LOW MOLECULAR WEIGHT HEPARIN PROPHYLAXIS IN RENAL IMPAIRMENT

Jin Hah, Specialist Clinical Pharmacist
Renal & Vascular, Royal Infirmary of Edinburgh
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Outline

Pros and cons of low molecular weight heparin (LMWH)

Review of existing literature

Excretion of LMWHs and unfractionated heparin (UFH)

NHS Lothian Venous thromboembolism (VTE) risk assessment

VTE prophylaxis guideline in Edinburgh Renal Unit

Evaluation of peak anti-factor Xa level - results

Case studies

Areas of concern
Pros and Cons of LMWH

**Pros:**
- Dosing frequency
- Ease of administration
- Risk of HIT
- More predictable anticoagulation response
- Dose independent elimination
- More cost effective

**Cons:**
- Risk of accumulation in renal impairment
- Not licensed in severe renal impairment
- Variation among different LMWHs in elimination, half-life and bioavailability
A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency

Ferdows Atiq¹ · Patricia M.L.A. van den Bemt¹ · Frank W.G. Leebeek² · Teun van Gelder¹,³ · Jorie Versmissen³

**Lack of data for patients on chronic renal replacement therapy**
Schmid et al 2009 (n=42): Compared peak anti-factor Xa levels in normal to mild to moderate and severe renal impairment on prophylactic dalteparin (dose adjusted with weight) in medical & surgical wards.
Table 3. Serial Anti-Xa Levels at 0, 1, 2, 4, 8, 12, 20, and 24 Hours After a Targeted 3, 10, and 17 Days of Dalteparin Treatment

<table>
<thead>
<tr>
<th>Hours After Dalteparin Administration</th>
<th>After 3 Days of Dalteparin Prophylaxis (n=102)</th>
<th>After 10 Days of Dalteparin Prophylaxis (n=46)</th>
<th>After 17 Days of Dalteparin Prophylaxis (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Before treatment)</td>
<td>&lt;0.06 (&lt;0.06-&lt;0.06)</td>
<td>&lt;0.06 (&lt;0.06-&lt;0.06)</td>
<td>&lt;0.06 (&lt;0.06-0.08)</td>
</tr>
<tr>
<td>1</td>
<td>0.16 (0.10-0.26)</td>
<td>0.20 (0.11-0.29)</td>
<td>0.23 (0.19-0.25)</td>
</tr>
<tr>
<td>2</td>
<td>0.28 (0.19-0.40)</td>
<td>0.29 (0.18-0.39)</td>
<td>0.32 (0.25-0.38)</td>
</tr>
<tr>
<td>4</td>
<td>0.29 (0.20-0.42)</td>
<td>0.35 (0.24-0.43)</td>
<td>0.34 (0.27-0.45)</td>
</tr>
<tr>
<td>8</td>
<td>0.19 (0.11-0.30)</td>
<td>0.23 (0.09-0.31)</td>
<td>0.17 (0.10-0.27)</td>
</tr>
<tr>
<td>12</td>
<td>0.09 (&lt;0.06-0.15)</td>
<td>0.11 (&lt;0.06-0.18)</td>
<td>0.10 (&lt;0.06-0.29)</td>
</tr>
<tr>
<td>20</td>
<td>&lt;0.06 (&lt;0.06-0.06)</td>
<td>&lt;0.06 (&lt;0.06-0.06)</td>
<td>&lt;0.06 (&lt;0.06-0.11)</td>
</tr>
<tr>
<td>24</td>
<td>&lt;0.06 (&lt;0.06-&lt;0.06)</td>
<td>&lt;0.06 (&lt;0.06-&lt;0.06)</td>
<td>&lt;0.06 (&lt;0.06-0.06)</td>
</tr>
</tbody>
</table>

Douketis et al 2009 (n=138) the DIRECT study: Assessed peak and trough anti-factor Xa level after a dalteparin 5000units dose in critically ill patients in ITU with severe renal impairment.
Fig. 2. Mean plasma anti-Xa activity in the four groups of study participants on Day 4.

