Il dosaggio dell'attività anti-Xa: come, quando, a chi

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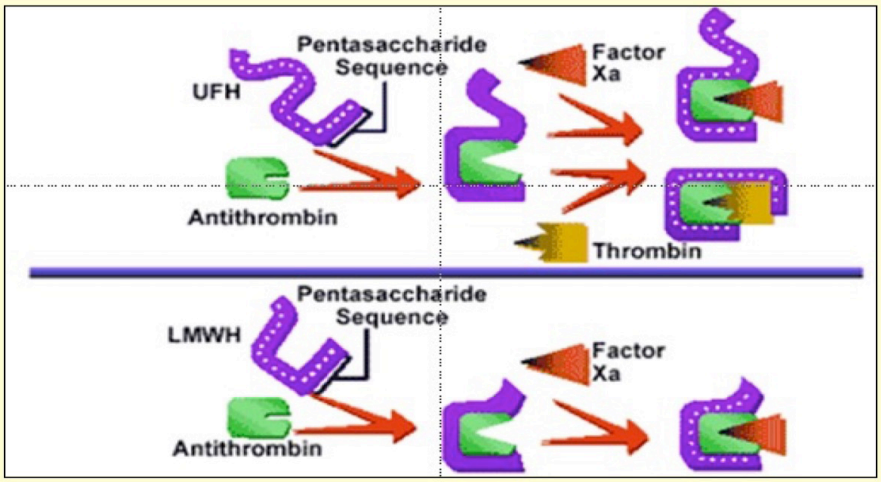
Mechanism of action of LMWH



- Heparin is made of polysaccharide chains of varying lengths
- Unique pentasaccharide sequence binds to AT
- Heparin does not have to bind to FXa to inactivate it
- Heparin has to bind to both AT and IIa to inactivate IIa
- Heparin **must be >18** monosaccharides long to do this

- Molecular wt: UFH 15,000 vs LMWH 4000-5000
- LMWHs inactivate Xa but have little effect on thrombin (most molecules not long enough)
  - ratio of anti-Xa to anti-thrombin activity of 2-5:1

Advantages of LMWH over UFH

- Lower plasma protein and cell binding
- More predictable and reproducible anticoagulant effect
- Higher bioavailability (~100% vs 30%) (s.c. administration)
- Half life essentially independent of dose (unlike UFH)
- Lower risk of HIT

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Methods for testing in vivo LMWH activity

- aPTT (correlated to the anti-Xa/anti-IIa ratio of the LMWH used): scarcely affected (only high levels of LMWH modify it)
- Heptest: sensitive to both anti-Xa and anti-IIa activity; may give different results from the standard chromogenic method
- Plasma thrombin neutralization assay: (formation of T-AT complexes): sensitive to high anti-IIa activity
- Thrombin generation assay: cumbersome, not widely available, only few studies

Anti-Xa assay (chromogenic): gold standard

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Anti-FXa assay

- Levels measured by chromogenic-based anti-Factor Xa assay
- Patient plasma + known amount of excess Factor Xa
- LMWH binds antithrombin and inhibits Factor Xa
- Residual Factor Xa is measured
  - Factor Xa cleaves a chromogenic substrate similar to its natural substrate, releasing color detected by a spectrophotometer
- Residual FXa is inversely proportional to the amount of LMWH
- Calibration should be done with the same brand of LMWH that the patient is using
- Sample should be obtained at peak plasma concentration (4 h after s.c. injection)

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Reasons why LMWHs do not require monitoring

- Evidence available does not support laboratory monitoring: in thromboprophylaxis trials monitoring never performed, in treatment trials no rigorously defined therapeutic range
- Anticoagulant activity of body weight adjusted LMWH is highly predictable
- Antithrombotic effect and risk of bleeding do not correlate with anti-FXa activity
- Safety of body-weight-adjusted LMWH demonstrated in thousands of patients
- Anti-FXa measurement in plasma has pitfalls

