

LMWH Use In Renal Failure

Karen Shalansky, Pharm.D.
Pharmacotherapeutic Specialist, Nephrology
Vancouver General Hospital
karen.shalansky@vch.ca
Sept 2007

I have no potential/actual conflicts of interest to declare

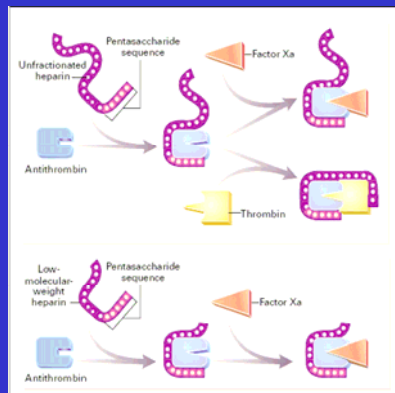
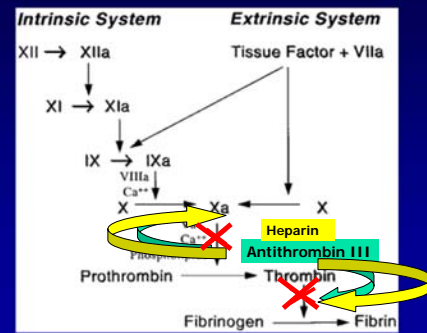
Outline

- Review of Coagulation System
- Differences between UFH and LMWH
 - MOA, pharmacology
- Anti-Xa Levels
- Studies assessing LMWH in CKD
 - Full dose
 - Prophylactic dose

Heparin

- Heterogenous mixture of polysaccharide chains
- MW 3000-30,000d
- Mechanism of Action
 - Binds to Antithrombin III causing a conformational change that accelerates its inhibition of both thrombin (factor II) and factor Xa

The coagulation cascade



Factor Xa – requires only pentasaccharide chain

Thrombin – requires 18 saccharide units

NEJM 1997;337:688

Comparison of Heparin and LMWH

Agent	Average MW (daltons)	AntiXa:IIa Ratio
Heparin	15,000	1:1
Tinzaparin	6500	1.9:1
Dalteparin	5600	2.0-2.7:1
Enoxaparin	4500	2.7-4.1:1
Nadroparin	4300	3.2-3.7:1

(Pharmacotherapy 2001;21:218-34; Pharmacotherapy 2005; 25:881-5)

Clearance

- Heparin –
 - Rapid Saturable – binds to liver endothelial receptors and macrophages
 - Long heparin chains depolymerized
 - Slower Non-Saturable – Renal
- LMWH
 - Slower Non-Saturable - Renal
 - Smaller chains have reduced binding to endothelium and macrophages, thus less hepatic elimination

Anticoagulant Options in Renal Failure

- No significant renal clearance
 - Unfractionated heparin (UFH)
 - Warfarin
 - Direct Thrombin Inhibitors (Argatroban)
- Dependent on renal clearance
 - LMWHs
 - Heparinoids: Danaparoid
 - Direct Thrombin Inhibitors: Lepirudin, Bivalirudin
 - Pentasaccharide (Anti-Xa): Fondaparinux

Chest 2004 Guidelines

- CrCl < 30 mL/min
 - UFH for full therapeutic anticoagulation therapy
 - PCK in impaired renal function differ amongst LMWHs
 - No single CrCl cutoff value that correlates with increased risk of bleeding for all LMWH products
 - If LMWH chosen
 - Monitor anti-Xa levels (exact range not established)

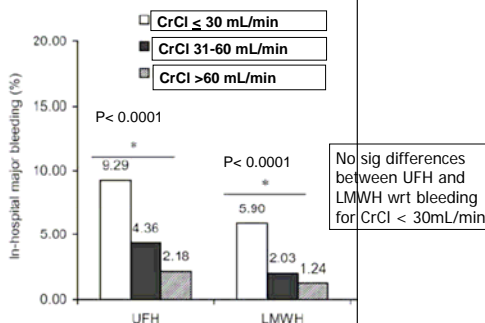
(Chest 2004;126:196S)

Questions

- What is the risk of using LMWH in CKD?
- What Anti-Xa level to aim for and when?
- Which LMWH to use, if any, in CKD ?

