The Role of Heparin Related Drugs in the Management of Venous and Arterial Thrombosis

Hirmerova J
Clinical development of LMWHs in the 1980s

Low dose s.c. heparin (unfractionated heparin – UFH)
– efficient in thromboprophylaxis in surgical patients
- attributed to the absorption of the low-molecular–weight components of heparin (mostly anti-Xa activity, long-lasting effect, high bioavailability)

LMWHs developed by chemical, enzymatic, or physical depolymerization of UFH

Advantageous pharmacokinetics, convenience of administration

Promising results in animal studies

Hoppensteadt, Hematol Oncol Clin N Am 2003
Gray, Thromb Haemost 2008
Early clinical studies in general surgery

- Single daily dose of LMWH was able to prevent DVT in 97 of 100 patients (no control group)  
  *Kakkar, Brit Med J 1982*

- Double-blind study versus UFH in 400 patients better efficacy for the LMWH (DVT rate of 2.5% compared to 7.5% for UFH)  
  *Kakkar, Brit J Surg 1985*

- Excessive bleeding after LMWH in 2 studies – retrospectively explained by too high dosage  
  *Schmitz-Huebner, Klin Woch 1984  Koller, Thromb Haemost 1986*

- After decreasing the dose to a third – bleeding comparable to UFH  
  *Koller, Thromb Haemost 1986*

- Following studies with various LMWHs searching for optimal dosage and timing in relation to surgery  

- Commercial use of LMWHs began in the mid-1980s for hemodialysis and for DVT prophylaxis in general surgery.  
  *Hoppensteadt, Hematol Oncol Clin N Am 2003*
Early clinical studies in orthopaedic surgery

- Major reduction in DVT in patients undergoing hip surgery, compared to a placebo group (12% vs. 42%)  
  *Turpie, N Engl J Med 1986*

- Improved efficacy, compared to dextran (20% vs. 45%)  
  *Eriksson, Brit J Surg 1988*

- No reduction in DVT rate (28%) compared to a dextran group (39%)  
  *Mätzsch, Acta Chir Scand Suppl 1988*

- Significantly reduced DVT rate (12.5%) compared to UFH (25%)  
  *Planes, Thromb Haemost 1988*

- No reduction in overall DVT compared to UFH  
  *Levine, Ann Intern Med 1991*

Use of different LMWHs, different dosage and administration regimens, most of the trials were small!
Metaanalyses of studies of LMWHs in thromboprophylaxis in surgical patients

Each LMWH – distinct drug entity (depolymerization specific changes, physical and chemical heterogeneity, variations in biologic actions)

LMWHs are a closely related family of drugs with a shared mechanism of action

Hoppensteadt, Hematol Oncol Clin N Am 2003

Gray, Thromb Haemost 2008

52 randomised trials – thromboprophylaxis in general or orthopedic surgery:
LMWH vs. placebo or dextran: OR 0.31, and 0.44,
vs. UFH: OR 0.85, p = 0.02

LMWH vs. UFH: no significant difference in the incidence of major haemorrhage
Leizorovicz, Br Med J 1992

Metaanalysis of studies with strong methodology
OR 0.91, NS; no difference in major bleeding
Nurmohamed, Lancet 1992
Early studies in the treatment of VTE

- 6 small trials – pooled analysis:
  97 patients received LMWH, 97 patients receiving UFH, followed development of venographic changes
  - LMWH could be at least as effective and safe as UFH
  Levine & Hirsh, Bailliere’s Clinical Haematology – Antithrombotic Therapy 1990

- Larger studies ☺ comparable efficacy and safety as UFH (no reduction in bleeding risk)

- advantage in the ease of application and no need for laboratory monitoring
Metaanalyses of studies of LMWHs in VTE treatment

- 16 randomised trials, over 2,000 patients
  - significant reduction of the incidence of thrombus extension (OR 0.51)
  - trends in favor of LMWH for lower recurrence of thromboembolism, reduced incidence of major haemorrhage, and lower total mortality
  