Greaves M et al., TH 2002;87:162
Bounameaux H et al., JTH 2004, 2:551-554
Haremberg JJ et al., JTH 2004;2:547

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Target anti-factor Xa ranges for therapeutic low molecular weight heparin

LMWH	Target anti-factor Xa, IU/ml	
	Twice daily	*Once daily*
Enoxaparin	0.6-1.0	1.0-2.0
Dalteparin		0.5-1.5
Nadroparin	0.6-1.0	1.3
Tinzaparin		0.85

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from Wei MY et al., Hematology Reports 2015;7:5844

Target anti-factor Xa ranges for prophylactic low molecular weight heparin

Study	Target A-FXa	Patient group
Leyvraz (1991) Desjardins (2004)	Mean AFXa; day 1=0.29 IU/ml; day 3=0.25 IU/ml; day 4=0.33 IU/ml; day 10=0.37 IU/ml Day 10 mean AFXa; 0.21 IU/ml (enoxa 20mg daily); 0.41 IU/ml (enoxa 40 mg/daily)	Orthopaedic Medical
Weitz (2009) Lim (2010)	0.2-0.5 IU/ml	All
Micromedex. DRUGDEX	0.2-0.6 IU/ml	All
Nutescu (2009)	0.2-0.4 IU/ml	All
Nohe (1999)	0.2-0.4 IU/ml	Pediatric
Fox (2008)		
Pettila (1999)	0.2-0.4 IU/ml	Pregnancy
Bates (2014)	0.2-0.6 IU/ml	Pregnancy

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From Wei MY et al., Hematology Reports 2015;7:5844

Relationship between anti-Xa levels and major bleeding during treatment of acute VTE by UFH or LMWH

	Anti-Xa Level (U/mL)			
	≤0.8	>0.8-≤1.0	>1.0	*P* Value
First anti-Xa level, 4 h after bolus				
All patients				
Bleeding present/absent	17/150	3/18	3/2	.003
Risk (%)	10	14	60	
Heparin group				
Bleeding present/absent	10/74	1/9	2/1	.022
Risk (%)	12	10	67	
Fragmin group				
Bleeding present/absent	7/76	2/9	1/1	.110
Risk (%)	8	18	50	

- Prospective double-blind trial in 194 acute VTE patients
- Continuous i.v. UFH (96 pts) or Fragmin (98 pts)
- Dose adjusted twice daily (anti-Xa targets 0.3-0.6 high risk bleeding; 0.4-0.9 low risk bleeding)

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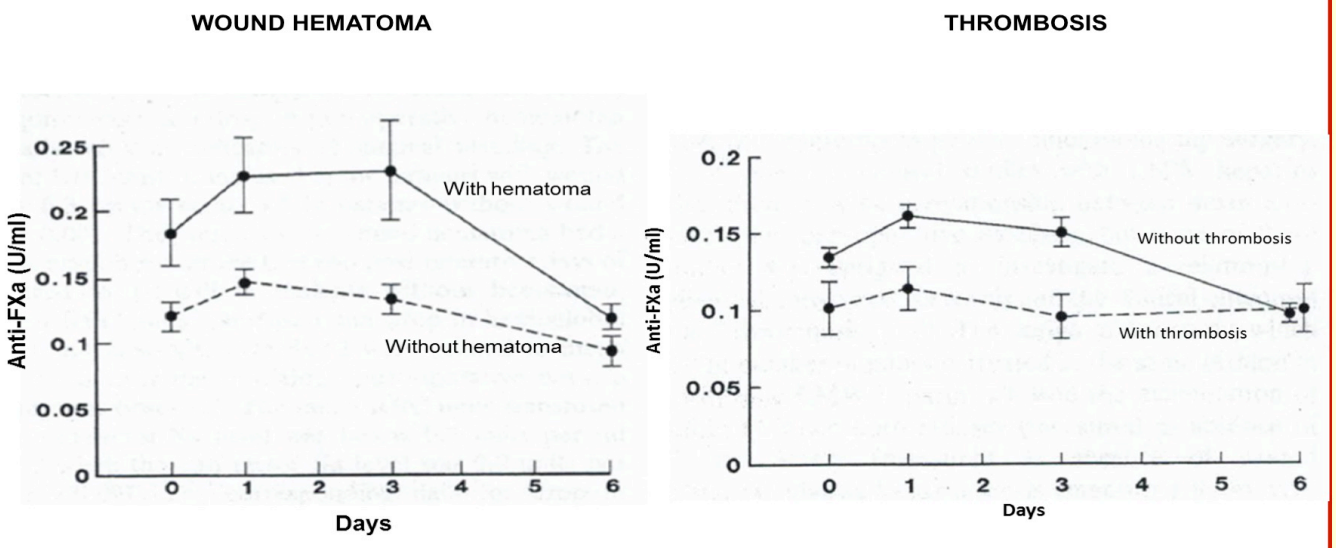
Nieuwenhuis K et al., Blood 1991;78:2337