In-hospital Major Bleeding according to Renal Status (GRACE Registry) Collet JP et al. Eur Heart J 2005;26:2285-93

- Prospective, multicentre, observational registry of 11,881 ACS pts
- ~40% with CrCl < 60mL/min given LMWH (primarily enoxaparin)



VTE in Patients with Renal Insufficiency – RIETE Registry

- Prospective, multicentre, observational registry of 10,526 patients with VTE
 - CrCl > 60 mL/min (88%)
 - CrCl 30-60 mL/min (7%)
 - CrCl < 30 mL/min (5%)
- ~90% patients in each group on tinzaparin
 - 2/3 patients on full dose (175 units/kg/day)
- Followed for first 15 days of therapy

Monreal M et al. Am J Med 2006;119:1073-9

Multivariate Analysis on Risk of Developing Fatal Bleeding

Variable	Odds ratio (95% CI)	P Value
Immobility \geq 4 d	3.3 (1.5-7.3)	0.003
Cancer	2.7 (1.2-6.0)	0.015
CrCL > 60 mL/min	Reference: 0.2% incidence	-
CrCl 30-60 mL/min	1.4 (0.3-5.9); 0.3% incidence	0.677
CrCl < 30 mL/min	5.0 (2.0-12); 1.2% incidence	< 0.001

No sig differences in rate of fatal bleeding between UFH and LMWH

Monreal M et al. Am J Med 2006;119:1073-9

Summary: LMWH and Bleeding

- Renal dysfunction (CrCl < 30 mL/min) independent risk factor for major bleeding from anticoagulants
 - whether on LMWH or UFH

Anti-Xa Levels

Not an exact science!

Anti-Xa Monitoring

Semin Thromb Hemost 2001;27:519-22; Drug Safety 2002;25:725-33

- Chromogenic assay
- Measure in patients with renal failure (CrCl < 30 mL/min) or obesity
- Measure peak effect (~4 hours)
 - 3-4 hours after twice daily dosing
 - 4-5 hours after once daily dosing
 - Twice daily: **0.6-1** antiXa units/mL
 - Once daily: Tinzaparin: **0.6-1.5** antiXa units/mL
- Trough levels (current study in Toronto)
 - < **0.5** antiXa units/mL

Mean Target Anti-Xa Levels (Normal Renal Function)

Table 1 Peak Plasma Anti-Factor Xa Activities (U/mL) Generated by Some LMWHs to Treat a DVT According to the Therapeutic Scheme

Therapeutic Scheme	
80-100 Anti-Factor Xa U/kg/12 h	175-200 Anti-Factor Xa U/kg/24 h
Dalteparin : 0.6	Dalteparin : 1.05
Nadroparin : 0.9	Nadroparin : 1.30
Enoxaparin : 1	Tinzaparin : 0.85

Boneau B. Semin Thromb Hemost 2001;27:519-22

LMWHs in Renal Dysfunction

Tinzaparin
Enoxaparin
Dalteparin
Nadroparin

Tinzaparin

- Highest MW – may be less dependent upon renal elimination
- Closest antiXa:IIa activity compared to heparin

Agent	Average MW (daltons)	AntiXa:IIa Ratio
Heparin	15,000	1:1
Tinzaparin	6500	1.9:1
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Tinzaparin – Safety in Elderly

(Pautas E et al. Drug Safety;2002:25:725-33)

- Prospective trial of 200 consecutive pts > 70 yrs with CrCl > 20 mL/min
 - primarily VTE (n= 132) & atrial fib
- Tinzaparin 175 units/kg daily – followed for up to 30 days
- Peak anti-Xa levels measured 5 hours after injection at start then qweekly
 - 20% dose reduction if anti-Xa level > 1.4

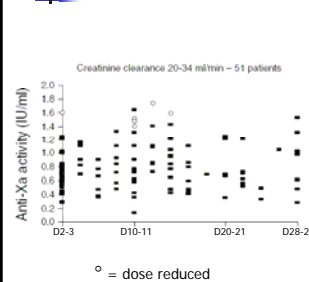
Tinzaparin Safety: Results

(Pautas E et al. Drug Safety;2002:25:725-33)

