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Gruppo Italiano per la Medicina Basata sulle Evidenze

Evidence-Based Medicine Italian Group

Workshop

Evidence-based Medicine

Le opportunità di un linguaggio comune

Como, 9-11 maggio 2003

SNAMID

Sezione di Como

Workshop Clinici Interattivi (2)

Distorsioni e piccoli traumi agli arti inferiori: dobbiamo prescrivere eparine proprio a tutti?

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Discussant

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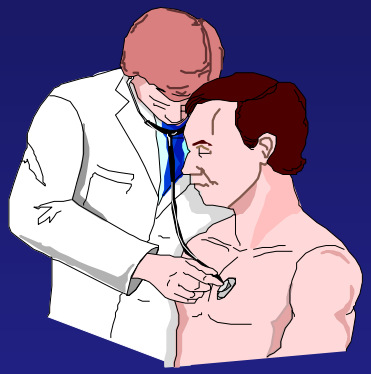
Scenario Clinico (1)

- La signora Anna, impiegata di 33 anni da sempre in buona salute, mi chiama per una visita domiciliare perché, in seguito a distorsione non complicata della caviglia, in P.S. le hanno prescritto 15 giorni di gambaletto gessato ed eparina a basso peso molecolare (LMWH) per 20 giorni.

- Circa un anno prima, per analoga distorsione, in altro ospedale le avevano consigliato solo fasciatura stretta per 10 giorni, senza prescrizione di sostanze eparino-simile.

Scenario Clinico (2)

- Sollecitato dalla perplessità della paziente sulla necessità delle prescrizioni, condivido l'immobilizzazione della caviglia, ma ho qualche perplessità sulla prescrizione di LMWH.



CLINICAL QUESTIONS

?

A. Quanto stimi il rischio di complicanze trombo-emboliche (TVP, EP) in una donna sana di 33 anni con distorsione della caviglia?
   1. Nessuno
   2. Basso
   3. Medio
   4. Elevato
   5. Molto elevato

Profilassi della Malattia tromboembolica
Linee guida

- SIGN, 2002
- American College of Chest Physicians, 2001

SIGN - Scottish Intercollegiate Guidelines Network

Prophylaxis of Venous Thromboembolism

October 2002

American College of Chest Physicians (ACCP)

Prevention of Venous Thromboembolism

January 2001

Table 1—*Criteria for Inclusion of Studies*

- Patients identifiable as belonging to the group of interest and similar enough to current patients to be relevant
- Outcome assessment:

  A. Orthopedic studies: contrast venography only (bilateral or unilateral)

  B. Nonorthopedic studies: contrast venography or fibrinogen leg scanning
- Sample size: at least 10 patients per group
- Numerator: objectively demonstrated deep vein thrombosis
- Denominator: patients with adequate outcome assessments

I. Baseline Risks of Thrombosis

- Design: either prospective cohort studies or control groups of randomized trials
- Interventions: no prophylaxis used

II. Prophylaxis Efficacy

- Design: randomized trials only
- Interventions: clinically relevant, available options; for drugs, currently approved or utilized agents and doses

ACCP, 2001

Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis

Level of Risk Examples	Calf DVT, %	Proximal DVT, %	Clinical PE, %	Fatal PE, %
Low risk Minor surgery in patients < 40 yr with no additional risk factors	2	0.4	0.2	0.002
Moderate risk Minor surgery in patients with additional risk factors; nonmajor surgery in patients aged 40–60 yr with no additional risk factors; major surgery in patients < 40 yr with no additional risk factors	10–20	2–4	1–2	0.1–0.4
High risk Nonmajor surgery in patients > 60 yr or with additional risk factors; major surgery in patients > 40 yr or with additional risk factors	20–40	4–8	2–4	0.4–1.0
Highest risk Major surgery in patients > 40 yr plus prior VTE, cancer, or molecular hypercoagulable state; hip or knee arthroplasty, hip fracture surgery; major trauma; spinal cord injury	40–80	10–20	4–10	0.2–5

ACCP, 2001

Isolated Lower Extremity Fractures

- Although DVT appears to occur with moderate frequency after isolated lower extremity fractures, there are few prospective studies available, and none have reported the incidence of clinically important VTE.

