LMWH Use In Renal Failure

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I have no potential/actual conflicts of interest to declare

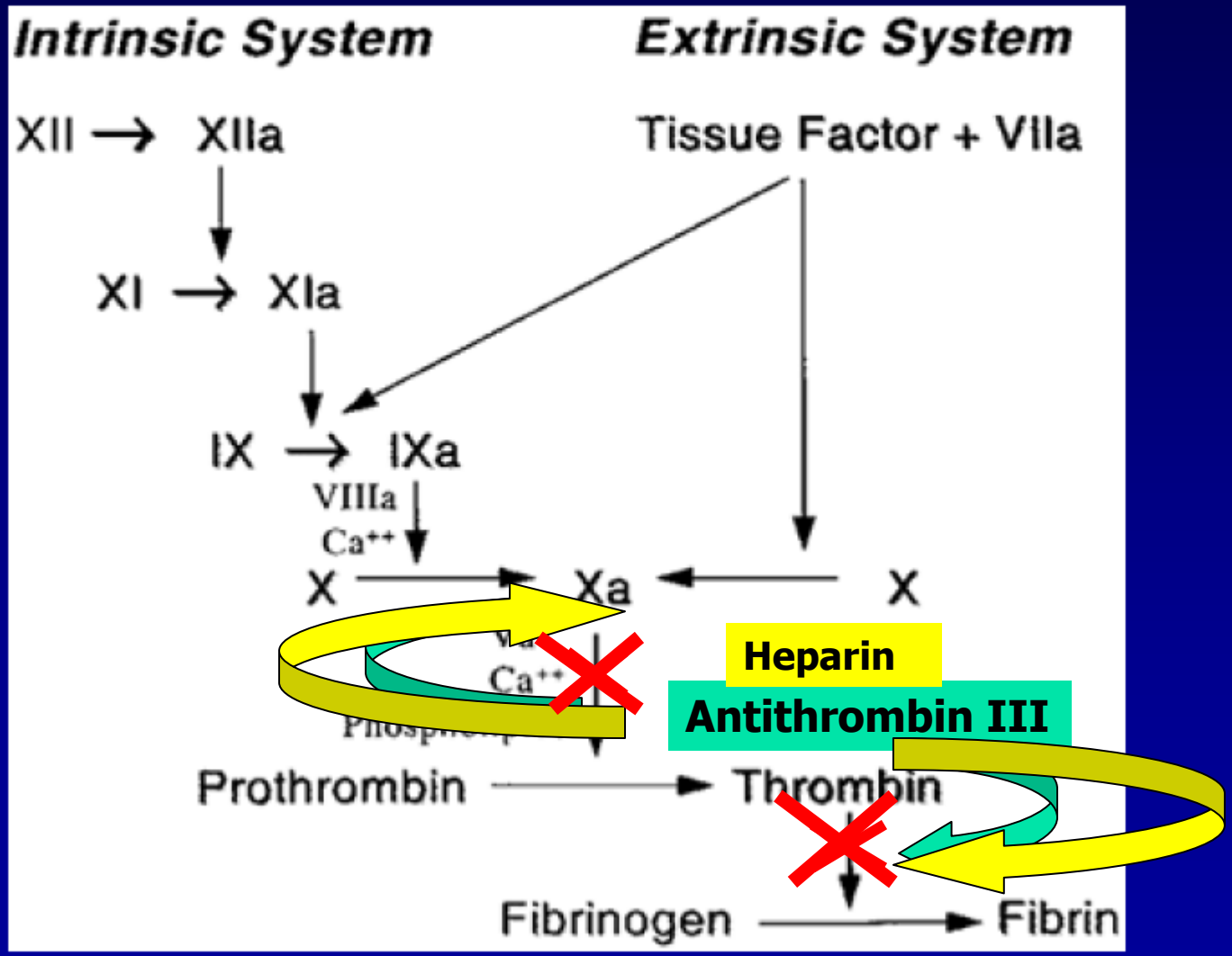
Objectives

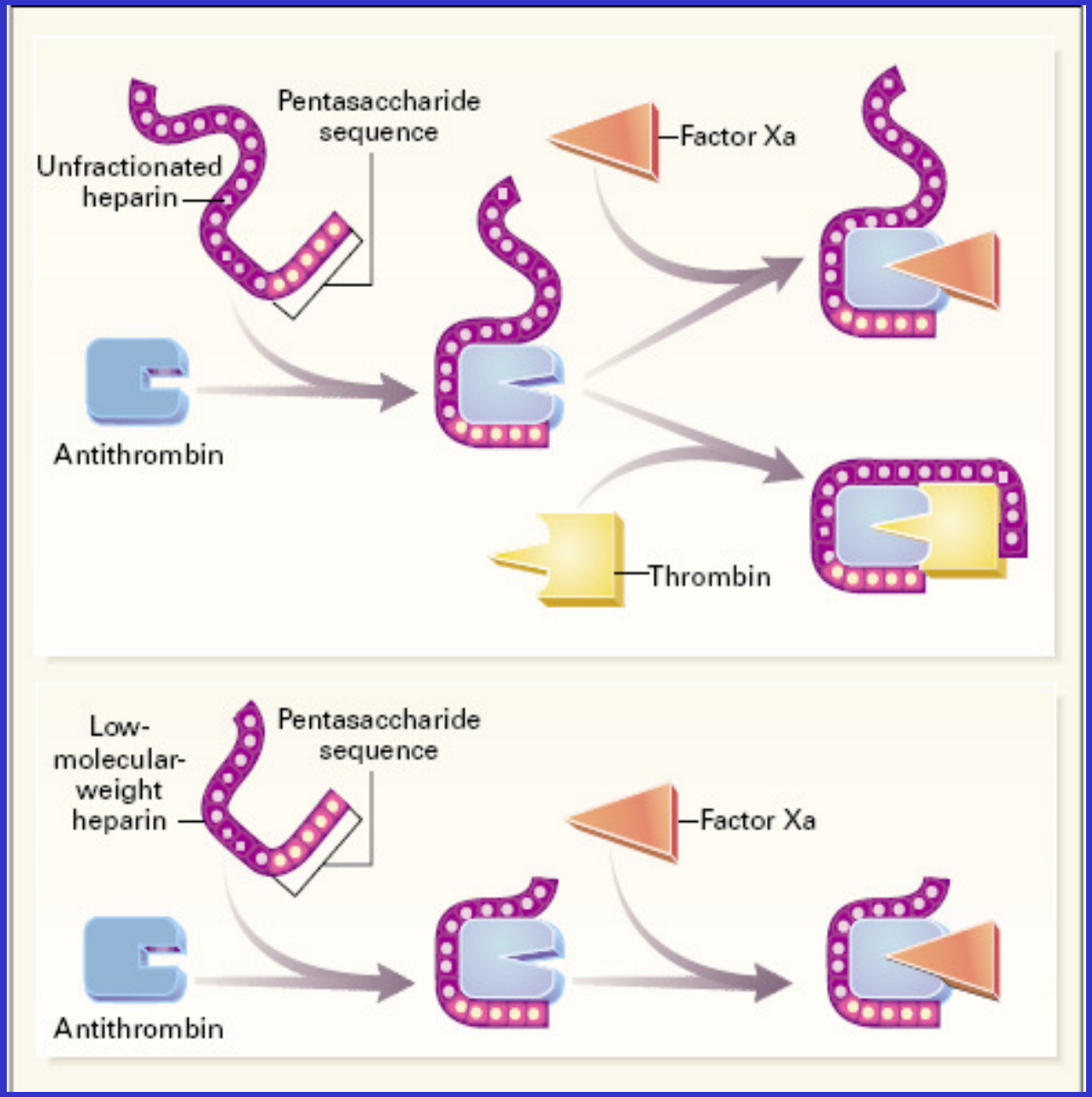
- To understand the differences between LMWH and unfractionated heparin
  - Effect on coagulation system
  - Total body clearance
- To review the role of LMWH in patients with renal dysfunction
  - Therapeutic use
  - Prophylactic use
- To review appropriate dosing of LMWH and monitoring in patients with renal dysfunction
  - Anti-Xa levels

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 2008 Guidelines

- CrCl < 30 mL/min
  - Suggest IV UFH over LMWH for treatment of VTE
    - 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)
  - Prophylactic doses
    - LMWH has not been shown to increase bleeding risk

(Chest 2008;133:149S)