- Mean Age: 85 years (70-102)
- Mean CrCl: 51.2 (20-161); divided 4 groups:
 - 20-34mL/min (n=51); 35-49mL/min (n=60); 50-64mL/min (n=44); ≥ 65mL/min(n=45)
- Mean tx duration: 19.1 days; 72% > 10d
- Dose reduction: 26/200 (13%)
 - Spread amongst all 4 groups
- Major bleeding: 3/200 (1.5%); CrCl 45-68 mL/min
 - 6 deaths; 1 linked to anticoagulation (subdural hematoma)
- Anti-Xa levels: similar dispersion in all 4 CrCl groups
 - No correlation between Anti-Xa Activity and CrCl
- No thromboembolic events (efficacy)

Tinzaparin Safety In Elderly

(Pautas E et al. Drug Safety;2002:25:725-33)



Conclusion

- Tinzaparin can safely be given to elderly as long as anti-Xa levels monitored

Limitations:

- Small sample size
- CrCl > 20mL/min
- No control group/UFH

Tinzaparin Use in the Elderly

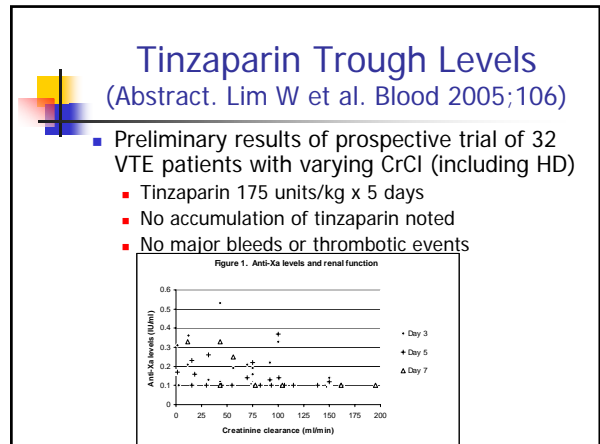
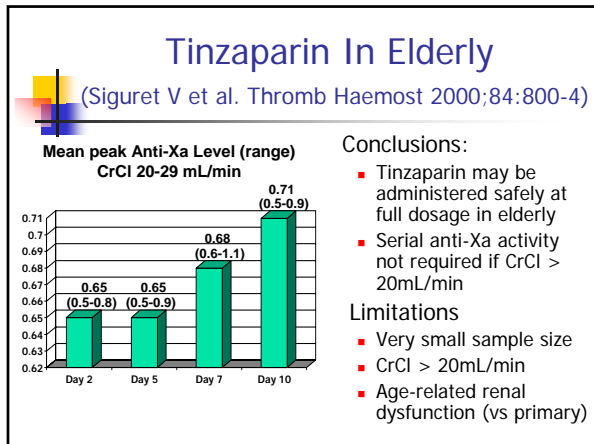
(Siguret V et al. Thromb Haemost 2000;84:800-4)

- Prospective trial of 30 patients > 70 yrs for VTE or atrial fib
 - 2 x PE; 15 x DVT
- Tinzaparin 175 U/kg/day for 10 days
- Peak anti-Xa levels measured 5 hours after initial injection, then on days 2, 5, 7 and 10

Tinzaparin In Elderly: Results

(Siguret V et al. Thromb Haemost 2000;84:800-4)