- Routine administration of LMWH in these patients, cannot currently be recommended because of uncertainty about whether the benefits of prophylaxis outweigh the risks and whether prophylaxis is cost-effective.

- Clearly, more research is required in this area.

ACCP, 2001

- La linea guida prodotta dal SIGN non riporta alcuna sezione sui traumi della caviglia

MEDLINE

1.	Ankle [mh]	3.367
2.	Embolism and Thrombosis [mh]	140.739
3.	Wounds and Injuries [mh]	392.728
4.	1 AND 2 AND 3	3

Nessuna delle 3 citazioni è pertinente!

B. Ritieni che, in una paziente con una distorsione della caviglia, l'applicazione del gambaletto gessato per 15 giorni, aumenti considerevolmente il rischio di complicanze tromboemboliche?
   1. Sì
   2. No

Table 1: Risk factors for venous thromboembolism

Age[1, 46-51]	Exponential increase in risk with age. In the general population - <40 years annual risk 1/10,000 60-69 years annual risk 1/1,000 >80 years annual risk 1/100 May reflect immobility and coagulation activation[52,53]
Obesity[1,46,50,51,54-56]	3 × risk if obese (body mass index ≥30 kg/m²) May reflect immobility and coagulation activation[52,53]
Varicose veins[50,51]	1.5 × risk after major general / orthopaedic surgery But low risk after varicose vein surgery[15,57]
Previous VTE[1,17]	Recurrence rate 5% / year, increased by surgery
Thrombophilias[58-62]	Low coagulation inhibitors (antithrombin, protein C or S) Activated protein C resistance (e.g. factor V Leiden) High coagulation factors (I, II, VIII, IX, XI) Antiphospholipid syndrome High homocysteine
Other thrombotic states[59,60]	Malignancy 7 × risk Heart failure Recent myocardial infarction / stroke Severe infection Inflammatory bowel disease, nephrotic syndrome Polycythaemia, paraproteinaemia Bechet's disease, paroxysmal nocturnal haemoglobinuria
Hormone therapy	Oral combined contraceptives, HRT, raloxifene, tamoxifen[63,64] 3 × risk High-dose progestogens 6 × risk *(see section 10)*
Pregnancy, puerperium	10 × risk *(see section 9)*
Immobility	Bedrest >3 days, plaster cast *(see section 5)*, paralysis *(see sections 5 &7)* 10 × risk; increases with duration
Prolonged travel	*see section 11*
Hospitalisation	Acute trauma, acute illness, surgery, 10 × risk
Anaesthesia	2× general vs spinal / epidural[65]

SIGN, 2002

Table 1: Risk factors for venous thromboembolism

IMMOBILITY

- Bedrest >3 days
- Plaster cast
- Paralysis

10 x risk
(increases with duration)

SIGN, 2002

Samama MM.

An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study

Arch Intern Med 2000;160:3415-20

Triggering risk factors associated with DVT included:

- application of a plaster cast to the lower extremities (OR 36.47)
- orthopedic surgery (OR 16.25)
- general surgery (OR 9.46)

Samama MM. Arch Intern Med, 2000

C. Ritieni appropriata nella sig.ra Anna la prescrizione di eparine a basso peso molecolare?

1. Sì
2. No

Note ed EBM

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.

