THROMBOEMBOLIC PROPHYLAXIS IN ORTHOPEDIC SURGERY AND TRAUMATOLOGY
# VTE prevalence without prophylaxis following orthopedic surgery

<table>
<thead>
<tr>
<th></th>
<th>Total DVT (%)</th>
<th>Proximal DVT (%)</th>
<th>Total PE (%)</th>
<th>Fatal PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THR</td>
<td>45-57</td>
<td>23-36</td>
<td>0.7-3.0</td>
<td>0.1-0.4</td>
</tr>
<tr>
<td>TKR</td>
<td>40-84</td>
<td>9.0-20</td>
<td>1.8-7.0</td>
<td>0.2-0.7</td>
</tr>
<tr>
<td>Hip fr.</td>
<td>36-60</td>
<td>17-36</td>
<td>4.3-24</td>
<td>3.6-12.9</td>
</tr>
</tbody>
</table>

THR: total hip replacement  
TKR: total knee replacement  

Geerts WH et al. Chest 2001  
Geerts WH et al. Chest 2004
Classification of risk factors for VTE in orthopedic surgery and traumatology

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor surgery (&lt;30’) in patients &gt; 40 years</td>
</tr>
<tr>
<td>Major surgery (&gt;30’) in patients with no other factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery (&gt; 30’) in patients &gt; 40 years with some associated factor</td>
</tr>
<tr>
<td>Minor surgery in patients with history of VTE</td>
</tr>
<tr>
<td>Relevant trauma or prolonged immobilization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major orthopedic surgery</td>
</tr>
<tr>
<td>Orthopedic surgery in patients &gt; 40 years with history of VTE</td>
</tr>
<tr>
<td>Hip of lower limb fractures</td>
</tr>
<tr>
<td>Lower limb amputation or paralysis</td>
</tr>
</tbody>
</table>

Hirsch J et al. CRC Pres 1987
Salzman EW. Br Med J 1992
## VTE incidence by risk group

<table>
<thead>
<tr>
<th>Risk</th>
<th>Distal DVT (%)</th>
<th>Proximal DVT (%)</th>
<th>Fatal PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 10</td>
<td>&lt; 1</td>
<td>0.01</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-40</td>
<td>1-10</td>
<td>0.1-1</td>
</tr>
<tr>
<td>High</td>
<td>40-80</td>
<td>10-30</td>
<td>1-10</td>
</tr>
</tbody>
</table>

Hirsch J et al. CRC Press 1987  
Salzman EW. Br Med J 1992
**Efficacy of thromboembolic prophylaxis in orthopedic surgery and traumatology (I)**

Many controlled studies have shown the efficacy of thromboembolic prophylaxis in orthopedic and traumatological surgery

- Overall mortality may be decreased by more than **60%**
- Risk of postoperative DVT may be reduced by **70%**

However, prophylaxis has not still been routinely assumed
Recent multicenter studies in the US on risk factors for VTE have found that
“*prophylaxis is only given to 17% of patients who need it*”

Anderson FA. Arch Intern Med 1992
# Efficacy of thromboembolic prophylaxis in orthopedic surgery and traumatology (II)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Reduction in DVT incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip replacement</td>
<td>63-77</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>74</td>
</tr>
<tr>
<td>Lower limb fractures</td>
<td>66</td>
</tr>
</tbody>
</table>

Spannagel U et al. Semin Thromb Haemost 1999
Factors that may have an influence on DVT occurrence

<table>
<thead>
<tr>
<th>Factor</th>
<th>Influence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of anesthesia</td>
<td>Favorable</td>
</tr>
<tr>
<td>Preventive ischemia</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Prolonged or careless surgical technique</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Prolonged postoperative immobilization</td>
<td>Determinant</td>
</tr>
</tbody>
</table>
Requirements for VTE prophylaxis in orthopedic surgery and traumatology

The following criteria should be considered for VTE prophylaxis:

