LOW MOLECULAR WEIGHT HEPARIN (LMWH) AHFS ???

Indications: Prevention and treatment of deep vein thrombosis, pulmonary embolism, †thrombophlebitis migrans, †disseminated intravascular coagulation (DIC).

Contra-indications: Active major bleeding, history of heparin-induced thrombocytopenia with unfractionated heparin, thrombocytopenia with positive anti-platelet antibody test, severe renal impairment (**certoparin, reviparin** (not USA)).

Pharmacology

Several different varieties of low molecular weight heparin (LMWH) are now available (e.g. **bemiparin**, **certoparin**, **dalteparin**, **enoxaparin**, **reviparin** and **tinzaparin**). Most are approved for the prevention of venous thrombo-embolism and some are also indicated for the treatment of deep vein thrombosis, pulmonary embolism, unstable coronary artery disease and for the prevention of clotting in extracorporeal circuits. All LMWH is derived from porcine heparin and some patients may need to avoid them because of hypersensitivity, or for religious or cultural reasons. The most appropriate non-porcine alternative is **fondaparinux**.

LMWH acts by potentiating the inhibitory effect of antithrombin III on Factor Xa and thrombin. It has a relatively higher ability to potentiate Factor Xa inhibition than to prolong plasma clotting time (APTT) which cannot be used to guide dosage. Anti-factor Xa levels can be measured if necessary, e.g. if a patient is at increased risk of bleeding, but routine monitoring is not generally required because the dose is determined by the patient's weight. LMWH is as effective as unfractionated heparin for the treatment of deep vein thrombosis and pulmonary embolism and is now considered the initial treatment of choice.[1,2] Other advantages include a longer duration of action which allows administration q.d., and possibly a better safety profile, e.g. fewer major hemorrhages.[1-5] LMWH is the treatment of choice for *chronic* DIC; this commonly presents as recurrent thromboses in both superficial and deep veins which do not respond to **warfarin**. **Tranexamic acid** and **aminocaproic acid** (antifibrinolytic drugs) should not be used in DIC because they increase the risk of end-organ damage from microvascular thromboses.

LMWH interacts with growth factors, other blood components and vascular cells. An anticancer effect has been seen, possibly via inhibiting angiogenesis.[6,7] Survival is improved in cancer patients receiving LMWH compared with unfractionated heparin, or when LMWH is given in addition to chemotherapy compared with chemotherapy alone. This effect cannot be attributed to differences in thrombosis or complications of bleeding.

LMWH is likely to be superseded by specific factor Xa inhibitors**,** e.g. **fondaparinux.** Some of these need be administered only once weekly, e.g. **idraparinux**.[8] For pharmacokinetic details, see Table 1.

Table 1 Selected pharmacokinetic data for dalteparin, enoxaparin and tinzaparin[9-12]

	Dalteparin	*Enoxaparin*	*Tinzaparin*
Bio-availability SC[a]	87%	100%	87%
Onset of action	3min IV 2–4h SC	5min IV 3h SC	5 min IV 2–3h SC
Time to peak plasma activity[a]	4h SC	2–6h SC	4–5h SC
Plasma activity halflife[a]	2h IV 3–5h SC	2–4.5h IV 4.5–7h SC	1.5h IV 3–4h SC
Duration of action	10–24h SC	>24h SC	24h

a. based on anti-factor Xa activity.

Cautions

Serious drug interactions: enhanced anticoagulant effect with anticoagulant/ antiplatelet drugs, e.g. NSAIDs; reduced anticoagulant effect with antihistamines**,** cardiac glycosides, **tetracycline** and **ascorbic acid**.

Risk of spinal (intrathecal or epidural) hematoma in patients undergoing spinal puncture or with indwelling spinal catheter, particularly if concurrently receiving a drug which affects hemostasis; monitor for neurological impairment. Increased risk of hemorrhage if underlying bleeding diathesis (e.g. thrombocytopenia), recent cerebral hemorrhage, recent neurological or ophthalmic surgery, uncontrolled hypertension, diabetic or hypertensive retinopathy, subacute bacterial endocarditis, current or past peptic ulcer, severe liver disease. Severe renal impairment: dose reduction is recommended for **enoxaparin** and may be necessary for **dalteparin** and **tinzaparin** (see below).