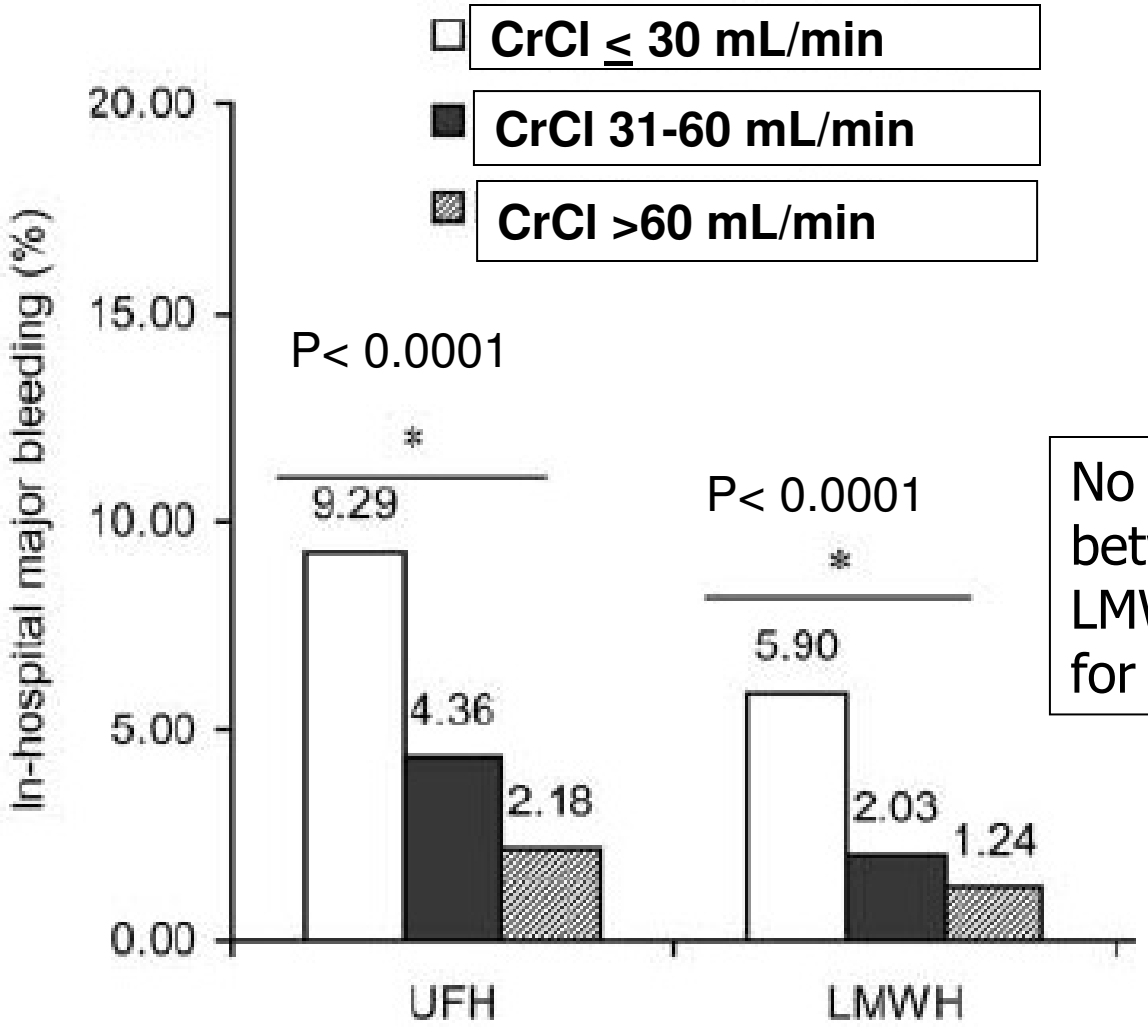
Questions

- 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)