• Prophylaxis should not be given to patients with general contraindications
• Prophylaxis should be given based on a protocol considering the different risk factors
• An adequate LMWH as regards characteristics, dosage, and duration should be used
• Prophylaxis should be associated to other mechanical and early mobilization measures
Physical measures to prevent VTE in orthopedic surgery and traumatology

- Functional techniques allowing for early patient mobilization (osteosynthesis)
- Ascending or graduated compression stockings
- Pneumatic cyclic compression pumps
- Early active and passive kinesitherapy
- Vena cava filters in very special cases

Meyer G et al. Chirurg 2004
Advantages of prophylaxis with LMWHs in orthopedic surgery and traumatology

- LMWHs have a greater bioavailability
- LMWHs have a longer half-life (easy management)
- LMWHs induce less thrombocytopenia
- LMWHs are less hepatotoxic
- LMWHs cause less bone demineralization
- LMWHs do not cross the placental barrier

CONCLUSIVE EVIDENCE IS AVAILABLE OF THE ADVANTAGES OF LMWHs OVER UFH
# Efficacy of VTE prophylaxis in total knee replacement


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (n)</th>
<th>DVT</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total (%)</td>
<td>Proximal (%)</td>
</tr>
<tr>
<td>LMWHs</td>
<td>1,753</td>
<td>31.3</td>
<td>5.9</td>
</tr>
<tr>
<td>WARFARIN</td>
<td>1,094</td>
<td>45.6</td>
<td>10.2</td>
</tr>
<tr>
<td>ASPIRIN</td>
<td>58</td>
<td>56.9</td>
<td>1.7</td>
</tr>
<tr>
<td>PNEUMATIC COMPRESSION</td>
<td>236</td>
<td>38.8</td>
<td>3.3</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>135</td>
<td>60.2</td>
<td>15.3</td>
</tr>
</tbody>
</table>
# Efficacy of VTE prophylaxis in total hip replacement


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (n)</th>
<th>Total DVT</th>
<th>Proximal DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>LMWHs</td>
<td>5,512</td>
<td>918</td>
<td>17.7</td>
</tr>
<tr>
<td>WARFARIN</td>
<td>1,493</td>
<td>334</td>
<td>23.2</td>
</tr>
<tr>
<td>ASPIRIN</td>
<td>687</td>
<td>214</td>
<td>30.6</td>
</tr>
<tr>
<td>UFH</td>
<td>1,859</td>
<td>429</td>
<td>31.1</td>
</tr>
<tr>
<td>PNEUMATIC COMPRESSION</td>
<td>431</td>
<td>94</td>
<td>20.7</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>947</td>
<td>546</td>
<td>48.5</td>
</tr>
</tbody>
</table>

Elective hip surgery

The risk: 50% for DVT
2,5% for PE

Prophylactic methods: (recommendations)
- LMWH: recom. Grade A (major bleeding 1.4%).
- Warfarin: recom. Grade A (less effective; major bleeding 5.5%)
- Fondaparinux: recom. Grade B
- IPC+GEC: recom. Grade B (additional method or high bleeding risk)

Duration of prophylaxis: 30-42 days
(risk duration: 3 months)

Int. Angiol 2006; 25:101-61
Hip fracture surgery

The risk: 46-60% for DVT
          2,5-7,5% for PE

Recommended prophylaxis methods:

- **Immediate surgery:**
  - LMWH: Rec. Grade A
  - Fondaparinux: Rec. Grade A
  - IPC+GEC: Rec. Grade B (only by contraindication of farmac prophylaxis)

- **Delayed Surgery:**
  - LMWH or IPC+GEC as close to fracture as possible (Rec. Grade C)

Duration of prophylaxis: 30-42 days

Duration of risk: 2-3 months after surgery

(overall death is 13% at 90-day risk)

Int. Angiol 2006; 25:101-61
Elective knee joint replacement

The risk:
- Data from THR should not be extrapolated to TKR.
- Asymptomatic DVT in TKR (65%) is higher than in THR (50%).
- Incidence of above Knee DVT in TKR patients is lower than in patients having THR.