Anti-Xa levels and occurrence of complications in patients receiving enoxaparin prophylaxis for hip replacement



163 pts undergoing hip replacement; 50 treated with 60 mg and 113 with 40 mg oid; anti-Xa measured 12 hrs after sc injection

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Levine MN et al., Thromb Haemost 1989;63:940-944

Conditions in which LMWH monitoring may be useful

Most clinical trials have excluded subjects at increased risk of bleeding or in whom anticoagulant responses may be less predictable.

PROLONGED ADMINISTRATION OF THERAPEUTIC DOSES
PATIENTS AT HIGH BLEEDING OR THROMBOTIC RISK

- Kidney failure (creatinine clearance <30ml/min)
- Pregnancy
- Extreme over- or under-weight
- Newborn
- Malignancy, myeloproliferative neoplasms, previous bleeders, aged

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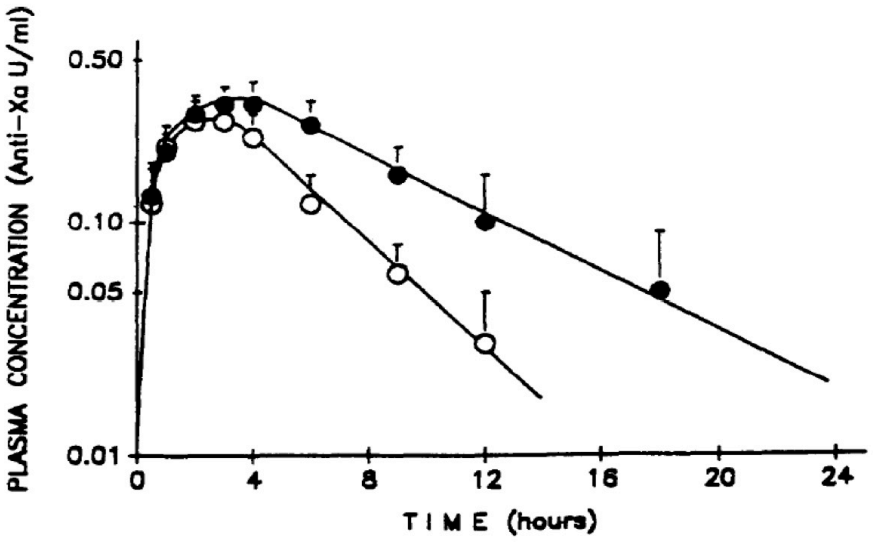
Harenberg J, JTH 2004;2:547-550

Delayed elimination of enoxaparin in patients with renal insufficiency

Time course after one single 0.5 mg/kg subcoutaneous injection



Creatinine clearance: 5-21 ml/min (mean 11.4 ml/min)

