**Scenario Clinico (1)**

- La signora Francesca è una pensionata, già casalinga, di 72 aa, sposata con tre figli, in sovrappeso (158 cm x 69 KG; BMI= 27.6).
- Da oltre 20 anni, ipertensione arteriosa in trattamento con ACE-inibitori (ramipril 5 mg) + diuretici (25 mg di idroroclorotiazide), con buon controllo pressorio; assenza di danni d’organo.
- Dal novembre del 2002, in seguito a diagnosi di arterite temporale di Horton, è in trattamento con prednisone, con buon controllo della sintomatologia. Attualmente, assume 5 mg/die.

**Scenario Clinico (1)**

- Terapia prescritta alla dimissione:
  - Nadroparina, 0.3 ml/die per 20 gg
  - Lanzoprazolo 30 mg/die
  - Ramipril 5 mg + idroroclorotiazide 25 mg
  - Prednisone 5 mg/die (sospeso in occasione dell’intervento)
  - Ferrograd 1 cpr/die
- Controllo clinico e radiologico il 16 settembre.
- Si consiglia di eseguire emocromo (per monitorare dell’anemia)

**Scenario Clinico (1)**

- Per eccesso di zelo la signora esegue privatamente un emocromo che, oltre a confermare i valori di emoglobina (9.8 gr%), rileva anche una piastrinopenia (110.000/mmc)
- In realtà, ad un’attenta verifica dei dati di laboratorio, il numero delle piastrine si era così evoluto:
  - Prima dell’intervento 180.000/mmc
  - Alla dimissione 102.000/mmc
  - Al controllo ambulatoriale 110.000/mmc

CLINICAL QUESTIONS

?
A. Nella prevenzione della malattia tromboembolica, ritiene che tutte le EBPM abbiano lo stesso profilo di efficacia e tollerabilità?

1. No
2. Sì

Profilassi della Malattia tromboembolica Linee guida

• SISET - Società Italiana per lo Studio dell’Emostasi e Trombosi
  - Diagnosi, Profilassi e Terapia del Tromboembolismo Venoso, 2003
  - Profilassi del tromboembolismo venoso in chirurgia ortopedica maggiore, 2002
• SIGN, 2002
• American College of Chest Physicians, 2001

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van der Heijden JF, Prins MH, Buller HR

Low-molecular-weight heparins. Are they interchangeable?

*Haemostasis* 2000;30(Supplement 2):146-157

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Are LMWH interchangeable?

• Several LMWHs (dalteparin, enoxaparin, reviparin and tinzaparin) are currently licensed in the UK for prophylaxis of VTE.
• They vary in their manufacture, chemistry and biology, but it is not clear whether or not these characteristics affect clinical efficacy or safety equivalence.

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McCart GM, Kayser SR.

Therapeutic equivalency of low-molecular-weight heparins

*Ann Pharmacother* 2002;36:1042-57
OBJECTIVE
To review the evidence for therapeutic equivalence between enoxaparin, dalteparin, ardeparin, and tinzaparin

DATA SOURCES
MEDLINE search (1993-January 2001) was conducted to identify English-language literature available.

STUDY SELECTION and DATA EXTRACTION
• All controlled trials evaluating LMWHs versus standard therapy powered to detect a significant difference were reviewed, with regard to safety and efficacy.

DATA SYNTHESIS
• LMWHs have chemical, physical, and clinical similarities and there is potential for therapeutic interchange between enoxaparin, dalteparin, ardeparin, and tinzaparin.
• Evaluation of clinical trials is limited because of differing diagnostic methods, drug administration times, dose equivalencies, and outcome measurements.

CONCLUSIONS
• Only 1 trial has evaluated 2 LMWHs in a direct comparison in the same study.
• There is insufficient evidence for determining the therapeutic equivalence of LMWHs.