Prophylaxis methods:
- IPC is very effective in reduced incidence of asymptomatic DVT.
- IPC is more effective than aspirin but less effective than LMWH.
- LMWH reduced venograph detected DVT from 65% in placebo to 19%.
- Fondaparinux is effective compared with enoxaparin, however major bleeding are also more frequent (2.1% versus 0.2%).

Recommendations:
- LWMH: Rec. Grade A
  - Warfarin: Rec. Grade A (although less effective)
  - Fondaparinux: Rec. Grade B
- IPC + GEC stockings are alternative options (Grade B)

Duration Prophylaxis
- The effect of extending prophylaxis 30-42 days on symptomatic DVT in patients having TKR is less than in patients having THR.

Int. Angiol 2006; 25:101-61
Knee arthroscopy

The risk:
- 7% in absence of prophylaxis (1.4% proximal)
- Increased if tourniquet > 1 hour
- Symptomatic only 0.6%

Prophylaxis methods:
- LMWH reduces the incidence of DVT from 8% to 1% (n: 239 pat.)

Recommendations:
- Diagnostic arthroscopy: Not recommended or recommended (Grade C), in presence of risk factors.
- Arthroscopy surgery: LMWH or IPC if contraindications for heparin.

Duration of prophylaxis:
- Until full deambulation (Grade C)
Multiple trauma

The risk:
- 50% DVT without prophylaxis.
- PE 3rd cause of death alter 1º day
- Risk higher in pat. with spinal cord injury or pelvic fracture.

Prophylaxis methods:
- Prophylaxis according with bleeding risk.
- LMWH started within 36 h. of injury is superior than LDUH.
- Mechanical methods are attractive when chemical prophylaxis is contraindicated.

Recommendations:
- LMWH starting as soon as bleeding risk is acceptable (Grade A)
- IPC in case of contraindication for LMWH (Grade B)

Duration:
- Until full deambulation

Int. Angiol 2006; 25:101-61
Isolated below knee injuries

The risk:
- Depending on additional immobilization and severity of injury:
  DVT: 10% - 35%
  PE: 0.4% - 2.1%

Prophylaxis methods:
- LMWH can reduce incidence of DVT with plaster cast from 17% (control) to 5%. (n:253).
- LMWH reduce 5-weeks incidence of DVT in lower leg fractures from 18% (control) to 10% (n:293).

Recommendation:
- Not recommended routine prophylaxis
- LMWH can be used by additional risk.

Duration:
- Until full deambulation

Int. Angiol 2006; 25:101-61
Elective spine surgery

The risk:
- 18% DVT by routine venography without prophylaxis
- 3.7% incidence of symptomatic DVT

Prophylaxis methods:
- LMWH and Enoxaparin reduces incidence of asymptomatic DVT from 20% to 0%.
- IPC reduces venographically detected DVT from 21% (control) to 6%.

Recommendations:
- Mechanical IPC (Grade B)
- LMWH (Grade B)

Duration:
- IPC preoperatively
- LMWH after op. and during hospitalization (Grade C)

Int. Angiol 2006; 25:101-61
Spinal cord injury

The risk:
- 35% of DVT in absence of prophylaxis.
- PE is the 3rd leading cause of death in a series of 1,649 rehabilitation patients.
- Symptomatic DVT occurred in 10% and PE in 3%.

Prophylaxis methods:
- LMWH + GEC were compared with no prophylaxis group:
  - The incidence was 47% (control) versus 7% in LMWH group.
  - Patients with spinal cord injuries appears as a highly resistant group to singles prophylaxis measures.

Recommendations:
- LMWH + IPC + GEC (Grade B)
- Initiation: IPC and GEC on admission and LMWH when bleeding risk is acceptable (Grade C).