- Metaanalysis of randomized trials comparing LMWH vs UFH
  - significant reduction in the risk of VTE recurrence and major bleeding
  - If only studies with strict methodology evaluated (blinded outcome assessment) no significant difference
  

- LMWH in the treatment of VTE: at least the same efficacy and safety, in some studies greater efficacy, less haemorrhagic effects
The impact of LMWH for home treatment of DVT

- improved convenience fixed dose s.c., without monitoring
- simplification of anticoagulant treatment

- LMWH given at home as safe and effective as UFH in the hospital in proximal DVT  

- home treatment with LMWH was as effective as inpatient treatment with LMWH  
  Boccalon, Arch Intern Med 2000

- early ambulation (vs bed rest) with compression stockings improved pain and counteracted swelling without increasing the risk of PE  
  Partsch, J Vasc Surg 2000

- home treatment became standard of care
  = a major advantage both for the patients and in economic terms
LMWHs in acute coronary syndromes

- Early studies comparing LMWHs with UFH in ACS: inconsistent results with nadroparin
  Gurfinkel J Am Coll Cardiol 1995  The FRAX.I.S. Study Group, Eur Heart J 1999

- No benefit of dalteparin compared to UFH  Cohen M, Thromb Res 2000

- Large study with enoxaparin - reduced incidence of the composite endpoint (death, MI, or recurrent angina), compared to UFH (both agents used in conjunction with aspirin)  Cohen M, N Engl J Med 1997

- Metaanalysis comparing enoxaparin to UFH as adjunctive antithrombotic therapy across the broad ACS spectrum: 49 088 patients in 12 trials, both STEMI and nonSTE-ACS
  - superior efficacy
  - increase of bleeding, offset by a reduction in death or MI
  Murphy, Eur Heart J 2007
LMWHs in cancer

Heparin - non-anticoagulant activities, e.g. inhibition of tumour growth
Zacharski, Thromb Haemost 1998

In studies comparing LMWH vs UFH in VTE, LMWH was associated with lower total mortality than UFH in cancer patients Hull, N Engl J Med 1992


 Trials designed specifically for cancer patients with VTE

CLOT
dalteparin 200U/kg s.c. OD, then 75-80% of the dose dose for 6 months

 Significant reduction of recurrence risk after LMWH

 Reduction of mortality after LMWH in nonmetastatic cancer
Recent trials with LMWH in cancer patients with VTE

- **CATCH**: randomized, open-label study
  - Tinzaparin (175 IU/kg) OD vs. conventional therapy (tinzaparin for 5 to 10 days followed by warfarin (target INR 2.0-3.0) for 6 months
  - 900 patients with active cancer
- LMWH was not associated with reductions in overall mortality or major bleeding
- Was associated with a lower rate of clinically relevant nonmajor bleeding
- Trend to lower risk of recurrence (NS)  
  

In long-term treatment of VTE in patients with cancer, LMWH compared to VKA reduces VTE recurrence but not mortality

Akl, Cochrane Database Syst Rev 2014
LMWH in thromboprophylaxis in oncologic patients

Surgery:

- **ENOXACAN**
  enoxaparin vs UFH – abdominal/pelvis surgery for cancer
  - Significant VTE reduction with LMWH
  *Br J Surg, 1997*

Extended prophylaxis:

- **ENOXACAN II**
  Abdominal surgery for cancer - enoxaparin 40mg 27-31 days vs 6-10 days
  - Significant VTE reduction with LMWH, without increasing bleeding risk
  *Bergqvist, N Engl J Med 2002*

- **FAME**
  dalteparin after abdominal surgery, subanalysis of cancer patients
  - Prolonged prophylaxis to 4 weeks - significant VTE reduction, compared to 1 week
  *Rasmussen, Blood 2003*
LMWH in thromboprophylaxis in ambulatory oncologic patients

– controversial results
LMWHs and VTE treatment and prophylaxis in pregnancy

No data from randomized trials

Guidelines – expert consensus based on data extrapolated from studies in nonpregnant patients, case reports, case series

Advantages of LMWH in pregnancy: usually one application daily, better predictability of effect, reduced risk of HIT and osteoporosis
Greer, Blood 2005

