Low Molecular Weight Heparin

All Wales Medicines Strategy Group (AWMSG)
Recommendations and advice
Starting Point

Low Molecular Weight Heparin (LMWH):

- Inhibits factor Xa and factor IIa (thrombin)
- Small molecular size \(\therefore Xa > IIa\)
- Some antithrombin III - independent effects
- Does not bind extensively to platelets
LMWH vs UFH

Compared with unfractionated heparin (UFH):

- Less binding to plasma proteins
- More predictable absorption
- Longer half-life
- SC od or bd

No dose adjustment in most patients
LMWH advantages

No monitoring in most patients

- Reduced incidence of thrombocytopenia
- Reduced incidence of osteoporosis
- Possible self administration
Using LMWH

Clinically similar but not interchangeable

Bemiparın (Zibor® ▼)
Dalteparin (Fragmin® ▼)
Enoxaparin (Clexane®)
Tinzaparin (Innohep®)
Indications

Treatment of VTE
Prophylaxis of VTE – surgical & medical patients
Acute coronary syndrome*
Haemodialysis*
Obstetrics (off-label use)*

Almost all use initiated in hospital setting
* Specialist use, as is use in neonates and infants
Main challenge

Prevention of VTE

Massive morbidity and mortality burden
NICE guidance

Specific to adult, hospitalised inpatients

Not covered:
A&E patients,
elderly infirmed, resident elsewhere
patients treated for DVT/PE
NICE

Provide discharge recommendations

Inform patients / carer / notify GP

Use is increasingly widespread

BUT is there sufficient guidance for primary care? re appropriate use, safety, availability of monitoring?
Shared Care

AWMSG has identified situations where shared care is appropriate.

Has issued good practice recommendations for emerging areas of concern.
AWMSG Shared care criteria (7)

The safety profile of the drug is such that inadequate monitoring may have serious implications.

Effects of LMWH persist for longer than UFH and only partially reversible with protamine.

Monitoring using anti-Xa assay (hospital based) provides some dosing guidance, but is poor predictor of bleeding risk.
Anti-Xa assay

Target values for ant-Xa activity vary by LMWH type, and are not well established.

Measurements should normally be taken 4-6 hours after dosing (to determine peak effect).

If monitoring using assay required - use should be restricted to specialist services (AWMSG).
What are the risks?

Most common AEs:

- bleeding events,
- injection site reactions (haematoma and/or ecchymosis),
- various skin reactions,
- reversible thrombocytopenia,
- allergic reactions,
- headache,
- and reversible increase in liver enzymes.
Bleeding risk, including major bleeding...

Haemorrhage (bleeding at any site) is common
i.e. 1-10%
(dalteparin, tinzaparin, and bemiparin SPC)

Overall bleeding risk approximately 11 %
Risk of major bleeding approximately 0.5%
(tinzaparin SPC)

Major events (including retroperitoneal and intracranial reported); rare instances fatal
(dalteparin and enoxaparin SPC)
Other AEs

Risk of heparin-induced thrombocytopenia (HIT)
  Measure platelet counts...

Rare cases of hyperkalaemia
  Measure plasma potassium in those at risk
  (diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, potassium-sparing drugs),
  especially if therapy prolonged > 1 week

Potential for osteoporosis (reported with heparin)
Platelet monitoring

Day of initiation
If any heparin within 100 days: repeat after 24 hours.
For all surgical and medical patients, and obstetric patients receiving treatment doses:
every 2-4 days from days 4-14.
‘Regular’ monitoring beyond this period is not defined

Intervals in clinical trials have varied widely –
guidance from a specialist may be necessary
a monthly interval is proposed for cancer patients in shared care
AWMSG Aims

To ensure adequate timely anticoagulation
To address concerns re safe prescribing
To promote consistency
To provide interim guidance where evidence base is yet to be established nationally
**PREScribing of Medicines RECommended by Hospital Specialists**

**Prescriber**
Complete this form if you are unwilling to take responsibility for prescribing medicines recommended by a hospital specialist.