Duration:
- LMWH + IPC during 3 months.
- GEC indefinitely (Grade C).
The risk:
- Depending of age, intensity- extension of burn, additional injuries and co-morbid diseases.
- The incidence of DVT varies between 6% -27% in absence of prophylaxis. (Symptomatic in 2.4% - 7%).

Prophylaxis methods:
- Lack of evidence-based data
- Same recommendations as in multiple trauma patients.

Recommendations:
- LMWH as soon as is considered safe.

Duration:
- As long as patient remains at risk (grade C)
New oral antithrombotics. Potential and expectations: oral heparin

- Potential advance in thromboembolic prophylaxis by eliminating the disadvantages of parenteral administration and facilitating extended outpatient treatment
- Berkowitz SD, 2003: A Phase II, multicenter, double-blind study in 123 patients undergoing total hip replacement comparing:

  **Oral heparin** 60,000 IU or 90,000 IU + drug delivery agent (SNAC) vs. **Unfractionated heparin** (UFH) SC (5,000 IU/8h)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Oral heparin n = 82</th>
<th>UFH SC n = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td>4 (4.9%)</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3 (3.7%)</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3 (3.7%)</td>
<td>4 (9.8%)</td>
</tr>
</tbody>
</table>

• “The need for prophylaxis against venous thromboembolic disease following lower-extremity trauma surgery or joint replacement is well documented and accepted”

• “Although LMWH is approved for inpatient and extended prophylaxis beyond the hospital environment, orthopaedic surgeons must determine the duration of the prophylaxis based on the period risk, individual factors, type of surgery and patient compliance with logistics of medication at home”
Duration of VTE prophylaxis

- Optimum duration of prophylaxis is difficult to establish.
- Some studies have shown that the risk of fatal PE in hip fractures persists for up to 30 days after the primary accident.
- In hip replacement, level A scientific evidence is available recommending maintenance of prophylaxis with LMWHs for 4-6 weeks after surgery.
- Many other current studies recommend similar regimens for knee replacement and other major orthopedic procedures.

Dobesh PP et al. Pharmacotherapy 2004
Geerts WH et al. Chest 2004
Krotenberg R. Am J Orthop 2004
Schobersberger W et al. Wien Med Wochenschrift 2004
• Most of the published works point out a significant reduction (up to 95%) of late events of VTE, though data are hardly comparable, because of the differences between diagnostic and treatment protocols

• Risk of PTE remains high until 2-3 months after major hip surgery (Dahl OE).

• Higher efficacy in severe traumas and hip surgery than in knee surgery or less severe injuries.
Clinical evidence on the efficacy of extended prophylaxis in Orthopedic Surgery and Trauma (II)

- Optimal prophylaxis duration remains uncertain, though its extension is recommended until 4-6 weeks post-op.

- Some authors (O’Donell, et al) suggest that the symptomatic VTE events reduction attributed to extended prophylaxis have been overestimated

- Extended thromboprophylaxis seems to be cost-effective, given that more than 98% of patients are free from VTE during this period, reducing the in-patient stay and its subsequent costs
# Prophylaxis extension in orthopedic surgery and traumatology

<table>
<thead>
<tr>
<th>Study</th>
<th>LMWHs n/n</th>
<th>Control n/n</th>
<th>Peto OR (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergqvist et al.</td>
<td>2/131</td>
<td>10/131</td>
<td></td>
<td>19.7</td>
<td>0.25 (0.08-0.79)</td>
</tr>
<tr>
<td>Dahl et al.</td>
<td>4/117</td>
<td>6/110</td>
<td></td>
<td>16.5</td>
<td>0.62 (0.17-2.19)</td>
</tr>
<tr>
<td>Heit et al.</td>
<td>7/607</td>
<td>10/588</td>
<td></td>
<td>28.8</td>
<td>0.68 (0.26-1.76)</td>
</tr>
<tr>
<td>Hull et al.</td>
<td>4/291</td>
<td>3/133</td>
<td></td>
<td>10.2</td>
<td>0.58 (0.12-2.91)</td>
</tr>
<tr>
<td>Lassen et al.</td>
<td>2/140</td>
<td>3/141</td>
<td></td>
<td>8.5</td>
<td>0.67 (0.11-3.92)</td>
</tr>
<tr>
<td>Planès et al.</td>
<td>3/90</td>
<td>7/49</td>
<td></td>
<td>16.3</td>
<td>0.43 (0.12-1.52)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>22/1,376</td>
<td>39/1,192</td>
<td></td>
<td>100</td>
<td>0.50 (0.30-0.83)</td>
</tr>
</tbody>
</table>

