

LOW MOLECULAR WEIGHT HEPARINS (LMWH)

LMWHs have distinct pharmacologic and pharmacokinetic properties as compared to unfractionated heparin (UFH). The LMWHs have reduced anti-factor IIa activity relative to anti-Xa activity. LMWHs have been shown to be at least as safe and effective as unfractionated heparin in the prevention and treatment of DVT and PE, in the treatment of unstable angina and non-Q wave MI.

The LMWHs available in the United States include ardeparin (Normiflo[®], FDA-approved May 1997), dalteparin (Fragmin[®], December 1994), enoxaparin (Lovenox[®], March 1993), and tinzaparin (Innohep[®], July 2000). Other LMWHs available outside the US include certoparin (Alphaparin[®]), nardroparin (Fraxiparin[®]), parnaparin (Fluxum[®]), and reviparin (Clivarin[®]).

All LMWHs differ in their FDA-approved indications. One LMWH cannot be used interchangeably (unit for unit) with UFH or another low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-factor Xa and anti-factor IIa activities, units, and dosage.

I. MECHANISM OF ACTION

Antithrombin III (AT-III) mediated selective inhibition Xa and to a lesser extent IIa.

Any pentasaccharide chain inhibit factor Xa, but only those at least 18 saccharide units long can inactivate thrombin (IIa).

Does not inhibit platelet function.

Inhibits the release of tissue factor pathway inhibitor (TFPI) from endothelial cells.

Distinguishing Features: Although all LMWHs contain heparin fragments smaller than UFH, which typically ranges between 3,000–30,000 daltons, the range and thus the anti Xa to anti IIa ratio varies between the LMWH products available.

• **Ardeparin:** 5500–6500 daltons; anti Xa:IIa ratio 1.7–2.4:1.

• **Dalteparin:** 2000–9000 daltons (14–26% are > 8000 daltons); anti Xa:IIa ratio 2.7:1.

• **Enoxaparin:** 2000–8000 daltons (average 4500 daltons); anti Xa:IIa ratio 2.7–4:1.

• **Tinzaparin:** 2000–8000 daltons (average 5500–7500 daltons); anti Xa:IIa ratio 2.8:1.

II. PHARMACOKINETICS

A) Administered subcutaneously.

B) Compared to UFH, there is reduced binding to plasma proteins leading to improved bioavailability, increased plasma half-life, lower incidence of HIT (less PF4 binding), and lower incidence of osteoporosis (less osteoblast binding).

C) The half-life of enoxaparin, dalteparin, and ardeparin are similar at 4.5, 3–5, and 3 hours, respectively. The half life of tinzaparin is shorter at 1.5 hours.

D) The time to peak anti-Xa effect is 3–5 hours for dalteparin and enoxaparin, while it is shorter for ardeparin (2–3 hours) and longer for tinzaparin (4–6 hours).

E) In most cases the duration of anti-Xa activity is about 12 hours.

F) Clearance is primarily renal. Significant dose reduction or monitoring levels is recommended in the renally impaired, low weight, and elderly.

III. DOSAGE AND ADMINISTRATION

A) All formulations are primarily given subcutaneously.

B) Dose reduction is necessary for renally impaired. See package insert for specific recommendations.

	DVT/PE PROPHYLAXIS*	DVT/PE TREATMENT	UNSTABLE ANGINA/MI
ENOXAPARIN	30 mg SQ BID or 40 mg SQ daily	1 mg/kg BID or 1.5 mg/kg once daily	1 mg/kg q 12 hours
DALETPARIN	2500–5000 units QD	200 units/kg QD or 100 units/kg BID	120 units/kg (max 10,000) q12 hours
TINZAPARIN	2500–4500 anti-Xa units	175 anti-Xa units/kg once daily	xxxxx
ARDEPARIN	50 anti-Xa units/kg SC BID	xxxxx	xxxxx

*Prophylactic doses may differ based on medical and surgical indications. Timing of dosing prior to surgery may differ. Refer to clinical trials and package inserts.