1. Appropriatezza e sicurezza delle eparine a basso peso molecolare

B. Quale tra i seguenti fattori influenzano il dosaggio delle EBPM?

1. Età
2. Peso corporeo
3. Rischio tromboembolico
4. 1 + 2
5. 2 + 3

C. Per quanti giorni, dopo l’intervento di artroprotesi, ritieni appropriato prolungare la profilassi con EBPM?

1. 7-10 gg
2. 11-20 gg
3. 21-28 gg
4. > 28 gg
• The routine duration of UFH or LMWH prophylaxis is until discharge from hospital (usually 7-15 days). However, in contrast to non-orthopaedic surgery, there is a high risk of recurrent asymptomatic DVT when venography is repeated at 4-5 weeks after surgery.

• LMWH prophylaxis can also be continued for 4-5 weeks after surgery, and was more effective than conventional LMWH (or warfarin) prophylaxis for 7-15 days in reducing risks of asymptomatic DVT and symptomatic VTE

• Because of its logistic problems and costs, it should be reserved for very high-risk patients (e.g. previous VTE and/or multiple risk factors).

3 Revisioni Sistematiche


Table 2. Characteristics of the Studies Included in the Systematic Review

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Year</th>
<th>Endpoint</th>
<th>Follow-up</th>
<th>VTE Rate in Control Group</th>
<th>VTE Rate in Treatment Group</th>
<th>Number of Patients</th>
<th>Anticoagulant Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen AT et al.</td>
<td>2001</td>
<td>DVT</td>
<td>In-hospital</td>
<td>3.3%</td>
<td>1.8%</td>
<td>398</td>
<td>LMWH (enoxaparin)</td>
</tr>
<tr>
<td>Hull RD et al.</td>
<td>2002</td>
<td>DVT</td>
<td>In-hospital</td>
<td>1.5%</td>
<td>0.3%</td>
<td>150</td>
<td>LMWH (enoxaparin)</td>
</tr>
</tbody>
</table>

Table 3. Methodological Quality of Studies Included in the Systematic Review

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Year</th>
<th>Methodological Quality (Sequence Generated)</th>
<th>Methodological Quality (Sequencing Blinded)</th>
<th>Double-blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen AT et al.</td>
<td>2001</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Hull RD et al.</td>
<td>2002</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Hull RD, Pino GF, Stein PD, et al.

Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty

A systematic review.

Ann Intern Med 2001;135:858-869
Table 4. Symptomatic Venous Thromboembolism at 2 Months Following Total Hip Arthroplasty

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of Patients</th>
<th>% Asymptomatic</th>
<th>% Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH 1</td>
<td>18 (9.0)</td>
<td>10 (5.6)</td>
<td></td>
</tr>
<tr>
<td>LMWH 2</td>
<td>18 (9.0)</td>
<td>10 (5.6)</td>
<td></td>
</tr>
<tr>
<td>LMWH 3</td>
<td>18 (9.0)</td>
<td>10 (5.6)</td>
<td></td>
</tr>
<tr>
<td>LMWH 4</td>
<td>18 (9.0)</td>
<td>10 (5.6)</td>
<td></td>
</tr>
</tbody>
</table>
Alcune riflessioni sull’appropriatezza nell’uso dei farmaci

- Un trattamento è appropriato se:
  - è di efficacia provata
  - la prescrizione riguarda indicazioni cliniche per le quali è stata dimostrata l’efficacia
  - gli effetti sfavorevoli sono “accettabili” rispetto ai vantaggi terapeutici

Il rischio basale

“Trattare i pazienti a basso rischio è una strategia molto rischiosa perché il vantaggio che il singolo individuo può ottenere da un programma di prevenzione può essere annullato dal rischio - anche minimo - che implica lo stesso intervento preventivo.

Rose G. Int J Epidemiol 1985

Il rischio basale

- Il beneficio che il paziente individuale può ottenere da un intervento terapeutico cresce proporzionalmente al rischio basale di sviluppare un evento sfavorevole.
- Il rischio di eventi avversi conseguenti al trattamento é indipendente dal rischio basale del paziente.