Cohen AT et al. Thromb Haemost 2001
Biological evidences for the need of extended prophylaxis

• Arnesen H. et al., included 218 patients who underwent surgery for hip replacement. It was shown that fragment 1+2 of prothrombin (F1+2), thrombin-antithrombin complex (TAT), D-dimer and fibrinogen, seemed to be significantly higher in the surgery group as compared to a non-surgery control group.

• The activation of coagulation after surgery is maintained at least until 35 days of post-op. and is substantially reduced with LMWH administration.

• This hypercoagulability was kept equally high until 35 days, in the placebo group patients with venographically-proven DVT.
Extended prophylaxis after major orthopedic surgery. Spanish experience

<table>
<thead>
<tr>
<th>Study period</th>
<th>Navarro et al. (1)</th>
<th>Abad et al. (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bemiparin n = 189</td>
<td>Bemiparin n = 1009</td>
</tr>
<tr>
<td></td>
<td>2000-2001</td>
<td>2002-2003</td>
</tr>
<tr>
<td>Extended prophylaxis, %</td>
<td>62%*</td>
<td>70%*</td>
</tr>
<tr>
<td>Clinical events during 6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented symptomatic VTE</td>
<td>1.2%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

*Thromboprophylaxis was maintained for 3-6 weeks in these patients
**Prophylaxis was maintained for 38 days (median) in these patients

Options in postoperative thromboprophylaxis

• Activation of coagulation occurring after surgery in general, and very particularly in orthopedic major surgery, does not decrease until the 5th postoperative week. During this period, it would be advisable to maintain a thromboprophylaxis adjusted to individual risk factors.

• Drugs available:

<table>
<thead>
<tr>
<th>Indirect thrombin inhibitors</th>
<th>LMWHs, unfractionated heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct thrombin inhibitors</td>
<td>Hirudin and analogues</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>Acenocoumarol, warfarin</td>
</tr>
<tr>
<td>Selective Factor Xa inhibitors</td>
<td>Fondaparinux</td>
</tr>
</tbody>
</table>

• Drug prophylaxis is usually performed with LMWHs, the current drugs of choice for VTE prevention.
Recommendations for thromboembolic prophylaxis

- With type A evidence levels, primary antithrombotic prophylaxis is recommended in all patients with risk factors because of its cost-effectiveness profile.

- This particularly includes patients undergoing major orthopedic surgery, with hip fractures, or other trauma, who should maintain a prolonged immobilization.

- There is also adequate level A evidence to recommend use of LMWHs, administered before or after surgery, as the prophylaxis of choice.

### Approved intervals in Spain between the first dose of LMWHs and surgery

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bemiparin</td>
<td>-2h/+6h</td>
<td>-2h/+6h</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>-2h/-4h</td>
<td>-2h/-4h</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>-2h</td>
<td>-12h</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>-2h/-4h</td>
<td>-2h/-4h</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>-2h</td>
<td>-12h</td>
</tr>
</tbody>
</table>

Approved SPCs, SMA, May 2005
Role of primary care in monitoring postoperative prophylaxis

PROBLEMS FOR MONITORING OUTPATIENT PROPHYLAXIS

- Difficulties for patient self-administration
- Lack of communication between orthopedic surgeons and primary care physicians
- Need for primary care physicians to emphasize the significance of the problem
- Travelling and availability problems of home nursing staff

Samama M et al. 1991