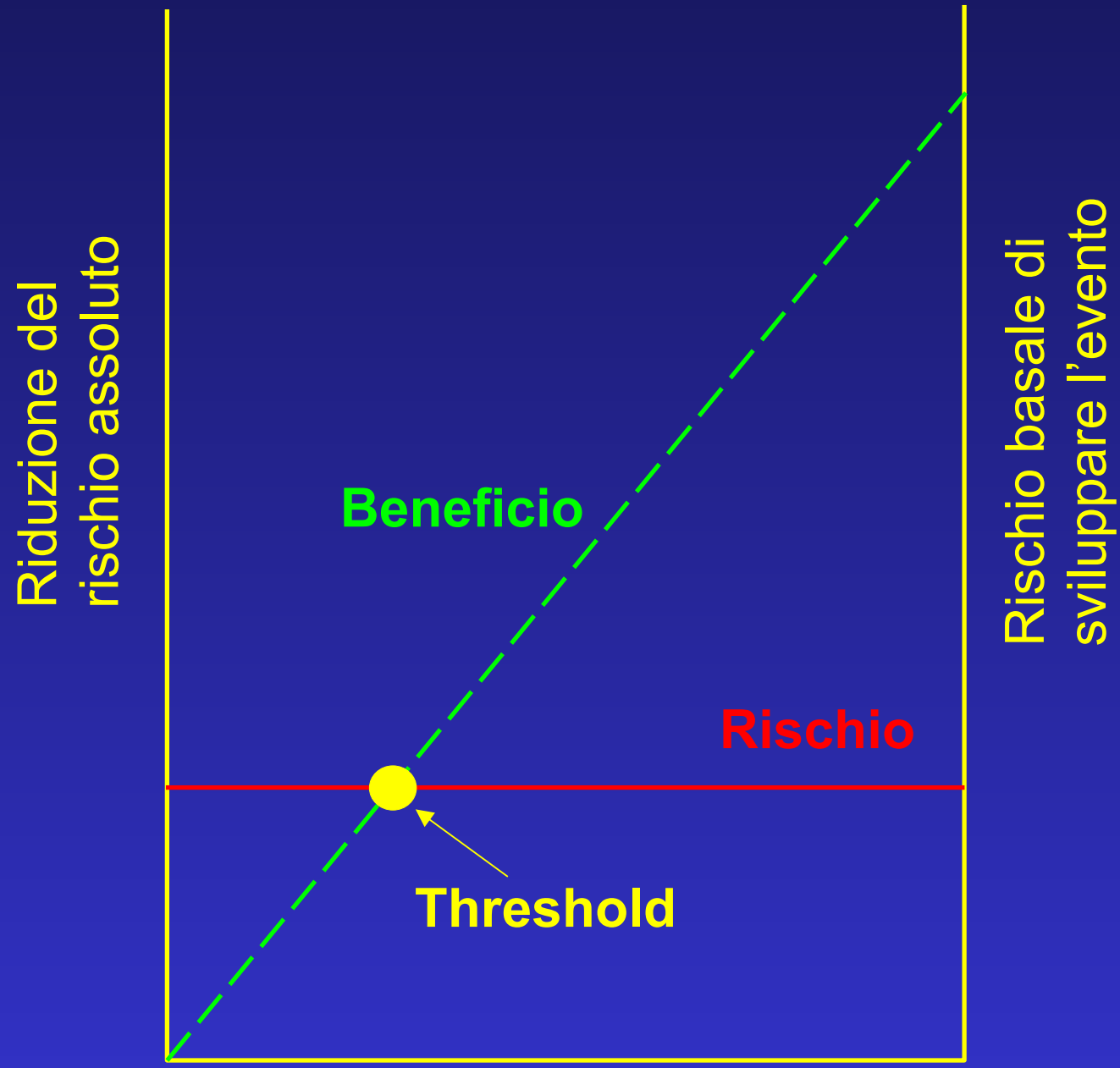
Rose G. Int J Epidemiol 1985

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.

Glasziou P et al. BMJ 1995



Glasziou P, et al. BMJ 1995

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ACCP, 2001

Trauma

1. Trauma patients with an identifiable risk factor for thromboembolism should receive prophylaxis if possible. If there is no contraindication, we recommend that clinicians use LMWH, starting treatment as soon as it is considered safe to do so (grade 1A).