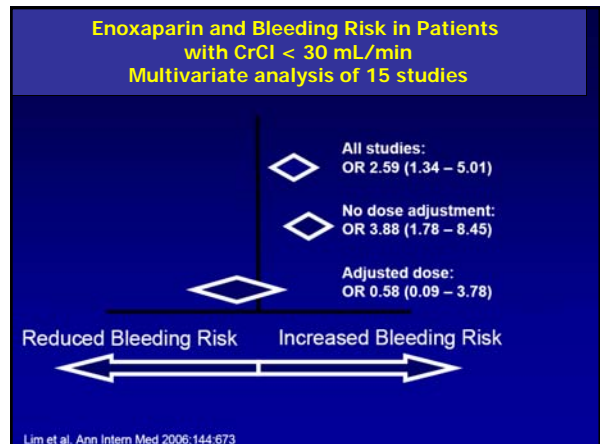
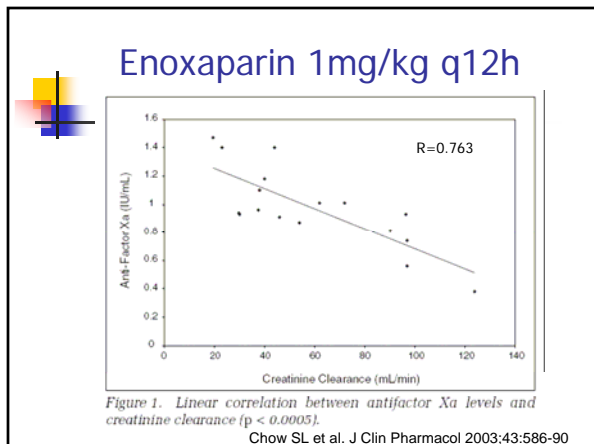
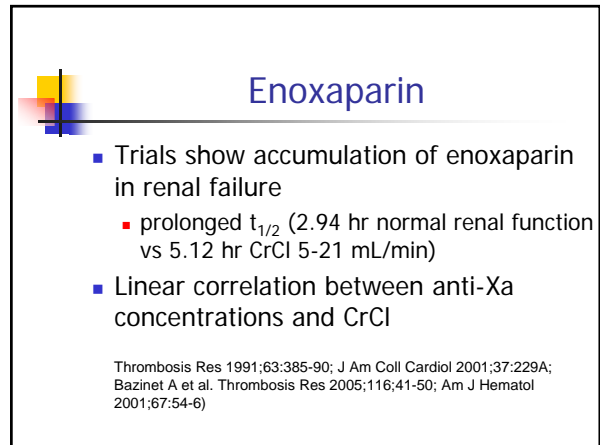
- Mean age: 87 years (71-96)
- Mean CrCl: 40.6 mL/min
 - 20-29mL/min (n=8); 30-39mL/min (n=9); 40-49mL/min (n=6); ≥ 50mL/min(n=7)
- 1 minor hematoma at injection site on day 7 (anti-Xa value = 1.04 units/mL)
- Anti-Xa levels: all levels < 1.5 units/mL
 - No increase in anti-Xa levels over 10 days
 - Mean anti-Xa activity: 0.66 (0.26-1.04)
- No thromboembolic events (efficacy)



VGH Case: RG 73 yo female, 80kg on HD since Oct 2006

- PMH: Breast CA 1997; Antiphospholipid antibody syndrome (DVT/PE 2000, IVC filter, warfarin failure)
- Tinzaparin lifelong

Date	Event	Tinzaparin Dose (SC)	Peak Anti-Xa level (IU/mL)
June-06		20,000 U daily (250 U/kg/d)	
Oct-06	Started Dialysis	↓ 10,000 U daily (125 U/kg/d)	0.6 (Oct 17/06) 0.68 (Jan 18/07)
Apr 10-07	?PE (neg)	↑ 14,000 U daily (175 U/kg/d)	0.68 (Apr 20/07)
May 27-07	L Shoulder hematoma	↓ 10,000 U daily (125 U/kg/d) (? Patient took double dose)	2.0 (Aug 4/07)
Aug 4-07	High level	↓ 7,000 U daily (88 U/kg/d)	1.06 (Aug 23/07)



CPS Guidelines for Enoxaparin

Indication	Cr Cl > 30mL/min	CrCl < 30mL/min
Prophylaxis hip/knee	30mg q12h	30mg q24h
GI Sx/Medical	40mg q24h	20-30 mg q24h
ACS	1mg/kg q12h	1mg/kg q24h
DVT/PE	1mg/kg q12h or 1.5mg/kg q24h	1mg/kg q24h

ExTRACT-TIMI 25 Trial

(Antman EM et al. NEJM 2006;354:1477-88)

- Randomized trial of 20,506 patients with STEMI comparing enoxaparin vs UFH plus fibrinolysis
- CrCl < 30mL/min – dose ↓ 1mg/kg SC q24h (n=212)