LMWH recommended for VTE treatment and prophylaxis
Bates, Chest 2012   Nicolaides, Int Angiol 2013

Obstetrical antiphospholipid syndrome:
antepartum administration of prophylactic or intermediate dose UFH or prophylactic LMWH combined with low-dose aspirin, 75 to 100 mg/d
Bates, Chest 2012
LMWH in thromboprophylaxis in medical patients

- Medical patients >65 years (270) enoxaparin 60mg s.c./d DVT 3% vs 9% vs. placebo (p=0.03)
  Dahan, Haemostasis 1986

- COPD patients (223) nadroparin 3800 or 5700/d DVT 15.5% vs 28.2% vs. placebo (p=0.045)
  Fraisse, Am J Respir Crit Care 2000

- MEDENOX
  Acute medical patients (1102) enoxaparin 20mg s.c./d VTE 15% vs 14.9% (NS) vs. placebo
  40mg s.c./d 5.5% vs 14.9% (p < 0.001)
  Samama, N Engl J Med 1999

- PREVENT
  Acute medical patients (3706) dalteparin 5000/d VTE, sudden death 2.8% vs 5.0% vs. placebo (p=0.0015)
  Leizorovicz, Circulation 2004
Current indications for LMWH

- VTE prophylaxis in surgical and medical patients
- VTE treatment – initial phase
- Adjunctive antithrombotic treatment of ACS
- Hemodialysis

LMWH hardly replaceable in:

- VTE treatment and prophylaxis in pregnancy

(Cancer patients, fragile patients, paediatric patients)
Fondaparinux

synthetic pentasaccharide
selective FXa inhibitor mimics the site of heparin that binds to AT
# Prophylaxis in orthopaedic surgery

<table>
<thead>
<tr>
<th>Surgery</th>
<th>No of patients</th>
<th>Fondaparinux</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VTE</td>
<td>Prox. DVT</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1711</td>
<td>8.3%*</td>
<td>0.9% *</td>
</tr>
<tr>
<td>THR</td>
<td>2309</td>
<td>4.0%*</td>
<td>0.7% †</td>
</tr>
<tr>
<td>THR</td>
<td>2275</td>
<td>6.1%</td>
<td>1.7%</td>
</tr>
<tr>
<td>TKR</td>
<td>1034</td>
<td>12.5%*</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

*<p<0.001  †<p=0.0021
Prophylaxis in orthopaedic surgery

- **PENTHIFRA PLUS**
  Prolonged prophylaxis after hip fracture surgery
  656 patients
  extending fondaparinux prophylaxis from 1 to 4 weeks - compared to placebo
  - delayed VTE reduced from 35% to 1.4% (RRR 95.9%, \( p < 0.001 \))
  
  Eriksson, Arch Intern Med 2003

- **FLEXTRA**
  delaying the first dose of fondaparinux from 6 to 8 hours post-operatively to the first post-operative morning did not influence the outcome (1.9% VTE vs 1.8%)
  - fondaparinux can be started post-operatively and therefore does not increase surgical bleeding.
  
  Clifford, J Arthroplasty 2006
Prophylaxis in abdominal surgery

- **PEGASUS**
  - 2927 high risk abdominal surgery patients:
  - 2.5 mg fondaparinux started 6 hours after surgery
  - vs. dalteparin started 2 hours before the surgery 5000 s.c./d
  - 10 days after the surgery: VTE 4.6% (fonda) vs 6.1% (dalteparin)
    - RRR 24.6%  $p=0.144$
    - major bleeding 3.4% vs. 2.4%  $p=0.122$  noninferiority
  - *Agnelli, Br J Surg, 2005*

- **APOLLO**
  - 1070 patients - fondaparinux + IPC vs. IPC
    - fondaparinux 2.5 mg, 6-8 hours after surgery, 7±2 days
    - VTE: 1.7% (fonda+IPC) vs. 5.3% (IPC)  $p=0.004$
    - major bleeding 1.6% vs. 0.2%  $p=0.006$
  - *Turpie, J Thromb Haemost 2005*
Prophylaxis in medical patients

