GIMBE®

Gruppo Italiano per la Medicina Basata sulle Evidenze

Evidence-Based Medicine Italian Group

Workshop

Decisioni Cliniche e Prove di Efficacia

Seconda Edizione

Riccione, 26-27 marzo 2004

medicina e persona

Workshop Clinici Interattivi (1)

Appropriatezza e sicurezza delle eparine a basso peso molecolare. Siamo certi di seguire le migliori evidenze?

Modesto Fantini

Discussant

Ettore Ranocchi, Eros Tiraferri

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 idoroclorotiazide), 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)

- Il 12 agosto 2003, a seguito di un incidente stradale, ha riportato la frattura traumatica del collo del femore sinistro.

- Ricoverata in UO di Ortopedia, il 14 agosto è stata sottoposta ad intervento di artroprotesi d'anca.

- Il 18 agosto la paziente è stata trasferita in UO di riabilitazione per eseguire fisiokinesiterapia, con l'indicazione di proseguire il trattamento con enoxaparina,4000 UI/die, iniziato la sera prima dell'intervento.

- Il 26 agosto viene dimessa in buone condizioni generali, con una modesta anemia (GR 3.410.000, Hb 9.5 gr%)

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.

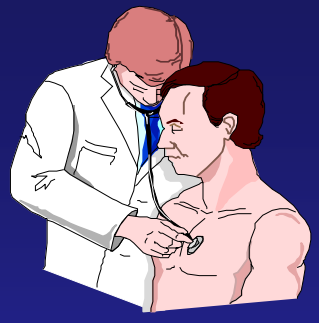
- Si consiglia di eseguire emocromo (per monitorare dell'anemia)

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, ritieni 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**

van der Heijden JF, Prins MH, Buller HR

Low-molecular-weight heparins. Are they interchangeable?

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

Are LMWH interchangeable?

- LMWHs had increased efficacy and safety in comparison with UFH.

- There was no definitive evidence that LMWHs differed in their efficacy and safety.

van der Heijden JF, et al. Haemostasis 2000

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.

SIGN. October 2002

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.

McKart GM, et al. Ann Pharmacother 2002

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.

McKart GM, et al. Ann Pharmacother 2002

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

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. Chest 2001

General surgery, moderate risk:
- Dalteparin, 2,500 U SC 1–2 h before surgery and once daily postop
- Enoxaparin, 20 mg SC, 1–2 h before surgery and once daily postop
- Nadroparin, 2,850 U SC 2–4 h before surgery and once daily postop
- Tinzaparin, 3,500 U SC 2 h before surgery and once daily postop

General surgery, high risk:
- Dalteparin, 5,000 U SC 8–12 h before surgery and once daily postop
- Danaparoid, 750 U SC 1–4 h before surgery and q12h postop
- Enoxaparin, 40 mg SC, 1–2 h preop and once daily postop
- Enoxaparin, 30 mg SC, q12h starting 8–12 h postop

Orthopedic surgery
- Dalteparin, 5,000 U SC 8–12 h preop and once daily starting 12–24 h postop
- Dalteparin, 2,500 U SC 6–8 h postop; then 5,000 U SC once daily
- Danaparoid, 750 U SC 1–4 h preop and q12h postop
- Enoxaparin, 30 mg SC q12h starting 12–24 h postop
- Enoxaparin, 40 mg SC once daily starting 10–12 h preop
- Nadroparin, 38 U/kg SC 12 h preop, 12 h postop, and once daily on postop days 1, 2, and 3 then increase to 57 U/kg SC once daily
- Tinzaparin, 75 U/kg SC once daily starting 12–24 h postop
- Tinzaparin, 4,500 U SC 12 h preop and once daily postop

Major trauma
- Enoxaparin, 30 mg SC q12h starting 12–36 h postinjury if hemostatically stable

Acute spinal cord injury
- Enoxaparin, 30 mg SC q12h

Medical conditions
- Dalteparin, 2,500 U SC once daily
- Danaparoid, 750 U SC q12h
- Enoxaparin, 40 mg SC once daily
- Nadroparin, 2,850 U SC once daily

ACCP. Chest 2001

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).

