactic doses of LMWH prior to most procedures; however, anesthetic guidelines and local anesthetic practices should be followed for patients receiving neuroaxial anesthesia.
• The half-life of fondaparinux is approximately 17-21 hours in normal renal function. Stopping at least 24 hours prior to most procedures is suggested. Anesthetic guidelines and local anesthetic practices should be followed for patients receiving neuroaxial anesthesia.

**BLEEDING MANAGEMENT OR EMERGENCY SURGERY:**

UFH, LMWH and fondaparinux should be stopped in case of serious bleeding. When reversal of IV UFH is required, protamine sulfate can be used to reverse the anticoagulant effect. 1 mg of protamine reverses 100 U of UFH. One approach to determine the required dose of protamine is: take 100% of the UFH dose given in the previous hour + 50% of the UFH dose given in the hour before + 25% of the UFH dose given in the hour before that; this is an estimate of the amount of UFH to be reversed. The usual initial dose of protamine is 20-50 mg by slow intravenous infusion over 15-20 minutes due to the risk of anaphylactoid reactions.

LMWH rarely needs to be reversed acutely, and protamine is much less effective than for UFH.

No reversal agent is currently available in Canada for fondaparinux.

Andexanet alfa, an antidote that rapidly reverses the anticoagulant activity of all factor Xa inhibitors (UFH, LMWH, fondaparinux, and direct factor Xa inhibitors such as rivaroxaban, apixaban and edoxaban) has shown efficacy in clinical trials, but is not yet approved by Health Canada.

**SPECIAL CONSIDERATIONS:**

**Overlap with warfarin**

In most cases, warfarin can be started on the same day as UFH, LMWH or fondaparinux. Warfarin and UFH, LMWH or fondaparinux should overlap for at least 5 days and until the INR value is within therapeutic range for 2 consecutive days.

**Pregnancy**

The management of thromboembolism during pregnancy requires LMWH or, less commonly, UFH. Consultation with a specialist is advised. Peripartum management of anticoagulation requires advanced planning. Secondary prevention in the postpartum period can be achieved with LMWH or warfarin. Women can breastfeed while being treated with LMWH or warfarin therapy. There are very limited clinical data available on the use of fondaparinux in pregnant women.

**Renal Impairment**

LMWHs are renally excreted and thus bioaccumulation may occur in patients with renal impairment. There are data to suggest differences exist in the rate of accumulation among various LMWH agents. CrCl should be calculated using the Cockcroft-Gault equation in all patients receiving LMWH. In patients receiving therapeutic doses of LMWH who have a CrCl <30 mL/min, consultation with a
specialist is advised. For tinzaparin, available evidence demonstrates no accumulation in patients with CrCl levels down to 20 mL/min. There are limited data available in patients with an estimated CrCl <20 mL/min. If therapeutic doses of LMWH are used in patients with severe renal dysfunction (<30 mL/min), testing anti-factor Xa levels to monitor for accumulation should be considered. Some experts suggest a dose reduction should be considered if the trough anti-Xa level is >0.4 IU/mL; however, good data showing a correlation between these levels and poor clinical outcomes are lacking. Fondaparinux is excreted unchanged in the urine and bioaccumulation is expected to occur in patients with renal impairment. Fondaparinux is contraindicated in patients with a CrCl <30 mL/min.

**Pediatrics**

In children, studies have demonstrated age-dependent dosing of UFH and LMWH. Therapeutic UFH is titrated to achieve a target anti-Xa range of 0.35-0.7 U/mL or an aPTT range that correlates with this anti-Xa range. If UFH boluses are used to initiate therapy, the bolus should be no greater than 75-100 U/kg, and boluses should be withheld or reduced if there are significant bleeding risks. Where possible, pediatricians with expertise in thromboembolism should manage pediatric patients with thromboembolism. When this is not possible, coordinated care by a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

**OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**

- Cancer and Thrombosis
- Deep Vein Thrombosis (DVT): Treatment
- Heparin-Induced Thrombocytopenia (HIT)
- Pregnancy: Thromboprophylaxis
- Pregnancy: Venous Thromboembolism Treatment
- Pulmonary Embolism (PE): Treatment
- Superficial Phlebitis / Superficial Vein Thrombosis
- Thromboprophylaxis: Hospitalized Medical Patients
- Thromboprophylaxis: Nonorthopedic Surgery
- Thromboprophylaxis: Orthopedic Surgery
- Warfarin: Perioperative Management

**REFERENCES:**


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Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.