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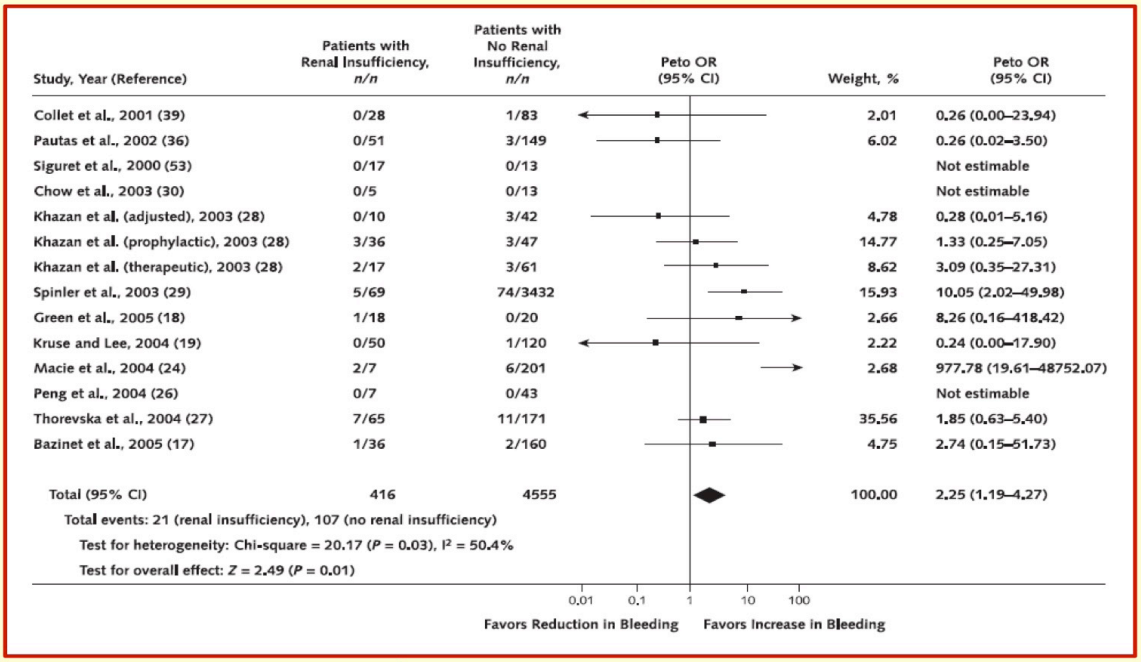
Cadroy Y et al., Thromb Res 1991;63:385.

Major bleeding with standard therapeutic dose enoxaparin in patients with kidney failure (cr cl ≤30 ml/min)

A metaanalysis



Study, Year (Reference)	Patients with Renal Insufficiency, *n/n*	Patients with No Renal Insufficiency, *n/n*	Peto OR (95% CI)	Weight, %	Peto OR (95% CI)
Collet et al., 2001 (39)	0/28	1/83		2.01	0.26 (0.00–23.94)
Pautas et al., 2002 (36)	0/51	3/149		6.02	0.26 (0.02–3.50)
Siguret et al., 2000 (53)	0/17	0/13			Not estimable
Chow et al., 2003 (30)	0/5	0/13			Not estimable
Khazan et al. (adjusted), 2003 (28)	0/10	3/42		4.78	0.28 (0.01–5.16)
Khazan et al. (prophylactic), 2003 (28)	3/36	3/47		14.77	1.33 (0.25–7.05)
Khazan et al. (therapeutic), 2003 (28)	2/17	3/61		8.62	3.09 (0.35–27.31)
Spinler et al., 2003 (29)	5/69	74/3432		15.93	10.05 (2.02–49.98)
Green et al., 2005 (18)	1/18	0/20		2.66	8.26 (0.16–418.42)
Kruse and Lee, 2004 (19)	0/50	1/120		2.22	0.24 (0.00–17.90)
Macie et al., 2004 (24)	2/7	6/201		2.68	977.78 (19.61–48752.07)
Peng et al., 2004 (26)	0/7	0/43			Not estimable
Thorevska et al., 2004 (27)	7/65	11/171		35.56	1.85 (0.63–5.40)
Bazinet et al., 2005 (17)	1/36	2/160		4.75	2.74 (0.15–51.73)
Total (95% CI)	416	4555		100.00	2.25 (1.19–4.27)