No sig differences between UFH and LMWH wrt bleeding for CrCl < 30mL/min

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 ≥ 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 failue (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
Dalteparin	5600	2.0-2.7:1
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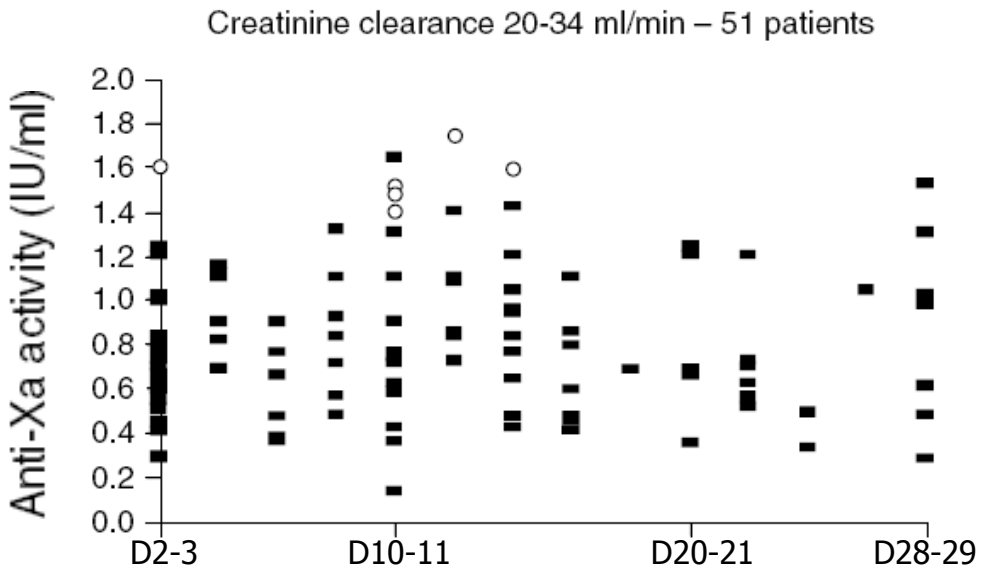
Tinzaparin – Safety in Elderly
(Pautas E et al. Drug Safety;2002:25:725-33)

- 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); $\geq$ 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)



° = dose reduced

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

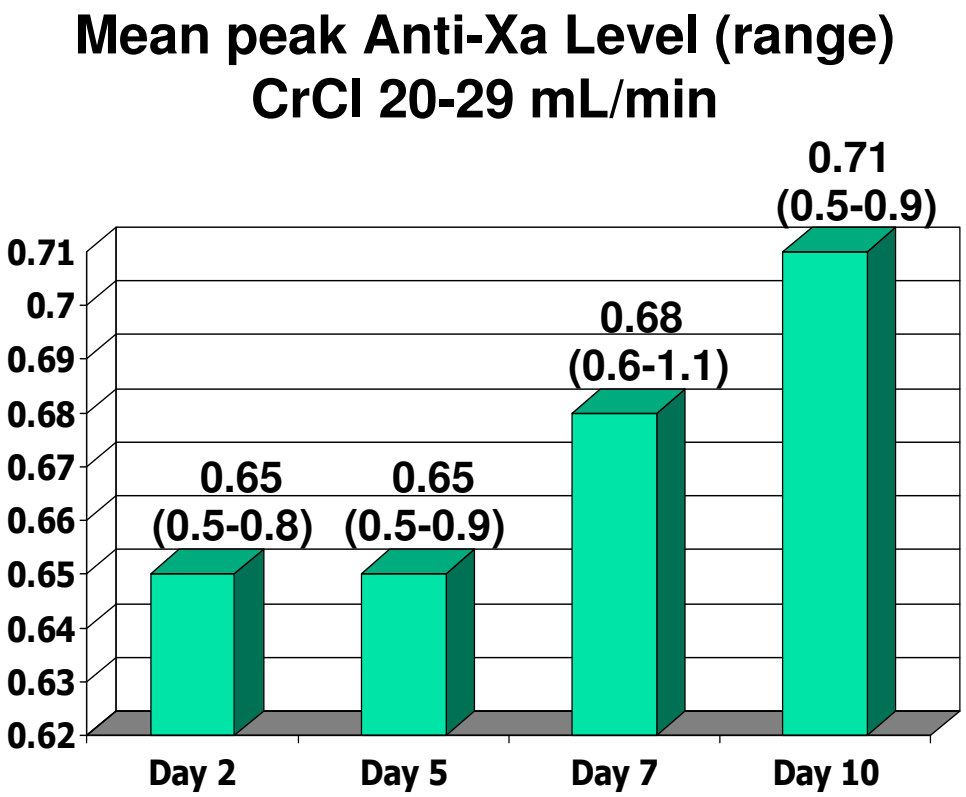
Tinzaparin In Elderly: Results

(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); $\geq$ 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)

Tinzaparin In Elderly

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



Conclusions:

