Unfractionated Heparin, Low Molecular Weight Heparin and Fondaparinux

Thrombosis Canada
Thrombose Canada

Objective:

To aid practitioners in prescribing unfractionated heparin (UFH), low molecular weight heparin (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, XIa, and XIIa. This ultimately reduces the formation of thrombin and fibrin.

LMWH is 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. LMWH has more predictable pharmacokinetic properties compared with UFH; this allows LMWH to be administered in fixed doses based on patient weight, without the need for adjustment based on laboratory monitoring in most clinical settings.

Fondaparinux is a synthetic and specific inhibitor of factor Xa. It also acts by potentiating antithrombin's activity. AT-fondaparinux complexes selectively inhibit factor Xa. Neutralization of factor Xa reduces the formation of thrombin and fibrin. Fondaparinux does not inactivate thrombin.

Indications for UFH and LMWH:

1. Prevention and treatment of venous thromboembolism (VTE) (see **Clinical Guides:** **Thromboprophylaxis: Hospitalized Medical Patients**, **Thromboprophylaxis: Non-Orthopedic Surgery**, **Thromboprophylaxis: Orthopedic Surgery**, **Cancer and Thrombosis**, **Deep Vein Thrombosis (DVT): Treatment**, **Pulmonary Embolism (PE): Treatment**).
2. Treatment of superficial venous thrombosis (SVT), depending on extent and most proximal location of SVT (see **Clinical Guide:** **Superficial Thrombophlebitis / Superficial Vein Thrombosis**)
3. Acute coronary syndromes (unstable angina, NSTEMI, STEMI managed with or without PCI)
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 select patients (see **Clinical Guide:** **Warfarin: Perioperative Management**, and **Clinical Tool** Perioperative Anticoagulant Management Algorithm)
7. Anterior wall myocardial infarction (MI) for prevention of LV thrombus
8. Intracardiac thrombus

9. Systemic arterial embolism, eg. acute limb ischemia
10. Selected stroke syndromes, but **not** typically in those associated with atrial fibrillation
11. Cervical artery dissection
12. Purpura fulminans
13. Anticoagulation during pregnancy (see **Clinical Guides:** **Pregnancy: Venous Thromboembolism Treatment** **and** **Pregnancy: Thromboprophylaxis**)

Uses for fondaparinux:

1. Prevention and treatment of VTE (see
2. **Clinical Guides:** **Thromboprophylaxis: Hospitalized Medical Patients**, **Thromboprophylaxis: Non-Orthopedic Surgery**, **Thromboprophylaxis: Orthopedic Surgery**, **Cancer and Thrombosis**, **Deep Vein Thrombosis (DVT): Treatment**, **Pulmonary Embolism (PE): Treatment**).
3. Treatment of SVT, depending on extent and most proximal location of SVT (see **Clinical Guide:** **Superficial Thrombophlebitis / Superficial Vein Thrombosis**)
4. Acute coronary syndromes (unstable angina, NSTEMI, STEMI managed without PCI)
    - Note: In patients undergoing PCI, the use of fondaparinux as the sole anticoagulant is genereally not recommended because of an increased risk of guiding-catheter thrombosis. The addition of an anti-thrombin agent (eg, UFH) at the time of PCI has been shown to reduce angiographic complications. The ultimate choice of agent(s) should be guided by institution-specific protocols.

5. Prevention and treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) (see **Clinical Guide:** **Heparin-induced Thrombocytopenia**)

Dosing 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 units (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 or anti-factor Xa assay (or based on local institutional guidelines).
- **Acute VTE treatment for non-hospitalized patients:** initial dose of 333 U/kg SC followed by 250 U/kg SC q12h. This protocol is validated for patients with serum creatinine levels below 200 µmol/L.
- **Acute coronary syndromes** (intermediate and high-risk UA/NSTEMI): 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 or anti-factor Xa assay (follow local institutional guidelines).
- **STEMI 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 or anti-factor Xa assay (follow institutional guidelines).