SIGN. October 2002

A The duration of UFH or LMWH prophylaxis should be 7-15 days after lower limb arthroplasty, extended to 4-5 weeks in very high-risk patients.

SIGN. October 2002

3 Revisioni Sistematiche

- Cohen AT, et al. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty. A meta-analysis. Thromb Haemost 2001;85:940-1

- Eikelboom JW, et al. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement. A meta-analysis of the randomised trials. Lancet 2001;358:9-15

- Hull RD, 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

Hull RD, Pineo 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 1. **Characteristics of the Studies Included in the Systematic Review***

Study (Reference)	Year	Time of Randomization	Venograms	Patients	In-Hospital, Out-of-Hospital Prophylaxis	Preoperative or Postoperative Initiation of Therapy	Duration of Prophylaxis		Frequency of Administration	Initial Dose	Subsequent Doses
							In-Hospital	Out-of-Hospital			
			n				*d*				
Bergqvist et al. (29)	1996	At discharge	1								
LMWH group				131	Enoxaparin, enoxaparin	Preoperative	10	19	Once daily	4000 IU	4000 IU
Control group				131	Enoxaparin, placebo	Preoperative	11	18	Once daily	4000 IU	4000 IU
Planes et al. (30)	1996	At discharge	2†								
LMWH group				90	Enoxaparin, enoxaparin	Preoperative	14	21	Once daily	4000 IU	4000 IU
Control group				89	Enoxaparin, placebo	Preoperative	14	21	Once daily	4000 IU	4000 IU
Dahl et al. (31)	1997	At discharge	2†								
LMWH group				117	Ealteparin, dalteparin	Preoperative	7	28	Once daily	5000 IU	5000 IU
Control group				110	Dalteparin, placebo	Preoperative	7	28	Once daily	5000 IU	5000 IU
Lassen et al. (32)	1998	At discharge	1								
LMWH group				140	Dalteparin, dalteparin	Preoperative	7	28	Once daily	5000 IU	5000 IU
Control group				141	Dalteparin, placebo	Preoperative	7	28	Once daily	5000 IU	5000 IU
Hull et al. (45)	2000	Before surgery	2†								
LMWH group				389	Dalteparin, dalteparin	Preoperative, postoperative‡	6	29	Once daily	2500 IU	5000 IU
Control group				180	Warfarin, placebo	Postoperative	6	29	Once daily	5–10 mg	INR 2–3§
Comp et al. (46)	2001	At discharge	1								
LMWH group				224	Enoxaparin, enoxaparin	Postoperative	8	19	Once daily, twice daily‖	30 mg	30–40 mg‖
Control group				211	Enoxaparin, placebo	Postoperative	8	19	Once daily, twice daily‖	30 mg	30–40 mg‖

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

Study (Reference)	Year	Randomized Allocation Sequence Generated	Randomized Allocation Sequence Masked	Double-Blinded
Bergqvist et al. (29)	1996	Yes	Yes	Yes
Planes et al. (30)	1996	Yes	Yes	Yes
Dahl et al. (31)	1997	Yes	Yes	Yes
Lassen et al. (32)	1998	Yes	Yes	Yes
Hull et al. (45)	2000	Yes	Yes	Yes
Comp et al. (46)	2001	Yes	Yes	Yes

Hull RD, et al. Ann Intern Med 2001

Outcomes at 18 to 29 days NNT (95% CIs)

- All deep venous thrombosis 10 (8 to 14)
- Proximal deep venous thrombosis 18 (13 to 30)
- Symptomatic venous thromboembolism 50 (33 to 80)

Hull RD, et al. Ann Intern Med 2001

O'Donnell M, Linkins LA, Kearon C, et al.

Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low-molecular-weight heparin following elective hip arthroplasty: a systematic review.