Sanderink et al 2002 (n=48): Compared peak anti-factor Xa levels in healthy volunteers with different renal function after enoxaparin 40mg daily.
Mahe et al 2007 (n=50):

Compared anti-factor Xa activity between prophylactic enoxaparin and tinzaparin in patients aged ≥75 years with CrCl 20-50ml/min and body weight <65kg.
Excretion of LMWHs and UFH

<table>
<thead>
<tr>
<th></th>
<th>MW (Da)</th>
<th>$T_{1/2}$ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>15,000</td>
<td>0.5 to 1.5</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>6,500</td>
<td>1.5</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>6,000</td>
<td>3.5 to 4</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4,400</td>
<td>5 to 7</td>
</tr>
</tbody>
</table>

Cellular elimination

Dependence on renal elimination
VTE Risk Assessment

**Risk Factors**
- Age >60 years
- BMI ≥ 40
- Recent surgical procedure
- Chronic conditions (COPD, CCF, Diabetes)
- Critical care admission
- Haematological disorders
- Dehydration
- Nephrotic syndrome
- COC/HRT or tamoxifen
- Acute infection
- Immobility due to hospital admission
- Active cancer or chemotherapy
- Personal/family history of VTE
- Recent cardiac event or stroke

**VTE Prophylaxis**

**Bleeding Risk**
- Severe renal disease
- Planned procedure within 6 hours
- Active bacterial endocarditis
- Platelets <70 x 10⁹/l
- Post-surgery or biopsy
- Severe hepatic disease
- Recent bleeding episode
- Major trauma
- Low dry weight (<46kg)

Assessed individually on a case-by-case basis
# VTE Prophylaxis in Renal Unit

If **low risk**, encourage mobility or consider mechanical thromboprophylaxis

<table>
<thead>
<tr>
<th>eGFR &gt; 30 ml/min/1.73m²</th>
<th>SC dalteparin 5000 units daily</th>
</tr>
</thead>
</table>
| eGFR 10-30 ml/min/1.73m² | SC dalteparin 2500 units daily  
If very high thrombotic risk, consult specialist registrar or consultant – may consider 5000 units daily. Monitor anti-factor Xa level **after 10 days**. |
| eGFR < 10 ml/min/1.73m² or patients on renal replacement therapy/conservative management | No heparin for thromboprophylaxis unless high risk. If high risk use SC dalteparin 2500 units daily. Monitor anti-factor Xa level **after 10 days**. |

- Target anti-factor Xa **peak** range is 0.1-0.4units/ml
- For patients requiring biopsy/surgical procedure, withhold evening dose of dalteparin and take a **trough** anti-factor Xa level at the same time
Results – Peak Anti-Factor Xa level

Percentage within target range (n=37)

- Low: 60%
- Target: 37%
- High: 3%

- SC dalteparin 2500 units were used in all cases except 1 very high thrombosis risk
- No dose increase for cases with low levels except high thrombotic risk
- No related bleeding or thrombosis events reported

*Feb 2017 to March 2018*
Assessment Based on Renal Function

- **n=1**
  - Within target range
  - eGFR 32
  - Dose 2500 units

- **n=7**
  - eGFR 10-30ml/min/1.72m²
  - 43% on target
  - 4 cases ‘low’

- **n=9**
  - eGFR <10ml/min/1.72m²
  - 78% on target
  - 2 cases ‘low’

- **n=2**
  - Peritoneal Dialysis
  - 100% ‘low’

- **n=18**
  - Haemodialysis
  - 61% on target
  - 1 case ‘high’
Case 1

Thrombosis
- AF
- Heart Failure
- High BMI 105kg
- Type 2 Diabetes

Bleeding
- eGFR <10
- High Urea

71 years
Diabetic nephropathy

- Admitted for intensive diuresis for fluid overload
- 12 day admission

- SC dalteparin 2500units – low anti-factor Xa level (0.02units/ml)
- Dose increased to 5000units due to high thrombosis risk
- Low anti-factor Xa level may be attributed to
  - Reasonable residual urine output
  - High body weight
Case 2

Thrombosis

- Paroxysmal AF
- Acute infection
- Recent DVT
- Fracture with surgical repair

Bleeding

- Haemodialysis
- Borderline low BMI
- ?Cardiac tamponade
- PR bleeding

72 years
Polycystic kidney disease

- Admitted for acute start of HD
- 30 day admission
- Warfarin stopped due to bleeding events

- SC dalteparin 5000 units – high anti-factor Xa level (0.59 units/ml)
- Dose reduced to 2500 units due to high bleeding risk – repeated anti-factor Xa level within range
- Withheld during bleeding episodes
- High anti-factor Xa level may be attributed to
  - Low dry weight
  - No urine output
Areas of Concern

• In the immediate transplant period where biopsy is urgent and unpredictable
• Patients who require spinal anaesthesia
• Patients with extreme low body weight
• Patients requiring surgical intervention or invasive procedures
Conclusion

- Prophylactic LMWHs can be used in severe renal impairment including patients on renal replacement therapy

- Routine anti-factor Xa monitoring is useful to determine accumulation but should be interpreted with clinical observation

- Larger studies required to further establish its safety and efficacy
Thank You