Undesirable effects

For full list, see manufacturers' PIs

Common (<10%, >1%): headache, dizziness, pain at the injection site, minor bleeding (generally hematoma at the injection site), major bleeding in surgical patients receiving thromboprophylaxis and patients being treated for deep vein thrombosis or pulmonary embolism, tachycardia, chest pain, peripheral edema, hypotension, hypertension, anemia, nausea, constipation, reversible increases in transaminases, back pain, hematuria.

Uncommon (<1%, >0.1%): major bleeding in patients receiving thromboprophylaxis, thrombocytopenia (see below), abdominal pain, diarrhea.

Both standard heparin and LMWH can cause thrombocytopenia (platelet count $<100 \times 10^9$/L). An early (<4 days) mild fall in platelet count is often seen after starting heparin therapy, particularly after surgery. This corrects spontaneously despite the continued use of heparin and is asymptomatic.[13] However, occasionally, an immune heparin-induced thrombocytopenia (HIT) develops associated with heparin-dependent IgG antibodies.[4,13] The antibodies form a complex with platelet factor 4 and bind to the platelet surface, *causing disruption of the platelets and a release of procoagulant material.* It can occur up to 4 weeks after starting heparin and manifests as venous or arterial thrombo-embolism which may be fatal. HIT is less common with prophylactic regimens (low doses) than with therapeutic ones (higher doses) and with LMWH rather than unfractionated heparin. Cross-reactivity between unfractionated

heparin and LMWH is rare. HIT typically develops 5–8 days after starting heparin and, for this reason, some centers check the platelet count at this time (Box 2.A). LMWH should be stopped immediately if there is a fall in the platelet count of >50% and the advice of a hematologist obtained. Because the procoagulant material released by the disintegrating platelets increases the risk of thrombosis, anticoagulation should be continued with a non-heparin anticoagulant, such as a direct thrombin inhibitor, e.g. **argatroban**, or a hirudin derivative, e.g. **lepirudin**, even if there is no clinically evident thrombosis.[14]

Box 2.A Diagnosis and management of HIT[4,14]

High clinical suspicion for HIT
Platelet count fall of >50%, generally after 5 days of heparin use, sometimes sooner and occasionally several days after heparin has been stopped.
New thrombotic or thrombo-embolic event.
Necrosis or erythematous plaques at injection sites.

Laboratory confirmation
Do one of the following tests but if negative or borderline, do both.
Functional assay for antibodies using washed platelets or citrated platelet-rich plasmas.
Antigen assay (platelet factor 4/heparin ELISA).

Therapeutic approach
Stop heparin or LMWH.
Start treatment with a non-heparin anticoagulant, e.g. argatroban or lepirudin, whether or not there is clinical evidence of a deep vein thrombosis. Ultrasonography of the lower limb veins is recommended because there is a high frequency of subclinical deep vein thrombosis.
Do *not* use warfarin alone in acute HIT because this may increase the risk of venous limb gangrene. Warfarin should be given only when the patient is fully anticoagulated with danaparoid or lepirudin. Allow the thrombocytopenia to resolve before continuing with warfarin alone.
Do *not* give prophylactic platelet transfusions.

Dose and use
Recurrent thromboembolism occurs in 21% of cancer patients compared with 7% of non-cancer patients (Box 2.B).[15-17] Particularly in the presence of multiple risk factors, anticoagulation should be considered for cancer patients who:

- develop a DVT (indefinite anticoagulation, using LMWH for at least the first 3–6 months)[18]
- sustain a pulmonary embolus (indefinite anticoagulation, using LMWH for at least the first 3–6 months)[18]
- become bedfast for any reason for ≥3 days (short-term anticoagulation).[19]

Generally, indefinite anticoagulation is discontinued only if contra-indications develop, or when the patient reaches the stage when symptom relief alone is appropriate, e.g. in the last few weeks of life.

Box 2.B Risk factors for thrombo-embolism in medical patients [19-24]

1. Age ≥60 years
2. Obesity
3. Cancer
4. Chronic respiratory or cardiac disease
5. Other serious medical conditions, e.g. sepsis, lower limb weakness, inflammatory bowel disease, collagen disorder
6. Varicose veins/chronic venous insufficiency
7. Previous thrombo-embolism
8. Cancer chemotherapy
9. Hormone therapy (e.g. oral contraceptives, hormone replacement, tamoxifen, anastrozole, and possibly progestins)
10. Thrombophilia.