Arch Intern Med 2003;163:1362-6

BACKGROUND

• Numerous trials and meta-analyses have shown that extended out-of-hospital prophylaxis with LMWH reduces asymptomatic and symptomatic venous thromboembolism after total hip arthroplasty.

• We hypothesized an overdiagnosis of symptomatic venous thromboembolism in many of these studies.

• The purpose of this analysis was to obtain an accurate estimate of the absolute risk reduction of symptomatic venous thromboembolism after discharge

O'Donnell M, et al. Arch Intern Med 2003

METHODS

- Articles were identified using MEDLINE, EMBASE, and the Cochrane Library databases (January 1980-April 2002).
- Studies were eligible if the assessment of symptomatic venous thromboembolism was standardized and performed independently of mandatory objective testing.

RESULTS

- 2 studies (907 patients) were eligible for assessment of symptomatic venous thromboembolism
- 5 studies (1.917 patients) for symptomatic pulmonary embolism
- 7 studies (2.425 patients) for fatal pulmonary embolism.

O'Donnell M, et al. Arch Intern Med 2003

Table 4. Symptomatic Venous Thromboembolism at 3 Months Following Total Hip Arthroplasty

Source	No. (%) of Patients		OR (95% CI)	NNT
	Low-Molecular-Weight Heparin	Placebo		
Eikelboom et al,[9] 2001*	NA (1.4)	NA (4.3)	0.33 (0.19-0.56)	34
Hull et al,[10] 2001	15/1091 (1.4)	36/862 (4.2)	0.35 (0.19-0.66)†	45
Current analysis	5/465 (1.1)	12/442 (2.7)	0.39 (0.14-1.11)	64

O'Donnell M, et al. Arch Intern Med 2003

CONCLUSIONS

The absolute reduction in symptomatic venous thromboembolism attributed to extended prophylaxis in some studies and meta-analyses seems to have been overestimated.

O'Donnell M, et al. Arch Intern Med 2003

È tempo di cambiare le raccomandazioni? È ancora accettabile la limitazione dell'ACCP alla profilassi prolungata soltanto nei pazienti ad alto rischio? Ed in questo caso, può essere definito in modo più preciso il paziente ad alto rischio? Il dato di fatto è che la profilassi prolungata è già una realtà in alcuni dei nostri ospedali. Il timore è che la scelta sia frutto più di una spinta del marketing o di timori medico-legali che di una valutazione ponderata.

La SISET ritiene che sia prematura una modificazione delle raccomandazioni in questo ambito anche se è prevedibile che in un prossimo futuro possano essere suggeriti diversi atteggiamenti.

SISET. Aprile 2002

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.