IV. TOXICITY

- A) Bleeding is the major toxicity.
- B) Cases of spinal hematoma have been reported with epidural anesthesia or spinal puncture leading to long-term injury or permanent paralysis. Use with extreme caution and hold dose for 12–24 hours prior to procedure, based on half life.
- C) Failure of the LMWHs has been reported in some cases with mechanical valves, but true failure rates are uncertain and may be low. Use with caution and close monitoring in these settings.
- D) Thrombocytopenia has been <2% of cases, with HIT reported to be generally <1%.
- E) Elevated hepatic enzymes, injection site reactions and allergic reactions may occur.
- F) True incidence of osteoporosis is uncertain, but less than UFH.
- G) Rare cases of hyperlipidemia have been reported.

V. CLINICAL MONITORING

- A) Monitoring has not been thought to be necessary unless patients are elderly, renally impaired, obese, or at very high thrombotic risk.
- B) If levels are to be followed anti-Xa levels should be checked 4 hours after the dose. Therapeutic ranges differ whether the drug is given once daily or BID.
- C) PT and PTT not/minimally elevated unless given in large doses.

ULTRA LOW MOLECULAR WEIGHT HEPARINS

FONDAPARINUX (ARIXTRA®)

FDA approved for the extended prophylaxis of DVT in patients undergoing hip surgery, inpatients undergoing abdominal surgery, and in the treatment of DVT/PE. Used off label to treat heparin induced thrombocytopenia (HIT).

I. MECHANISM OF ACTION

Antithrombin III (AT-III) mediated selective inhibition Xa.

Potentiates AT-III's ability to inhibit Factor Xa by 300-fold.

Does not inhibit or inactivate thrombin and has no effect on platelet function.

II. PHARMACOKINETICS

A) Administered subcutaneously.

B) Peak concentrations occur within 2 hours of a dose.

C) 100% bioavailability.

D) Minimal binding to other proteins, including PF4, thus HIT not likely.

E) Elimination half-life is 18 hours with normal renal function.

F) Clearance is primarily renal. Significant dose reduction is recommended in the renally impaired, low weight, and elderly.

III. DOSAGE AND ADMINISTRATION

A) The FDA-approved dosage for treatment of DVT and PE is 5 mg SC once daily for weight less than 50 kg; 7.5 mg SC once daily for weight 50–100 kg; or 10 mg SC once daily for weight greater than 100 kg.

B) For DVT or PE prophylaxis 2.5 mg SC once daily, starting 6 to 8 hours postoperatively after hemostasis has been established.

C) For off label use in the treatment of HIT, dosing is not well worked out. Doses between 2.5–7.5 mg/day can be considered based on the clinical scenario.

D) Administration before 6 hours after surgery has been associated an increased risk of major bleeding.

IV. TOXICITY

A) Bleeding is the major toxicity.

B) Moderate thrombocytopenia (platelet counts between 100 and 150 x 10⁹/L) occur in 3% of patients, and severe thrombocytopenia (platelet counts less than 50x 10⁹/L) occurred in 0.2% of patients receiving 2.5 mg of fondaparinux during prophylaxis.

C) Elevated AST (1.7% of patients) and ALT (2.6% of patients) were documented, but patients remained asymptomatic.

D) Adverse local and dermatological reactions have included: injection site reactions or bleeding, rash (unspecified) (7.5%), bullous eruption (3.1%), and pruritus. Increased wound drainage (4.5%) also occurred.

V. CLINICAL MONITORING

A) Monitoring has not been thought to be necessary.

B) If levels were to be followed anti-Xa levels should be followed. Little information exists about therapeutic levels.

C) PT and PTT not/minimally elevated.

DIRECT THROMBIN INHIBITORS

LEPIRUDIN (REFLUDAN®)

FDA approved for the prophylaxis and treatment of patients with heparin induced thrombocytopenia (HIT). It has also been studied for unstable angina and acute coronary syndromes.

I. MECHANISM OF ACTION

Specific and irreversible direct thrombin inhibitor.

Yeast derived recombinant form of the natural anticoagulant hirudin.

Interferes with fibrin generation, platelet aggregation, and other related biologic activities.

Does not require AT-III for activity.

No antagonists available.