In palliative care, because hemorrhagic complications with **warfarin** occur in nearly 50% (possibly related to drug interactions and hepatic dysfunction), LMWH is preferable. It has been used indefinitely, and is acceptable to patients.[15,16,25] Compared with **warfarin**, treatment with LMWH is more straightforward (no blood tests or dose adjustments).

SC injections

May cause transient stinging and local bruising.[25] Rotate injection sites daily between left and right anterolateral and left and right posterolateral abdominal wall; introduce the total length of the needle vertically into the thickest part of a skin fold produced by squeezing the skin between the thumb and forefinger. Do not rub the injection site. For the manufacturers' recommended sites for injection, see respective PIs and **dalteparin** and **enoxaparin** monographs (p.000 and p.000)

Severe renal impairment (creatinine clearance <30ml/min)

Clearance of **enoxaparin** is reduced by 65% and **tinzaparin** clearance is decreased by 25%. The anti-Factor X activity halflives of **dalteparin** and **tinzaparin** are prolonged. The manufacturers recommend dose reduction for **enoxaparin** (see p.000), and caution in the use of **dalteparin** and **tinzaparin**. Specialist guidelines suggest using unfractionated heparin IV instead of LMWH in severe renal impairment but the evidence is not strong (grade 2C; i.e. not based on RCT).[18]

Routine platelet count monitoring

All patients should have a baseline platelet count before starting LMWH. Subsequent routine monitoring depends on the relative risk of HIT:[14]

- for patients starting LMWH treatment and who have received unfractionated heparin in the last 3 months (HIT risk 0.1–1%), repeat the platelet count after 24h to exclude rapid-onset HIT
- surgical thromboprophylaxis with LMWH (HIT risk 0.1–1%), when practical monitor platelet count every 2–3 days from day 4 until LMWH is discontinued
- medical thromboprophylaxis or treatment with LMWH (HIT risk <0.1%), no routine platelet count monitoring is required.

Thromboprophylaxis

For **dalteparin** and **enoxaparin** monographs, see p.000 and p.000 respectively.

Patients with cancer undergoing surgery

Patients with cancer undergoing major surgery are at high risk of thrombo-embolism; they have twice the risk of developing a deep vein thrombosis and three times the risk of a fatal pulmonary embolism.[26] Four weeks of thromboprophylaxis is more effective than one week.[27,28]

Patients with cancer with indwelling venous catheters

The presence of a central (subclavian) or peripheral indwelling venous catheter can lead to catheter-related thrombosis. It occurs in up to 2/3 of patients and is symptomatic in 10–30%, although more recent figures suggest the incidence is falling (5–15%), possibly as a result of improved catheter materials and placement. Routine thromboprophylaxis with LMWH is not recommended because RCTs have shown no benefit from their use (e.g. **enoxaparin** 40mg daily), or from low-dose **warfarin** (1mg daily).[29-32]

Patients with cancer who are immobile or confined to bed because of a concurrent acute medical illness

Compared with surgical patients, thromboprophylaxis is underused in medical patients, even though mortality and morbidity from thrombo-embolism (major/fatal pulmonary embolism) and its treatment (major/fatal hemorrhage) are higher in medical patients.[33] Thus, because of the increased risks associated with thrombo-embolism, cancer patients hospitalized with any acute medical illness likely to render them bedfast for ≥3 days should be considered for thromboprophylaxis, particularly in the presence of one or more additional risk factors (Box 2.B). Duration of treatment is generally ≤2 weeks.[21] If anticoagulation is contra-indicated, use graduated compression stockings instead.[19]

Patients with cancer undertaking long-distance air travel

The evidence for an association between prolonged travel and venous thrombo-embolism remains controversial.[19] The risk appears greatest in journeys of >6h and in those travelers with one or more pre-existing risk factors (Box 2.B). Although there is insufficient evidence to support routine thromboprophylaxis in any group, all travelers should follow some general recommendations (Box 2.C). The need for additional measures in those deemed to be at an increased risk (e.g. patients with cancer) should be made on an individual basis (Box 2.C).

Box 2.C Recommendations for preventing thrombo-embolism in long-distance travel (>6h)[19]

General recommendations for all travelers
Avoid constrictive clothing around the waist and lower limbs.
Avoid dehydration.
Frequently stretch the calf muscles by moving the feet up and down.