ACCP, 2001

A	**In patients with spinal cord injury, major lower limb fractures or multiple trauma, LMWH prophylaxis can be considered, unless contraindicated** *(e.g. by risk of intracranial bleeding).*

- Two RCTs have shown that outpatient LMWH reduced the incidence of asymptomatic DVT in patients with plaster cast immobilisation.

SIGN 2002

RCTs di prevenzione con LMWH

- Kujath P, et al. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. Haemostasis 1993;23 Suppl 1:20-6.

- Spannagel U, Kujath P. Low molecular weight heparin for the prevention of thromboembolism in outpatients immobilized by plaster cast. Semin Thromb Hemost 1993;19(Suppl 1):131-41

- Kock HJ, et al. Thrombophrophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. Lancet 1995;346:459-61.

- Jorgensen PS, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. Thromb Res 2002;105:477-80

- Lassen MR, et al. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med 2002;347:726-30.

Lassen MR, et al.

Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization

N Engl J Med 2002;347:726-30

BACKGROUND

• Deep-vein thrombosis is a well-recognized complication after trauma to the legs and subsequent immobilization, but there are no generally accepted approaches to preventing this complication.

METHODS

• Double-blind, placebo-controlled trial to evaluate the efficacy and safety of subcutaneous reviparin (1750 anti-Xa units given once daily) in 440 patients who required immobilization in a plaster cast or brace for at least five weeks after a leg fracture or rupture of the Achilles tendon.

• The study drug was given during the period of immobilization.

• Venography of the injured leg was performed within one week after removal of the plaster cast or brace, or earlier if there were symptoms suggesting deep-vein thrombosis.

Lassen MR, et al. N Engl J Med 2002

RESULTS

- Deep-vein thrombosis was diagnosed in 17 of the 183 patients (9%) assigned to receive reviparin and in 35 of the 188 patients assigned to receive placebo (19%)

- Most of the thromboses were distal (14 in the reviparin group and 25 in the placebo group).

- There were no differences between the two groups with respect to bleeding or other adverse events.

Lassen MR, et al. N Engl J Med 2002

TABLE 2. RISK OF THROMBOEMBOLIC EVENTS WITHIN ONE WEEK AFTER REMOVAL OF A PLASTER CAST OR BRACE AMONG PATIENTS RANDOMLY ASSIGNED TO TREATMENT WITH REVIPARIN OR PLACEBO.*

EVENT	REVIPARIN	PLACEBO	ODDS RATIO (95% CI)	P VALUE
	no./total no. (%)			
Thrombosis				
In any venous segment	17/183 (9)	35/188 (19)	0.45 (0.24–0.82)	0.01†
In a proximal segment	3/189 (2)	10/191 (5)	0.30 (0.09–1.02)	0.09‡
In a distal segment	14/183 (8)	25/188 (13)	0.54 (0.27–1.07)	0.09‡
Pulmonary embolism	0/217	2/221 (1)§	—	—

Lassen MR, et al. N Engl J Med 2002

CONCLUSIONS

- Deep-vein thrombosis is common in persons with leg injury requiring prolonged immobilization.
- Reviparin given once daily appears to be effective and safe in reducing the risk of this complication.

Lassen MR, et al. N Engl J Med 2002

- Our study suggests that the routine use of reviparin for prophylaxis against thrombosis during the period of leg immobilization after fracture of the leg or rupture of the Achilles tendon is beneficial.

- However, further evaluation is warranted before such treatment can be recommended for routine use.

- It will be important to determine whether this therapy can reduce the risk of long-term sequelae of deep-vein thrombosis, such as venous insufficiency, and to assess its cost effectiveness.

Lassen MR, et al. N Engl J Med 2002

- I pazienti inclusi avevano condizioni differenti da quelle della signora Anna (frattura della gamba o rottura del tendine d'Achille)

- L'end-point dello studio è surrogato (TVP venografiche e non TVP sintomatiche)

- Non è stata eseguita l'analisi dei dati (nonostante dichiarato) secondo il principio della *intention to treat*: infatti sono stati esclusi dall'analisi tutti i pazienti per i quali non era disponibile il dato venografico

- Il beneficio clinico è modesto: le TVP prevenute sono prevalentemente distali

Number Needed to Treat (NNT)

Quanti pazienti bisogna trattare per prevenire un episodio di trombosi venosa profonda?