II. PHARMACOKINETICS

A) Administered intravenously with immediate anticoagulant effects.

B) Follows a two compartment model.

C) Eliminated primarily by the kidney, with significant dose reductions needed in renal failure. Elimination half-life is 1.3 hours in healthy volunteers, but can be prolonged up to 2 days in patients with renal failure.

III. DOSAGE AND ADMINISTRATION

For rapid therapeutic anticoagulation (IV infusion):

LOADING DOSE: 0.4 mg/kg bolus IV (if no acute thrombosis may omit)

MAINTENANCE: 0.1 – 0.15 mg/kg/hour IV, with adjustments to maintain APTT 1.5 to 2.5 times the median of the normal laboratory range. In patients with high bleeding risk, use 0.1 mg/kg/hour dose.

NOTE: in obese patients the dose should be capped at a maximum weight of 110 kg.

DOSE MODIFICATIONS AND CLINICAL MONITORING:

A) The first aPTT should be checked 4 hours after the start of the lepirudin infusion.

B) Any aPTT out of the target range is to be confirmed at once before drawing conclusions with respect to dose modifications, unless there is a clinical need to react immediately.

C) If the confirmed aPTT ratio is above target range, the infusion should be stopped for two hours. At restart, the infusion rate should be decreased by 50% (no additional IV bolus). The aPTT ratio should be determined 4 hours later.

D) If the confirmed aPTT is below target range, the infusion rate should be increased in increments of 20%. The aPTT should be determined again in 4 hours after each change.

E) In general, an infusion rate of 0.21 mL/kg/hour should not be exceeded without checking for coagulation abnormalities, which might be preventive of an appropriate aPTT response.

RENAL adjustment: Initial bolus should also be reduced to 0.2 mg/kg IV with CrCl < or equal to 60 mL/minute.

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CREATININE CLEARANCE [ML/MIN]	SERUM CREATININE [MG/DL]	ADJUSTED INFUSION RATE [% DOSE REDUCTION]	DOSE REDUCTION OF THE BOLUS DOSE	ADJUSTED INFUSION RATE [MG/KG/HOUR]
45-60	1.6 - 2	50%	50% i.e. 0.2 mg/kg/hour	0.075
30-44	2.1 - 3	70%	50% i.e. 0.2 mg/kg/hour	0.045
15-29	3.1 - 6	85%	50% i.e. 0.2 mg/kg/hour	0.0225
< 15*	> 6.0*	Avoid or STOP	50% i.e. 0.2 mg/kg/hour	Avoid or STOP

*In hemodialysis patients or in case of acute renal failure (CrCL less than 15mL/minute or SCr greater than 6 mg/dL), infusion of lepirudin is to be avoided or stopped. Additional IV bolus doses of 0.1 mg/kg of body weight should be considered every other day only if the aPTT ratio falls below 1.5.

IV. TOXICITY

- A) Bleeding is the most common toxicity.
- B) Life threatening anaphylactic reactions have been reported.
- C) Allergic reactions have occurred in patients treated with lepirudin. The most common are airway reactions (cough, bronchospasm, stridor, dyspnea), in 1—10% of patients.
- D) Antibody formation has been found with prolonged exposure, leading to a decrease clearance of the drug and need for dose reduction.

ARGATROBAN

FDA approved for the treatment of patients with heparin induced thrombocytopenia (HIT). It has also been studied as an adjunct to thrombolytics in patients with acute MI, and also in the setting of interventional coronary procedures.

I. MECHANISM OF ACTION

Specific and reversible direct thrombin inhibitor.

N2-substituted derivative of arginine.

Interferes with fibrin generation, platelet aggregation, and other related activities.

Does not require antithrombin-III for activity.

No antagonists available.

II. PHARMACOKINETICS

A) Administered intravenously with immediate anticoagulant effects.

B) Peak concentrations occur within 3–4 hours of a dose.

C) Coagulation times return to normal approximately 1 hour after discontinuation.

D) Eliminated primarily by the liver, with significant dose reductions needed in hepatic failure.

E) Approximately 20% removed by hemodialysis.