Total events: 21 (renal insufficiency), 107 (no renal insufficiency)

Test for heterogeneity: Chi-square = 20.17 (P = 0.03), I^2 = 50.4%

Test for overall effect: Z = 2.49 (P = 0.01)

0.01 0.1 1 10 100

Favors Reduction in Bleeding Favors Increase in Bleeding

Anti-FXa: 1.27-1.58 vs 0.91-1.06

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Lim W et al., Ann Intern Med 2006;144:673

ACCP evidence based guidelines – 9th edition

For pregnant women with mechanical heart valves, we recommend one of the following anticoagulat regimens in preference to no anticoagulation (all Grade 1A):

- Adjusted-dose bid LMWH throughout pregnancy. We suggest that doses be adjusted to achieve the manifacturer's peak anti-Xa LMWH 4h post subcoutaneous injection.

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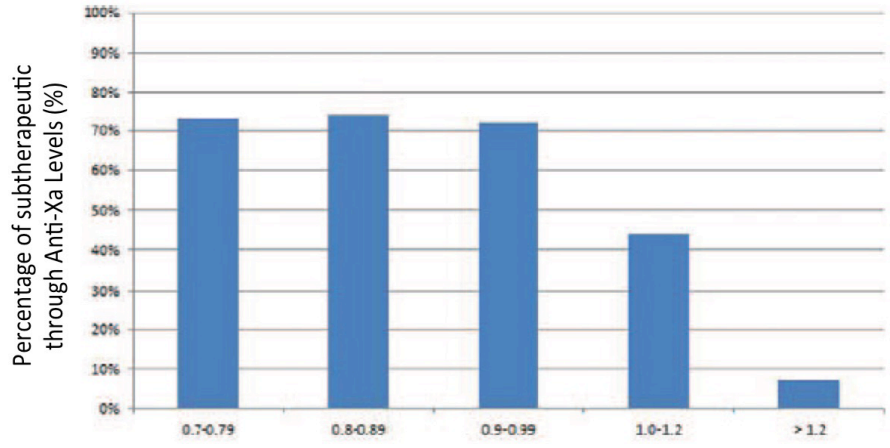
Bates SM et al., CHEST 2012;141:691S.

Subtherapeutic through anti-Xa levels are frequent in pregnant women on LMWH despite therapeutic peak levels



30 pregnant patients , 187 paired anti-Xa determinations

"... our study provides support to the importance of measuring through anti-Xa levels in pregnant women..."
"...in case therapeutic through levels are associated with peak levels >1.5 IU/ml , a twice daily dosing has to be considered..."

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Goland S et al., J Cardiovasc Pharm Ther 2014, 1-6:

Anti-Xa monitoring and dose adjustement in pregnants under prophylactic LMWH

No. of anti-Xa measurements per patient	Average (range) 4.8 (3-7)
Number of dose modifications	Number of patients (%)
Once	97 (56)
Twice	35 (20)
Three times	5 (3)
Total	137 (79)

- 162 pregant women undergoing LMWH prophylaxis throughout pregnancy
- Initial dose fixed (adjusted for obesity)
- Anti-Xa monitoring (3 or more times)
- Dose adjustement when anti-Xa <0.3 IU/ml (desired 0.2-0.6 IU/ml)

... we recommend conducting LMWH dose adjustement based on anti-Xa drug pregnancy...

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Boban A et al., Blood Coag Fibrinolys 2016

Reasons to monitor anti-Xa activity in LMWH-treated overweight patients

- In obese patients difference in body composition may affect LMWH PKs (sc absorption may be prolonged; volume distribution is limited to intravascular volume thus dosing by body weight may result in overdosage; renal clearance is increased in obesity; no specific PK data with LMWH in obese)
- Obese patients are at higher risk of thrombosis
- LMWHs in product monographs continue to have a maximum recommended dose

"... current guidelines do not support routine anti-Xa monitoring in obese...
...monitoring can be considered in special conditions, e.g. BMI>40..."