Tutte le TVP*	11 (6-43)
TVP prossimali	27 (14-4667)
TVP distali	18 (16-1291)

* Con l'analisi per *intention to treat* NNT=12 (7-50)

Conflict of interest in medical research

- The authors designed the study, interpreted the data, and wrote the article.
- All the data were collected by a Danish contract research organization and transferred to the statistical department of the sponsor, Knoll.
- The authors had full access to the data and reviewed the statistical plan and analyses.
- The final statistical analysis was performed by the sponsor.
- The central adjudication committee was independent of the sponsor.

Lassen MR, et al. N Engl J Med 2002

Conflict of interest in medical research

Supported by a grant from Knoll. Knoll provided the reviparin that was tested in the study.

Drs. Lassen and Borris have served as consultants to Knoll and other companies that develop antithrombotic compounds. Dr. Nakov is an employee of Knoll.

We are indebted to Silke Wurzinger of Knoll for contributions to the statistical analysis.

Lassen MR, et al. N Engl J Med 2002

D. Le eparine a basso peso molecolare possono causare piastrinopenia?

1. Sì
2. No

- 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.

- HAT should be considered in any patient whose platelet count falls by 50% or more.

SIGN 2002

College of American Pathologists

Platelet Count Monitoring and Laboratory Testing for Heparin-Induced Thrombocytopenia

Arch Pathol Lab Med 2002;126:1415–1423

• An unusual aspect of HIT is its variable frequency, depending on the type of heparin

• Unfractionated heparin (UFH) is more likely to cause both HIT antibody formation and clinical HIT, compared with low-molecular-weight heparin (LMWH).

CAP, 2002

E. Ritieni necessario, nella sig.ra Anna, monitorare il trattamento eparinico con indagini di laboratorio?

1. No
2. Conta piastrinica
3. PTT
4. Conta piastrinica + PTT

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 in high-risk pregnancy
  - if there are complications such as haemorrhage or accidental overdose
  -in in patients with renal failure given higher doses of LMWH

SIGN 2002

B

In order to detect heparin associated thrombocytopenia, a baseline platelet count should be obtained and platelet count monitored in all patients receiving heparins for five days or more.

SIGN 2002

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.

CAP, 2002

Table 4. Recommendations: Platelet Count Monitoring for Early Detection of Heparin-Induced Thrombocytopenia (HIT)*

1. Patients at highest risk for HIT (postoperative patients receiving prophylactic or therapeutic-dose unfractionated heparin): minimum monitoring during heparin therapy, every second day from day 4 to day 10.†[3,9,34,35,56] *Level 1*

   Patients at intermediate risk for HIT (medical/obstetrical patients receiving prophylactic- or therapeutic-dose unfractionated heparin, postoperative patients receiving prophylactic-dose low-molecular-weight heparin, or patients receiving intravascular catheter "flushes" with unfractionated heparin): minimum monitoring during heparin therapy, 2 or 3 times from day 4 to day 10,† when practical.‡[3,9,34,35,55] *Level 1*

   Patients at low risk for HIT (medical/obstetrical patients receiving prophylactic- or therapeutic-dose low-molecular-weight heparin, medical patients receiving only intravascular catheter "flushes" with unfractionated heparin): routine monitoring is not recommended.§[34,55] *Level 2*

CAP, 2002

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 PMWH 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.

Boneu B, et al. Semin Thromb Hemost 2001

Scenario Clinico (3)

- Malgrado non condividessi la prescrizione di LMWH fatta in PS, “per stare tranquillo” ho ritenuto di trascriverla.

- Non ho ritenuto necessario eseguire alcun esame di laboratorio per il monitoraggio del trattamento.