F) Elimination half-life is 39–51 minutes with normal hepatic function.

III. DOSAGE AND ADMINISTRATION

A) For the treatment of HIT, dose is 2 mcg/kg/min as continuous infusion. In patients with significant hepatic impairment dose should be reduced to 0.5 mcg/kg/min.

B) Initial dose reduction should be considered in ICU patients or critically ill patients especially if there is no documented thrombosis.

C) The recommended initial dose for PCI is a bolus of 350 mcg/kg over 3 to 5 minutes followed by 25 mcg/kg/min IV by continuous infusion.

D) Doses above 10 mcg/kg/min should not be used for the treatment of HIT.

IV. TOXICITY

A) Bleeding is the major toxicity.

B) Non-hemorrhagic adverse reactions have been reported during argatroban therapy in HIT/HITTS patients at a frequency of $\geq 2\%$ (n=568). These include (in decreasing order of frequency): hypotension, fever, diarrhea, cardiac arrest, nausea/vomiting, ventricular tachycardia, pain (unspecified), infection, cough, and abdominal pain. Dyspnea, sepsis, urinary tract infection, pneumonia, atrial fibrillation, abnormal renal function, and cerebrovascular disorder were also reported but occurred more frequently in historical controls than in argatroban-treated patients.

C) Rash and asymptomatic increase in LFT's has also been noted.

V. CLINICAL MONITORING

A) For the treatment of HIT, monitoring is with the aPTT with target levels of 1.5–3 patient's baseline. apTT's over 100 should be avoided.

B) When larger doses are used during PCI, monitoring is through the ACT with goals between 300–450 seconds.

C) Argatroban will increase the INR. Concomitant therapy with warfarin should be continued until the INR is greater than 4. At that point Argatroban should be stopped and a repeat level checked 4–6 hours later. If the INR is below 2 than Argatroban should be restarted and warfarin adjusted.

BIVALIRUDIN **(ANGIOMAX®)**

FDA approved for the treatment of patients with unstable angina undergoing PTCA and with the provisional use of glycoprotein IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention. The drug has also been used off label in the prevention of DVT, treatment of acute MI and in the treatment of heparin induced thrombocytopenia (HIT).

I. MECHANISM OF ACTION

Specific and reversible direct thrombin inhibitor.

Parental bivalent analog of hirudin.

Interferes with fibrin generation, platelet aggregation, and other related activities.

Does not require antithrombin III for activity.

No antagonists available.

II. PHARMACOKINETICS

A) Administered intravenously or subcutaneously.

B) Peak concentrations occur within 2 minutes of a bolus or 4 minutes following a 15-minute infusion. Bioavailability of subcutaneous administration is 40% with peak concentrations within 2 hours.

C) Coagulation times return to normal approximately 1 hour after discontinuation.

D) Eliminated by combination of renal and proteolytic cleavage.

E) Elimination half-life is 25 minutes with normal renal function. Clearance is reduced 20% in patients with moderate to severe renal impairment and 80% with chronic hemodialysis.

III. DOSAGE AND ADMINISTRATION

A) For off label use in the treatment of HIT, 0.15–0.20 mg/kg/hr IV continuous infusion. No bolus infusion necessary.

B) Dose in percutaneous coronary intervention, 0.75 mg/kg bolus followed by 1.75 mg/kg/hr. Additional 0.3mg/kg IV bolus doses are used based on target ACT.

C) Guidelines exist for dosing in MI with streptokinase and for DVT prophylaxis.

D) Protocols exist at Shands UF for use in cardiopulmonary bypass surgery.

IV. TOXICITY

A) Bleeding is a major toxicity.

B) The most frequent treatment-emergent adverse reactions other than bleeding reported during clinical trials were back pain (42%), pain (15%), nausea/vomiting (15%/6%), headache (12%), and hypotension (12%).

V. CLINICAL MONITORING

A) For the treatment of HIT monitoring is with the aPTT with target levels of 1.5–2.5 patient's baseline.

B) May increase the PT/INR.

C) When larger doses are used during PCI or CABG the ECT or ACT is used for monitoring with targets similar to interventions done with unfractionated heparin.