Results for RE (JACC 2007;49:2249-55):

- Inverse relationship between level of CrCl and death, stroke, intracranial hemorrhage, and bleeding
- Greater increased risk of major and minor bleeding in enoxaparin group for CrCl < 90mL/min
- Net clinical benefit between enoxaparin and UFH did not differ with CrCl < 60 mL/min

JACC 2007;49:2249-55

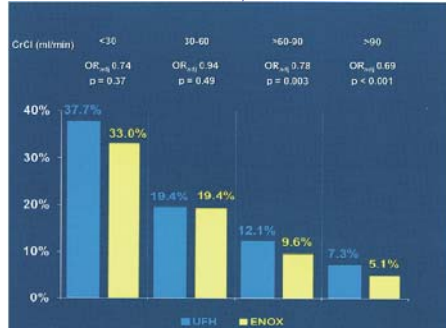


Figure 2 Death or Nonfatal Recurrent MI at 30 Days in Strata of CrCl According to Treatment Assignment

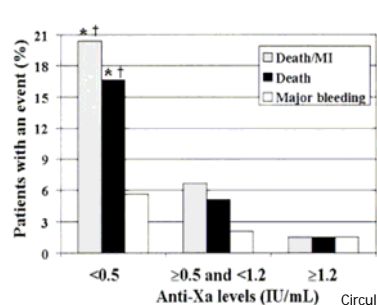
BID Dose Adjustments

(Kruse MW. Am Heart J 2004;148:582-9)

- Retrospective evaluation of a PCK program for adjusting enoxaparin in renal impairment
- LD 1mg/kg, then
 - 1mg/kg SC q12h for CrCl > 60mL/min
 - 0.75mg/kg q12h for CrCl 30-60mL/min
 - 0.5mg/kg q12h for CrCl ≤ 30mL/min
- 1 yr retrospective review of 170 patients
 - anti-Xa 4H post 3rd dose (goal 0.6-1 units/mL)
 - CrCl 30-60 (n=120): 10% sub; 80% ther; 10% supra
 - CrCl ≤ 30 (n= 50): 38% sub; 60% ther; 2% supra
- Limitation: only PCK study, no outcomes

•Prospective, observational study of 803 consecutive NSTEMI patients treated with enoxaparin

•Low peak anti-Xa levels independent risk factor for early (30-day) mortality



Circulation 2004;110:392-8

Collet JP et al. Int J Cardiol 2001;80:81-2

Letter to Editor:

30-60 mL/min:

- 84% full dose q12h x 3 doses then adjusted to peak anti-Xa

< 30mL/min:

- 64% full dose q12h x 3 doses then adjusted to peak anti-Xa

Assessment:

- N=28 both groups
- Mean peak anti-Xa levels 0.95 for both groups

Collet JP et al. Circulation 2003;41:8-14

- Review of pts excluded from ACS trials but managed with reduced dosages Enoxaparin
- 62 pts with CrCl < 30mL/min given 65% of usual dose

Results:

- Anti-Xa levels and bleeding outcomes similar to pts without renal impairment
- 4-fold increase in death and MI at one month follow-up

Other LMWHs

- **Nadroparin** (Thromb Hemost;1998;79:1162-5)
 - 180 U/kg/day SC x 6-10 days (n=36)
 - Drug accumulation with worsening RF
 - Linear correlation between CrCl and anti-Xa
 - No dosing strategies in literature
- **Dalteparin** (Pharmacotherapy 2005;25:881-5)
 - Case report of hematoma 3 days after femoral angioplasty in 84yo female with CrCl 26mL/min who had a DVT
 - Pt given Dalteparin 200 U/kg SC daily x 3 days

What About Prophylactic Dosing

Dalteparin Prophylaxis

(Rabbat CG et al. J Crit Care 2005;20:357-63)

- Prospective cohort study of 19 ICU pts with varying degrees of RF
 - Dalteparin 5000 units SC daily
 - Measured twice weekly trough (n=185) and 4H peaks (n=113) anti-Xa levels
- Results:
- CrCl range: 19-218 mL/min (mean 97 mL/min)
 - LOS in ICU: median 12 days (8-24)
 - No accumulation of LMWH detected (troughs)
 - Mean peak levels: 0.3 units/mL (< 0.1 to 0.66)
 - 1 thrombotic event (R IJ CVC thrombus)