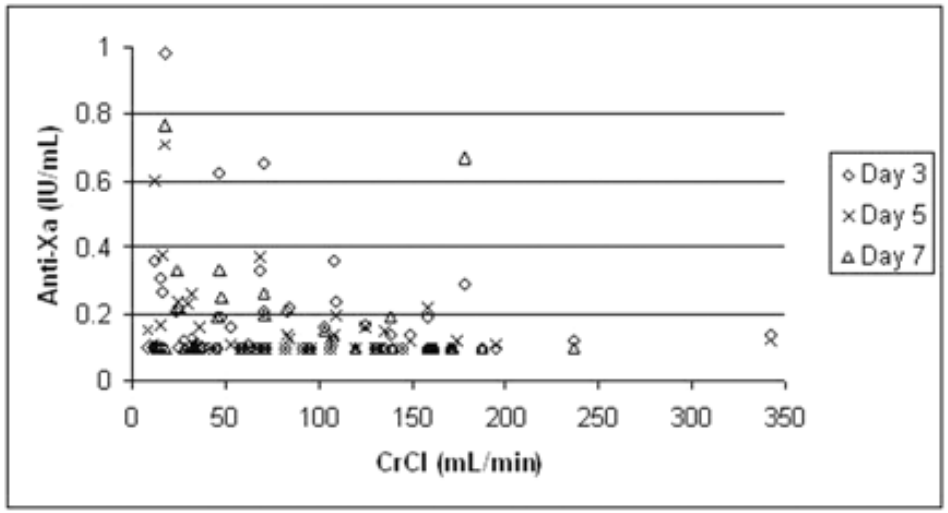
- Tinzaparin may be administered safely at full dosage in elderly
- Serial anti-Xa activity not required if CrCl > 20mL/min

Limitations

- Very small sample size
- CrCl > 20mL/min
- Age-related renal dysfunction (vs primary)

Tinzaparin Trough Levels (Abstract. Lim W et al. Blood 2006;108)

- Preliminary results of prospective trial of 78 VTE patients with varying CrCl (including HD)
  - Tinzaparin 175 units/kg x 5-7 days
  - Trough levels measured prior to doses 3, 5, 7
  - Doses adjusted if anti-Xa levels > 0.5 units/mL



- 5/78 patients (6.4%) required dose adjustment:
  - 1 x HD; 2 x CrCl <30; 1 x CrCl 30-60; 1xCrCl > 60
  - No patients developed VTE
  - 1 hematoma in HD patient after traumatic line insertion

Innohep in Renal Insufficiency Study (IRIS)

(funded by Leo Pharma)

- MC, OL, R, trial of tinzaparin 175 U/kg/d vs UFH x 5-10 days for DVT/PE treatment in elderly pts
  - $\geq$ 70 yrs with renal insufficiency ($\leq$ 30-60mL/min)
  - 542 patients followed x 90 days
- Study stopped early due to ↑ mortality in tinzaparin group (11.2% vs 6.3% UHF, p=0.049)
  - Deaths primarily due to cancer, sepsis, heart failure in patients $\geq$ 90 years, occurring $\geq$ 20 days post-tx
  - Imbalance in randomization with ↑'er % of pts in tinzaparin group having malignancy, infection, cardiac insuff, immobility and > 90 years
  - No difference in bleeding or recurrent VTE events

VGH Case

- 79 yo female with calciphylaxis & a fib
  - D/C warfarin, daily HD (5/7), hyperbaric unit, sodium thiosulphate, lanthanum
  - Started on tinzaparin 14,000 units SC daily (weight = 85kg, 175 U/kg = 14,874 U)
  - Day 3 peak (6h) = 0.85 units/mL
  - Day 16 peak (6h) = 0.88 units/mL
  - Day 37 peak (6h) = 0.78 units/mL

Tinzaparin Summary: 175mg/kg

- Pautus 2002 – dose reduction 13%
  - n=200 elderly with VTE, CrCl > 20 mL/min
- Siguret 2000 – no accumulation peaks
  - N=30 elderly with VTE, CrCl > 20 mL/min
- Lim 2005 (abstract) – dose reduction 6%
  - n=78 VTE including HD
- Personal experience (KS)