1. Appropriatezza e sicurezza delle eparine a basso peso molecolare

D. Le EBPM possono causare piastrinopenia?

1. No, mai
2. Si (= frequenza dell’eparina non frazionata)
3. Si (↓ frequenza dell’eparina non frazionata)
• Clinically important heparin induced thrombocytopenia (HIT) is immune mediated and usually occurs between five and 10 days (up to 20 days) after initiation of heparin.
• It can occur at any dose of either UFH or LMWH.
• LMWH is less likely than UFH to be associated with antiplatelet antibodies.
• HIT should be considered in any patient whose platelet count falls by 50% or more.

College of American Pathologists

Platelet Count Monitoring and Laboratory Testing for Heparin-Induced Thrombocytopenia

Arch Pathol Lab Med 2002;126:1415-1423

• The variable frequency of HIT depends on the type of heparin:
  - UFH 2-5%
  - LMWH < 0.2%

Jackson N.

Comparative incidence of heparin-induced thrombocytopenia syndrome (HITS) with unfractionated heparin and low molecular weight heparin

Centre for Clinical Effectiveness (CCE) November 2002

• Eight studies were identified which assessed thrombocytopenia or heparin-induced thrombocytopenia syndrome (HITS) in general surgery patients, orthopaedic surgery patients or cardiac surgery patients
• Six studies showed that the incidence of thrombocytopenia or HITS was lower in patients who received LMWH compared to patients who received unfractionated heparin (UFH), regardless of type of surgery

CCE, November 2002

• Only three studies confirmed the diagnosis of HITS by means of the presence of heparin-dependent antibodies
• Methodological limitations and small sample sizes of many of the studies identified limit the ability to determine the true incidence of HITS and time of onset
• Further research, examining HITS as a primary outcome, is required to elucidate the incidence of HITS with the use of UFH or LMWH for the prophylaxis of venous thromboembolism

CCE, November 2002
E. Avresti ritenuto appropriato, nella sig.ra Francesca, eseguire indagini di laboratorio per monitorare il trattamento con EBPM?
1. No
2. Conta piastrinica
3. PTT
4. Conta piastrinica + PTT

Platelet Count Monitoring
• The frequency of platelet count monitoring should take into account the risk for HIT, which depends on the type of heparin used and the patient population
• Medical and obstetrical patients receiving prophylactic or therapeutic doses of LMWH have a low risk of HIT (probably less than 0.2%), and many physicians would not perform routine platelet count monitoring.

2. The crucial time period for monitoring “typical onset” HIT is between days 4 and 10 after starting heparin, where the highest platelet count from day 4 (inclusive) onward represents the “baseline”
3. For a patient recently exposed to heparin within the past 100 d, a repeat platelet count obtained within 24 h following restart of heparin is recommended to identify patients with developing HIT due to already circulating HIT antibodies.
4. A platelet count should be measured promptly and compared with recent values in a patient who develops thrombocytopenia during or soon after heparin therapy, or in a patient who develops an unusual clinical event in association with heparin therapy, e.g. heparin-induced skin lesions, acute disseminated intravascular coagulation, or pulmonary embolism
5. A platelet count fall of 50% or greater from baseline can indicate HIT, even if the platelet count nadir remains above 50 x 10^9/L. Occasionally, platelet count declines of even lesser magnitude attributable to HIT can be associated with thrombotic events.

Administration, dosage and coagulation monitoring
• In general, monitoring of the anticoagulant effect of low dose UFH or LMWH is not required.
• As LMWHs have little effect on the APTT, plasma anti-Xa activity should be measured instead:
  - in high-risk pregnancy
  - if there are complications such as haemorrhage or accidental overdose
  - in patients with renal failure given higher doses of LMWH
Boneu B, de Moerloose P.

How and when to monitor a patient treated with low molecular weight heparin

Semin Thromb Hemost 2001;27:519-22

• Curative (but not prophylactic) administration of LMWH should be monitored with an anti–factor Xa assay in patients presenting renal insufficiency, in the elderly, and in patients presenting an increased hemorrhagic risk.