Dalteparin Prophylaxis

(Haematologica 2006;91:976-9)

- Prospective cohort study of 115 medical pts with CrCl < 90mL/min (n=12 CrCl < 30mL/min)
 - High risk (> 75yo; active cancer; history VTE): Dalteparin 5000 units SC daily x 6 days (n=93)
 - Low risk: Dalteparin 2500 units SC daily x 6 days
 - Anti-Xa measured @ BL and 4H peak on day 6
- Results:
- No major bleeding events or VTE
 - No evidence of accumulation of dalteparin irrespective of renal function
 - No patient had Day 6 anti-Xa level > 0.5 U/ml

Enoxaparin Prophylaxis

(Thrombosis Res 2002;105: 225-31)

- Open-label, Multi-Centre kinetic study
- Enoxaparin 40mg SC daily x 4 days in 12 healthy and 36 pts with mild, mod or severe RF
- Serial anti-Xa levels drawn

Results:

- Tendency towards increase in anti-Xa levels with worsening renal function, however no levels >0.6 on day 4
- Suggested dose modification if CrCl ≤ 30mL/min

Enox vs. Tinzaparin Prophylaxis

(Abstract. Mahe I et al. Blood 2005;106)

- Open, R, Parallel trial of 55 patients > 75 yrs with CrCl 20-50 mL/min (mean 35 mL/min)
 - Tinzaparin 4500 units SC daily x 8 days OR
 - Enoxaparin 40mg SC daily x 8 days
- Preliminary Results:
 - Statistically significant accumulation with Enoxaparin but not Tinzaparin after 8 days

Drug	Peak Anti-Xa	Trough Anti-Xa	Trough Anti-Xa
Enoxaparin	0.55 (day 1)	0.06 (day 1)	P<0.0001 P=0.027
	0.67 (day 8)	0.11 (day 8)	
Tinzaparin	0.44 (day 1)	0.06 (day 1)	NS NS
	0.46 (day 8)	0.06 (day 1)	

Summary: LMWH and Renal Failure (CrCl \leq 30mL/min)

- Patients with RF have increased bleeding risk with anticoagulants
- Prophylactic dose LMWH (< 10 days) appears safe with minimal accumulation
 - tinzaparin - 4500 units SC daily
 - dalteparin - if low risk: 2500 units daily
if high risk: 5000 units SC daily
 - enoxaparin - lower dose to 30mg SC daily

Summary: LMWH and RF Therapeutic Dose

- Therapeutic dose
 - "not all LMWHs are equal"
- Tinzaparin (< 10 days) 175 U/kg/day appears safe with minimal accumulation
 - Efficacy and safety data (small studies; CrCl > 20)
 - Follow peak anti-Xa levels if > 5 days therapy
 - Round down to closest syringe size (10,000, 14,000, 18,000 units) or 1000 unit increment
 - Cost: \$1.60/1000 units = \$22.40/14,000 units
 - Special Authority through PharmaCare

Summary: LMWH and RF Therapeutic Dose

- Enoxaparin accumulates in RF; needs dosage adjustment
 - Dose adjustments – PCK based (daily vs bid dosing); not well validated for efficacy
 - Follow anti-Xa levels to ensure appropriate dose
 - Preliminary data suggest LOW peak anti-Xa activity associated with early mortality in ACS
 - Randomized thrombolytic trial (STEMI) – loss of superiority of Enox over UFH for 1^o outcomes with CrCl < 60mL/min; more bleeding in enoxaparin group
 - VGH: UFH used in CCU/Cath for CrCl < 30mL/min
- Dalteparin – no data

Summary: LMWH and RF Anti-Xa Levels

- Need to follow anti-Xa levels for therapeutic doses of LMWH
 - 4H peak 0.6-1 units/mL (twice daily)
 - 4-5h peak 0.6-1.5 units/mL (once daily)
 - Trough < 0.5 units/mL
- Turnaround time (SPH) ~2-5 days
- Heparin (full dose) still preferred agent esp. if anti-Xa levels not available