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Egan G et al., CJHP 2015;68:83

Anti-Xa monitoring in patients with extreme body weight

A retrospective study at Cleveland clinic

- 96 patients <45kg, 111 patients >150kg treated with therapeutic dose enoxaparin (1mg/kg twice daily or 1.5 mg/kg once daily)
- Less than 30% had low molecular weight heparin anti-FXa levels measured
- Only half were drawn at peak level (4h post dose)
- Overall rates of anti-FXa monitoring was low
- **Obese patients achieved therapeutic anticoagulation with lower than recommended doses (0.89 IU/ml); underweight patients were often subtherapeutic (0.47 IU/ml)**

"...Enoxaparin has unpredictable pharmacokinetics in these high-risk patient populations and anti-FXa monitoring may be necessary to ensure therapeutic levels and appropriate dosing..."

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From Sacha GT et al., J Thromb Thrombolys 2016;42:479

ACCP evidence based guidelines – 9th edition

- We suggest , for neonates and children receiving either once- or twice-daily therapeutic low-molecular-weight heparin (LMWH), that the drug be monitored to a target anti-Xa activity range of 0.5 to 1.0 units/ml in a sample taken 4 to 6 h after subcutaneous injection or 0.5 to 0.8 units/ml in a sample taken 2 to 6 h after subcutaneous injection (Grade 2C).

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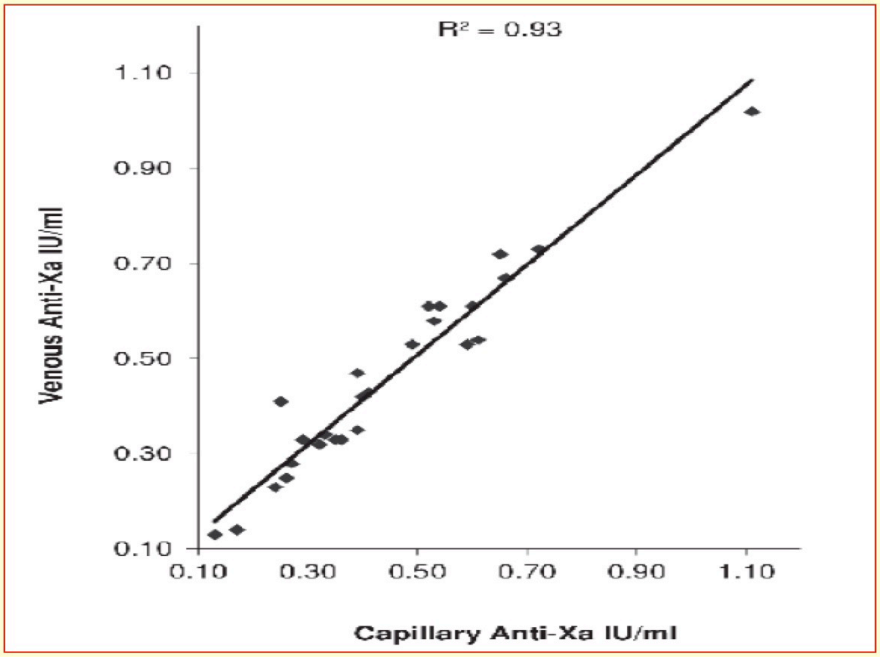
Monagle P et al., CHEST 2012;141:737S.