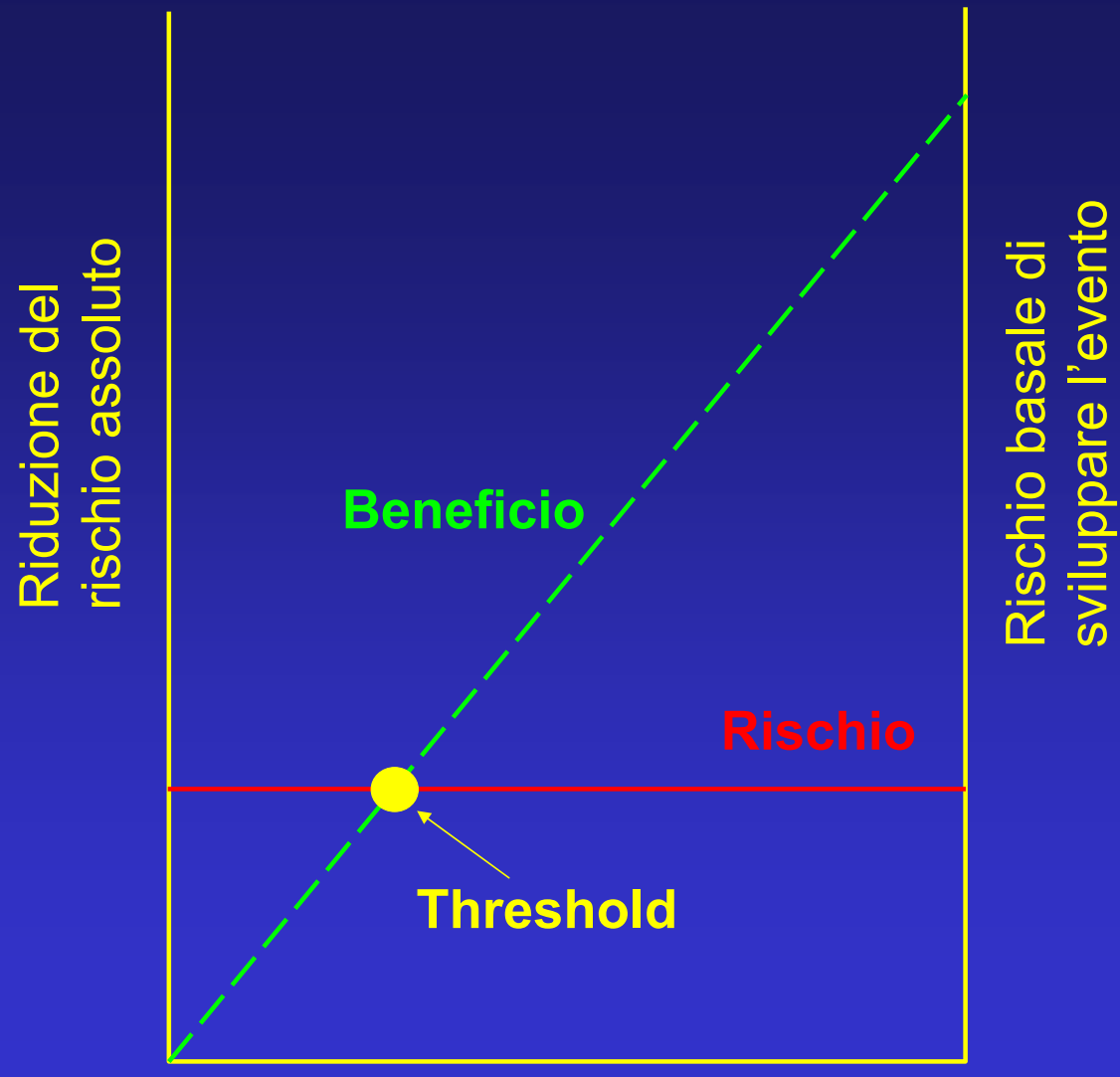
Rose G. Int J Epidemiol 1985

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

D. Le EBPM possono causare piastrinopenia?

1. No, mai
2. Sì (= frequenza dell'eparina non frazionata)
3. Sì (↓ 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.

SIGN, October 2002

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%

CAP, November 2002

Centre for Clinical Effectiveness

Enhancing patient outcomes through clinical application of the best available evidence

EVIDENCE CENTRE
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Series 2002: Intervention

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 UHF 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

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, November 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*

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."[3,5,25] *Level 1*
3. For a patient recently exposed to heparin (within the past 100 d), a repeat platelet count obtained within 24 h following reinitiation of heparin is recommended to identify patients with rapid-onset HIT due to already circulating HIT antibodies.[5,25,26] *Level 1*
4. A platelet count should be measured promptly and compared with recent values in a patient who develops thrombosis during or soon after heparin therapy, or in a patient who develops an unusual clinical event in association with heparin therapy (eg, heparin-induced skin lesions, acute systemic reaction post–intravenous heparin bolus).[5,25,26,58] *Level 2*
5. A platelet count fall of 50% or greater from baseline can indicate HIT, even if the platelet count nadir remains above 150×10^9/L; occasionally, platelet count declines of even lesser magnitude attributable to HIT can be associated with thrombotic events.[5,6,31] *Level 1*

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

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.

Boneu B, et al. Semin Thromb Hemost 2001