- **Patient's NHS Number:** [Redacted]
- **Name of consultant or other requesting specialist:** NOT DOCUMENTED
- **Speciality:**
- **Hospital/Trust:** [Redacted]

<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Dose &amp; Frequency</th>
<th>Indication</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEXANE</td>
<td>15mg</td>
<td>No documentation</td>
<td>NOT DOCUMENTED</td>
</tr>
</tbody>
</table>

I have been asked to accept the responsibility for prescribing this drug for the named patient, however I feel I am not in a position to do this for the following reason(s):

1. **Prescribing responsibility should stay with the specialist**

   - Drug is designated 'RED' in the right classification and is for specialist prescribing only.
   - Hospital CLINICAL TRIAL drug.
   - **UNLICENSED drug/dose/indication (delete as applicable)** where use is not endorsed by the BNF or BNFc and/or where an approved Shared Care Protocol does not exist and the GP is unwilling to take clinical responsibility.

2WeMeReC
Dosing

Consider risk associated with:

Patient – intrinsic risk of thrombosis / bleeding
Disorder / procedure
Product
Determining dose

Product SPCs give guide to use for specific indication. Dependent on treatment vs prophylaxis of VTE.

Prophylaxis: dosing usually standard. (exception – tinzaparin for orthopaedic surgery)

Treatment: once or twice daily (e.g. dalteparin)

May be adjusted for weight and renal function.
Dosing & Weight

Weight must be accurate (kgs), determined on reliable equipment **not** estimation or self-reporting.

Weight-determined recommendations usually sufficient for overweight patients but not necessarily morbidly obese at high risk (e.g. bariatric surgery).

Extremes are problematic; obese and under-weight patients may require extra care and specialist advice.
Dosing & Renal function

LMWH mainly renal clearance (vs hepatic for UHF)
Renal impairment leads to potential accumulation

Limited evidence
Options: avoid use, lower dose, monitor

Usually dose changes recommended in significant renal failure, i.e. CrCl < 30ml/min
Dosing in the Elderly

Limited evidence
No need to alter doses on the basis of age alone
BUT consider:
  - renal function
  - weight of frail patients
  - increase risk of bleeding

Higher risk in very old may preclude use
AWMSG recommendations

Recommendation 1

LMWH treatment for four weeks or less should be prescribed and monitored by the initiating physician (any indication).

Recommendation 2

Where there is a need to monitor LMWH treatment by measuring the anti-Xa level, patients should be prescribed and followed up regularly by specialist services.
**Recommendation 3**

Treatment doses of LMWH prescribed for venous thromboembolism (VTE) in cancer patients (i.e. patients undergoing cancer therapy or those who have metastatic disease) **are suitable for shared care for up to six months of treatment.**

Shared care should be agreed in writing with an invitation to participate by consultant and response from the General Practitioner.

**Recommendation 4**

Treatment doses of LMWH for VTE in pregnancy should be ‘hospital only’ prescribing.

**Recommendation 5**

Prophylactic doses of LMWH in pregnancy for medical conditions (excluding the indication of obesity) should normally be prescribed by Secondary Care. Mechanisms need to be agreed locally to support adequate supply between appointments (30-42 days). Further discussions are needed regarding the prescribing of prophylactic doses for obese patients.
Good practice points

Off-label use
Pregnancy
Cancer with AF
Sub-therapeutic INRs
Patient partnership
Off label

e.g. when warfarin not suitable

Haematologist assessment

Prescribing responsibility determined on case by case basis
Pregnancy (Off-label use)

Pre-conception counselling (Obstetrician / Haematologist)

Initiate when pregnancy confirmed, ideally within 2 weeks of missed period; before 6 weeks.

Continue postpartum after assessment until warfarin therapy re-established
Cancer with AF

Consider risk / benefit balance

- Use tools re risk of stroke e.g. CHADS$_2$
- Seek cardiology or stroke opinion
Sub-therapeutic INRs

LMWH should be prescribed by department responsible for dosing warfarin

LMWH cover only necessary in high risk patients on warfarin e.g. those with mechanical heart valves

Patients could be identified within anticoagulant register with INR threshold (as advised by specialist) recorded
Patient partnership

Aim to reduce waste and promote adherence

Advise patients on self-administration and sharps disposal
Ensure duration appropriate for indication
Consider establishing a register and recall system
Future issues for primary care?

Suspected DVT

Weight-related risk in pregnancy