Additional recommendations for travelers with one or more risk factors for thrombo-embolism (see Box 2.B)
Properly fitted, below-knee graduated compression stockings, providing 15–30mmHg of pressure at the ankle *or*
A single prophylactic dose of LMWH (e.g. enoxaparin 40mg) 2–4h before departure.

Treatment
For **dalteparin** and **enoxaparin** monographs, see p.000 and p.000 respectively
Deep vein thrombosis and pulmonary embolism
In patients with cancer undergoing treatment, LMWH appears as effective as (possibly more than) **warfarin**, with a similar (or reduced) risk of bleeding.[34,35] Some centers use a fixed-dose regimen (*see* **Dalteparin** monograph, p.000).[36]

- **tinzaparin**, give 175units/kg SC q.d. for at least the first 3–6 months of indefinite anticoagulation [18]
- **dalteparin** or **enoxaparin**, see p.000 or p.000.

Disseminated intravascular coagulation (DIC)

- confirm the diagnosis
  thrombocytopenia (platelet count <150 × 10^9/L in 95% of cases)
  decreased plasma fibrinogen concentration
  elevated plasma D-dimer concentration, a fibrin degradation product (85% of cases)
  prolonged prothrombin time and/or partial thromboplastin time.[37]

A normal plasma fibrinogen concentration (200–250mg/100ml) is also suspicious because fibrinogen levels are generally raised in cancer (e.g. 450–500mg/100ml) unless there is extensive liver disease. Infection and cancer both may be associated with an increased platelet count which likewise may mask an evolving thrombocytopenia.

- *do not use **warfarin** because it is ineffective*
- for *chronic* DIC presenting with recurrent thromboses, give LMWH as for treatment of deep vein thrombosis.
- for *chronic* or *acute* DIC presenting with hemorrhagic manifestations (e.g. ecchymoses, hematomas), seek specialist advice.

Thrombophlebitis migrans

- do not use warfarin because it is ineffective
- generally responds rapidly to small doses of LMWH
- continue treatment indefinitely[38]
- if necessary, titrate dose to maximum allowed according to weight.

Overdose
In emergencies, **protamine sulfate** can be used to reverse the effects of **tinzaparin**:

- for each 100units of **tinzaparin**, give 1mg of **protamine sulfate**
- give a maximum of 50mg by IV injection over 10min
- give a further 0.5mg of **protamine sulfate** per 100units of **tinzaparin** after 2–4h if APTT still prolonged.

Note: even with high doses of **protamine sulfate**, the anti-Xa activity of **tinzaparin** is not completely neutralized (maximum reversal ~60%).

Supply
Dalteparin and **enoxaparin**: see respective monographs, p.000 and p.000.

Tinzaparin
Innohep® (Pharmion)
Injection 20,000units/ml, 2ml multiple-dose vial = $???

---

1 van-den-Belt A (2004) Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism (Cochrane Review). *Cochrane Library.* **Issue 2**.
2 Quinlan D *et al.* (2004) Low-molecular weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism. *Annals of Internal Medicine.* **140:** 175-183.
3 Prandoni P (2001) Heparins and venous thromboembolism: current practiceand future directions. *Journal of Thrombosis and Haemostasis.* **86:** 488-498.
4 Hirsh J *et al.* (2001) Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest.* **119:** 64s-94s.
5 Fareed J *et al.* (2003) Pharmacodynamic and pharmacokinetic properties of enoxaparin : implications for clinical practice. *Clinical Pharmacokinetics.* **42:** 1043-1057.
6 Hettiarachchi RJ *et al.* (1999) Do heparins do more than just treat thrombosis? The influence of heparins on cancer spread. *Journal of Thrombosis and Haemostasis.* **82:** 947-952.
7 Khorana AA and Fine RL (2004) Pancreatic cancer and thromboembolic disease. *Lancet Oncology.* **5:** 655-63.
8 Prandoni P (2004) Toward the simplification of antithrombotic treatment of venous thromboembolism. *Annals of Internal Medicine.* **140:** 925-926.
9 Fareed J *et al.* (1990) Pharmacologic profile of a low molecular weight heparin (enoxaparin): experimental and clinical validation of the prophylactic antithrombotic effects. *Acta Chirurgica Scandinavica. Supplementum.* **556:** 75-90.
10 Bara L and Samama M (1990) Pharmacokinetics of low molecular weight heparins. *Acta Chirurgica Scandinavica. Supplementum.* **556:** 57-61.
11 Dawes J (1990) Comparison of the pharmacokinetics of enoxaparin (Clexane) and unfractionated heparin. *Acta Chirurgica Scandinavica. Supplementum.* **556:** 68-74.
12 Fossler MJ *et al.* (2001) Pharmacodynamics of intravenous and subcutaneous tinzaparin and heparin in healthy volunteers. *American Journal of Health-System Pharmacy.* **58:** 1614-21.
13 Warkentin T *et al.* (1995) Heparin-induced thrombocytopenia in patients treated with low molecular weight heparin or unfractionated heparin. *New England Journal of Medicine.* **332:** 1330-1335.