Dosing of LMWH:

Dosing of LMWH depends on the drug used. In Canada, the three commonly used LMWHs are dalteparin (Fragmin®), enoxaparin (Lovenox®), 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 SC once daily (OD)
  enoxaparin: 40 mg OD or 30 mg twice daily (BID)
  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
  tinzaparin: 175 U/kg OD

- **Acute coronary syndromes:**
  Intermediate- and high-risk UA/NSTEMI:
  enoxaparin: 1 mg/kg BID
  dalteparin: 100 U/kg BID
- STEMI 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 progressive and/or recurrent VTE. The use of a standardized UFH dosing nomogram is encouraged to help achieve and maintain the aPTT in the therapeutic range efficiently. As aPTT reagents vary in their sensitivity to UFH, 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 drawn. Monitoring of the aPTT is initially required q6h to guide adjustment of the infusion rate. Once a therapeutic range is achieved, the aPTT can be checked once daily. In patients with antiphospholipid syndrome, aPTT may be prolonged at baseline due to the presence of a lupus anticoagulant. Therefore, anti-Xa monitoring may be required, and a specialist is recommended. Monitoring of the platelet count in patients receiving IV UFH is advised if the infusion will be given for ≥4 days, due to the risk of developing HIT (see **Clinical Guide:** **Heparin-induced Thrombocytopenia**).
- **LMWH:** Prior to starting LMWH, a baseline CBC and creatinine should be checked. Laboratory monitoring is not generally required in patients receiving 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 (see section below on Renal Impairment).
- **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.
- **HIT** is an immune-mediated platelet activation disorder and has been reported in up to 5% of patients who receive UFH. 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 receiving LMWH. If HIT is suspected or diagnosed, all sources of heparin must be stopped (e.g. flushes, prothrombin complex concentrate, some total parenteral nutrition), 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 (see **Clinical Guide:** Heparin-induced Thrombocytopenia).
- **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-procedural 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, particularly before procedures with higher bleeding risk.
- There is no need to stop prophylactic doses of UFH or LMWH prior to most procedures; however, anesthetic guidelines and local anesthetic practices should be followed for patients receiving neuraxial anesthesia (e.g. epidural or spinal anesthetic).
- For OD therapeutic LMWH, the last dose should be given 2 days before the procedure, depending on renal function, risk of bleeding, and indication for anticoagulation. For select high-risk patients, a single BID dose of LMWH can be given >24 hours prior to procedure; depending on the timing of the baseline OD dose, this may require one or two BID doses (see **Table 1** below). For LMWH given BID at baseline, the last dose should be given >24 hours prior to the procedure (see Table 1). For patients receiving neuraxial anesthesia, anesthetic guidelines and local anesthetic practices should be followed.

Table 1: Preoperative management of LMWH depending on baseline dose and timing.

OD dose given in AM		
Day	AM	PM
-3	OD dose	0
-2	OD dose	0
-1	BID dose	0
0	0	0

OD dose given in PM		
Day	AM	PM
-3	0	OD dose
-2	0	BID dose
-1	BID dose	0
0	0	0

BID dosing		
Day	AM	PM
-3	BID dose	BID dose
-2	BID dose	BID dose
-1	BID dose	0
0	0	0

Day 0 represents the day of the procedure/surgery. For CrCl ≥ 30 mL/min, examples of OD LMWH doses are dalteparin 200 U/kg SC OD and enoxaparin 1.5 mg/kg SC OD, while examples of BID doses are dalteparin 100 U/kg SC BID or enoxaparin 1 mg/kg SC BID.

- The half-life of fondaparinux is approximately 17-21 hours in patients with normal renal function. The last dose should be given at least 48 hours prior to most procedures, depending on renal function, risk of bleeding, and indication for anticoagulation. Anesthetic guidelines and local anesthetic practices should be followed for patients receiving neuraxial anesthesia.
- Post-operatively, most inpatients require VTE prophylaxis starting the day after surgery (see "Dosing of LMWH" above). Full-dose LMWH can most often be restarted 48-72 hours after an invasive procedure or surgery, depending on the post-operative bleeding risk and the indication for anticoagulation.

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 to 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 IV 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, although it should still be used if necessary.

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 been approved by Health Canada. However, it has been declined by CADTH, INESSS, and Canadian Blood Services for public reimbursement, and hence may not be widely available.

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 (see **Clinical Guides:** **Pregnancy: Venous Thromboembolism Treatment** **and** **Pregnancy: Thromboprophylaxis**).

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 suggest dose-reduction be considered if the trough anti-Xa level is >0.4 IU/mL; however, good data showing a correlation between these levels and clinical outcomes are lacking. Fondaparinux is excreted unchanged in the urine and bioaccumulation is expected to occur in patients with renal impairment, and 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 Thrombophlebitis / Superficial Vein Thrombosis
- Thromboprophylaxis: Hospitalized Medical Patients
- Thromboprophylaxis: Nonorthopedic Surgery
- Thromboprophylaxis: Orthopedic Surgery
- Warfarin: Perioperative Management

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Date of Version: 30April2025

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.