Capillary blood sampling for anti-Xa monitoring in neonates

-Number of children receiving LMWH for VTE is increasing
-In children there is wide variation in dosing (neonates greatest variability)
-With growth dose-adjustement is required
-Multiple samples are required for dosing adjustement



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Ridsdale S et al., Thromb Haemost 2017;117:198

Management and outcomes of patients with cancer treated with LMWH adjusted by anti-FXa levels

- LMWH is the recommended anticoagulant therapy for cancer-associated VTE
- Cancer patients have 3-fold higher risk of recurrent VTE and 2-fold higher risk for major hemorrhage
- Renal insufficiency frequently develops during chemotherapy

Manuscript	Patients with cancer (n, %)	Medication	Therapeutic range	Reason for monitoring	Recurrent thrombosis	Bleeding
Alhenc-Gelas et al[6]	4/64 (6%)	Dalteparin	0.5-1 IU/mL	Randomization	2/64 (3%) vs 1/58 (1.7%)	3/64 minor (5%)
Busby et al[11]	1/1 (100%)	Enoxaparin	0.5-1.1 IU/mL	Bleeding	0/0 (0%)	0/0 (0%)
Cunningham et al[9]	1/1 (100%)	Enoxaparin	1 IU/mL	Recurrent thrombosis	0/0 (0%)	0/0 (0%)
Krajewski et al[10]	1/1 (100%)	Enoxaparin	0.5-1 IU/mL	Heparin Resistance	0/0 (0%)	0/0 (0%)

"... there is insufficient evidence to recommend routine monitoring and adjusting LMWH based on anti-Xa... we suggest anti-Xa monitoring in the setting of severe renal impairment ...in patients who have experienced bleeding/thrombosis while on LMWH therapy..."

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Baumann Kreuziger L. Haematology 2016: 206

American pathologists consensus conference on laboratory monitoring of anticoagulant therapies

Table 2. Consensus Recommendations

1. Clinically stable patients receiving low-molecular-weight (LMW) heparin preoperatively or postoperatively for prophylaxis of venous thromboembolism do not require laboratory monitoring. (Level 1)
2. Uncomplicated patients being treated for venous thromboembolism by a weight-adjusted, fixed-dose regimen of LMW heparin do not require laboratory monitoring. (Level 1)
3. Laboratory monitoring using an anti–factor Xa assay may be of value in certain clinical settings (Level 3)
4. Pediatric patients receiving LMW heparin should be monitored. (Level 2)
5. When LMW heparin is monitored, the sample should be obtained 4 hours after subcutaneous injection. (Level 3)
6. The target concentration for the peak LMW heparin level in patients treated with twice daily dosing for venous thromboembolism should be 0.5–1.1 IU/mL when measured by an anti–factor Xa method. (Level 3)
7. The chromogenic anti–factor Xa method is recommended for monitoring LMW heparin. (Level 2)
8. A calibrated LMW heparin should be used to establish the standard curve for the assay to measure LMW heparin.

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Laposata M et al., Arch Pathol Lab Med 1998; 122:799.

Conclusions

- Routine anti-Xa monitoring of LMWH is not indicated
- Prolonged therapy in special populations may benefit from anti-Xa monitoring and dose adjustement
- Therapy in kidney failure, pregnant women, pediatric (neonates), extreme body weight, previous bleeders/recurrent VTE under LMWH may be the most indicated clinical conditions

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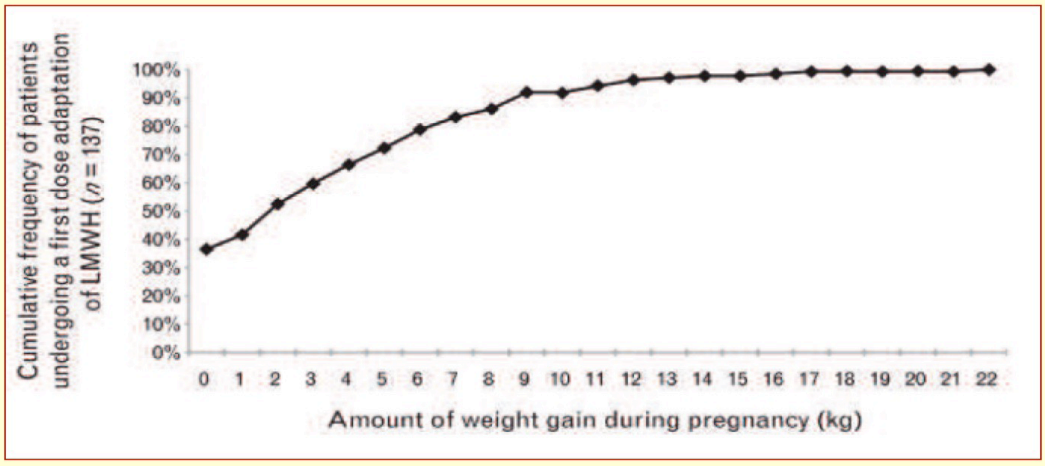
Cumulative frequency of pregnants undergoing LMWH dose adjustement in function of weight gain