14 Warkentin TE and Greinacher A (2004) Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* **126:** 311S-337S.
15 Johnson M (1997) Problems of anticoagulation within a palliative care setting: an audit of hospice patients taking warfarin. *Palliative Medicine.* **11:** 306-312.
16 Johnson M and Sherry K (1997) How do palliative physicians manage venous thromboembolism? *Palliative Medicine.* **11:** 462-468.
17 Prandoni P *et al.* (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* **100:** 3484-3488.
18 Buller HR *et al.* (2004) Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* **126:** 401S-428S.
19 Geerts WH *et al.* (2004) Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* **126:** 338S-400S.
20 Leizorovicz A *et al.* (2004) Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation.* **110:** 874-879.
21 Leizorovicz A and Mismetti P (2004) Preventing venous thromboembolism in medical patients. *Circulation.* **110:** IV13-19.
22 Samama MM *et al.* (1999) A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *New England Journal of Medicine.* **341:** 793-800.
23 De Cicco M (2004) The prothrombotic state in cancer: pathogenic mechanisms. *Critical Reviews in Oncology/Hematology.* **50:** 187-196.
24 Deitcher SR and Gomes MP (2004) The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma: a systematic review. *Cancer.* **101:** 439-449.
25 Noble SI and Finlay IG (2005) Is long-term low-molecular-weight heparin acceptable to palliative care patients in the treatment of cancer related venous thromboembolism? A qualitative study. *Palliative Medicine.* **19:** 197-201.
26 Kakkar AK and Williamson RC (1999) Prevention of venous thromboembolism in cancer patients. *Seminars in Thrombosis and Hemostasis.* **25:** 239-243.
27 Bergqvist D *et al.* (2002) Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *New England Journal of Medicine.* **346:** 975-980.
28 Kher A and Samama MM (2005) Primary and secondary prophylaxis of venous thromboembolism with low-molecular-weight heparins: prolonged thromboprophylaxis, an alternative to vitamin K antagonists. *Journal of Thrombosis and Haemostasis.* **3:** 473-481.
29 Tesselaar ME *et al.* (2004) Risk factors for catheter-related thrombosis in cancer patients. *European Journal of Cancer.* **40:** 2253-2259.
30 Geerts WH *et al.* (2001) Prevention of venous thromboembolism. *Chest.* **119:** 132S-175S.
31 Verso M *et al.* (2005) Enoxaparin for the Prevention of Venous Thromboembolism Associated With Central Vein Catheter: A Double-Blind, Placebo-Controlled, Randomized Study in Cancer Patients. *Journal of Clinical Oncology.* **23:** 4057-4062.
32 Couban S *et al.* (2005) Randomized Placebo-Controlled Study of Low-Dose Warfarin for the Prevention of Central Venous Catheter-Associated Thrombosis in Patients With Cancer. *Journal of Clinical Oncology.* **23:** 4063-4069.
33 Monreal M *et al.* (2004) The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients. Findings from the RIETE registry. *Journal of Thrombosis and Haemostasis.* **2:** 1892-1898.

34 Meyer G *et al.* (2002) Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Archives of Internal Medicine.* **162:** 1729-1735.
35 Lee A *et al.* (2003) Low molecular weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *New England Journal of Medicine.* **349:** 146-153.
36 Monreal M *et al.* (2004) Fixed-dose low-molecular-weight heparin for secondary prevention of venous thromboembolism in patients with disseminated cancer: a prospective cohort study. *Journal of Thrombosis and Haemostasis.* **2:** 1311-1315.
37 Spero J *et al.* (1980) Disseminated intravascular coagulation: findings in 346 patients. *Journal of Thrombosis and Haemostasis.* **43:** 28-33.
38 Walsh-McMonagle D and Green D (1997) Low-molecular weight heparin in the management of Trousseau's syndrome. *Cancer.* **80:** 649-655.