- **ARTEMIS**
  - 849 patients
  - fondaparinux 2.5mg s.c. OD vs. placebo, 6-14 days
  - VTE: 5.6% (fonda) vs. 10.5% (placebo)
  - RRR 46.7% \( p=0.029 \)
  - major bleeding 0.2% in both groups

*Cohen, BMJ 2006*
Fondaparinux in acute coronary syndromes

- **OASIS 5**
  - Randomized double-blind
  - 20,078 patients
  - fondaparinux 2.5 mg OD vs. enoxaparin 1 mg/kg BID
  - Fondaparinux similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long-term mortality and morbidity
    - *Yusuf, N Engl J Med 2006*

- **MICHELANGELO OASIS-6**
  - Randomized double-blind
  - 12,092 patients with STEMI
  - fondaparinux 2.5 mg OD vs control (UFH or placebo)
  - Fondaparinux significantly reduces mortality and reinfarction without increasing bleeding and strokes.
  - *particularly efficient in those not undergoing primary PCI*
    - *Yusuf, JAMA 2006*
Fondaparinux in VTE treatment

- **MATISSE-DVT**
  - 2200 with DVT, no PE
  - fondaparinux 5mg (weight <50kg); 7.5mg (50-100kg); 10mg (>100kg) OD vs. enoxaparin 1mg/kg s.c. BID
  - 7±2 days, VKA (INR 2-3) 90±7 days
  - recurrent VTE 1.6% (fonda) vs. 0.9% (enoxaparin)
  - noninferior effectivity and safety  
    - Büller, Ann Intern Med 2004

- **MATISSE-PE**
  - 2213 patients with acute PE
  - fondaparinux 5mg (weight <50kg); 7.5mg (50-100kg); 10mg (>100kg) OD vs. UFH i.v., APTT-R 1.5-2.5
  - 7±2 days, VKA (INR 2-3) 90±7 days
  - recurrent VTE 3.8% (fonda) vs. 5.0% (UFH)
  - major bleeding 1.3% (fonda) vs. 1.1% (UFH)
  - noninferior effectivity and safety  
    - Büller, N Engl J Med 2003
Fondaparinux in SVT treatment

- CALISTO
  randomized, double-blind trial
  3002 patients with SVT
  - fondaparinux 2.5 mg OD for 45 days vs placebo
  Primary efficacy outcome (composite of death, symptomatic PE/DVT, symptomatic ST extension/recurrence) 0.9% (fonda) vs. 5.9% (placebo)
  \( p<0.001 \); RRR85%

Fondaparinux in cardioversion of AF

Pilot study:

- **SAFE-AF**
  - fondaparinux vs standard treatment in patients undergoing TEE-guided cardioversion of AF
  - 344 patients
  - fondaparinux well tolerated, similar efficacy to UFH+VKA
  - a trend to greater thrombus resolution was observed

Cohen, *Arch Cardiovasc Dis 2015*
Ongoing studies:

- **PROTECT**
  - fondaparinux vs no treatment
  - Patients with a nonsurgical fracture of the lower extremity immobilised in a below-knee plaster cast

- **FONDACAST**
  - fondaparinux vs nadroparin
  - patients requiring rigid or semi-rigid immobilization for at least 21 days and up to 45 days because of isolated non-surgical below-knee injury

- **SWITCH 3 - PCI**
  - fondaparinux vs UFH or bivalirudin
  - patients with ACS undergoing PCI

http://www.trialresultscenter.org/
Current indications for fondaparinux

- VTE prophylaxis in major orthopaedic surgery
- VTE prophylaxis in high-risk abdominal surgery
- VTE prophylaxis in high-risk medical patients
- Adjunctive antithrombotic treatment in unstable angina/nonSTEMI in the patients not indicated to urgent PCI
- Adjunctive antithrombotic treatment in STEMI treated with thrombolysis or not treated with reperfusion therapy
- SVT treatment
“It is easy to get a thousand prescriptions but hard to get one single remedy.”

*Chinese Proverb*