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Boban A et al., Blood Coag Fibrinolys 2016

Target anti-factor Xa ranges of thromboprophylaxis in bariatric patients

Study	Target AFXa, IU/ml	LMWH
Simoneau (2008)	0.2-0.5	Dalteparin
Rowan (2008)	0.18-0.44	Enoxaparin
Simone (2008)	0.18-0.44	Enoxaparin
Imberti (2009)	0.1-0.4	Enoxaparin
Borkgren –Okonek (2008)	0.2-0.4	Enoxaparin

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From Wei MY et al., Hematology Reports 2015;7:5844

Significant LMWH dose variation in neonates and children depending on anti-Xa assay used

	Age					
	< 3 months		3 months to 2 years		>2 years	
	Old	*New*	*Old*	*New*	*Old*	*New*
No. of patients	28	31	42	28	39	45
Enoxaparin therapeutic dose (mg/kg^{-1})						
Mean	2.15	1.83	2.1	1.42	1.12	1.05
SD	0.58	0.34	0.55	0.35	0.28	0.18
P-value	0.01		<0.0001		0.18	

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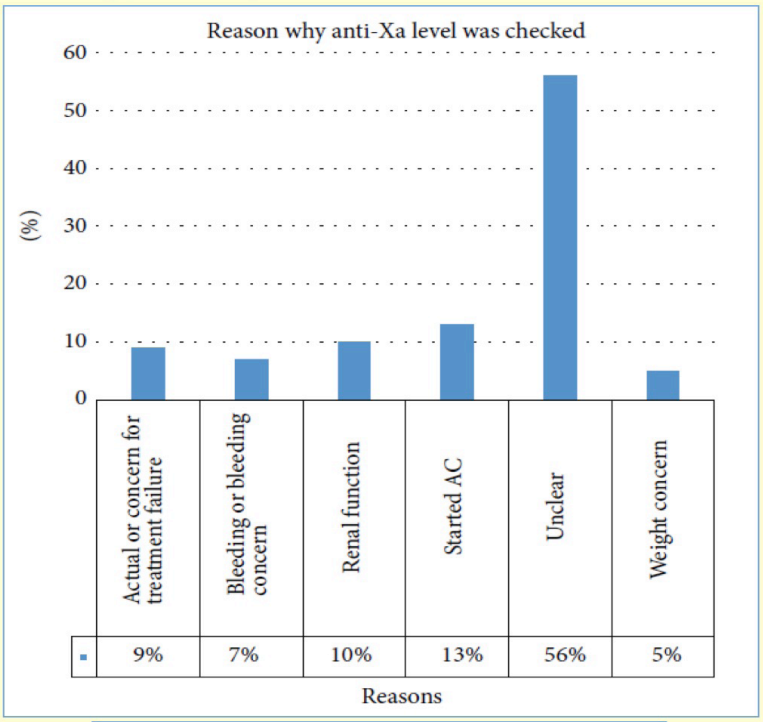
from Greene LA et al., JTH 2014;12:1554

Anti-Xa monitoring in malignancy-associated thrombosis



Retrospective, single institutions, study in 167 patients

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Yentz S et al., Thrombosis 2015