Enoxaparin

- Trials show accumulation of enoxaparin in renal failure
  - prolonged $t_{1/2}$ (2.94 hr normal renal function vs 5.12 hr CrCl 5-21 mL/min)
- Linear correlation between anti-Xa concentrations and CrCl

Thrombosis Res 1991;63:385-90; J Am Coll Cardiol 2001;37:229A; Bazinet A et al. Thrombosis Res 2005;116;41-50; Am J Hematol 2001;67:54-6)

Enoxaparin 1mg/kg q12h

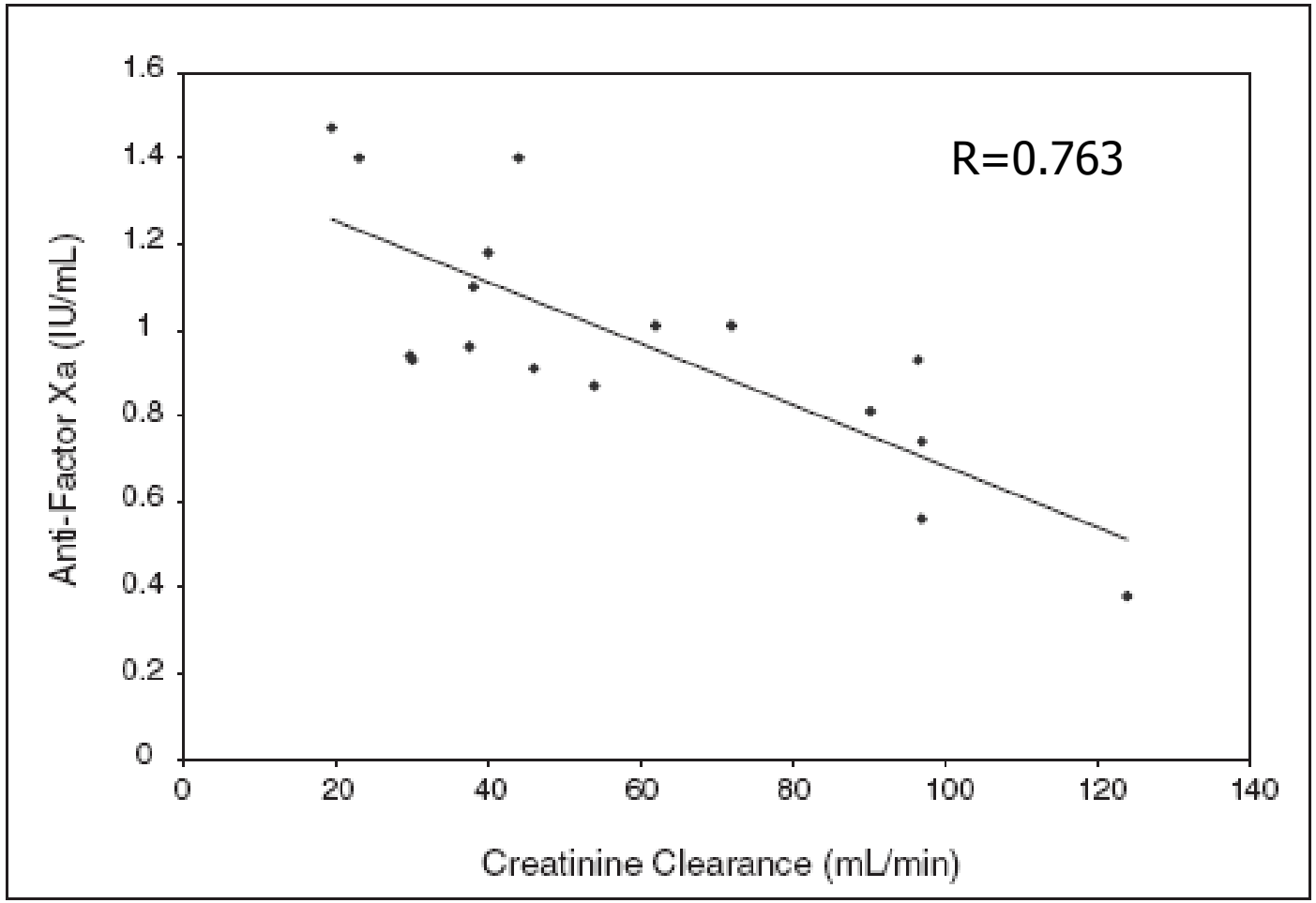
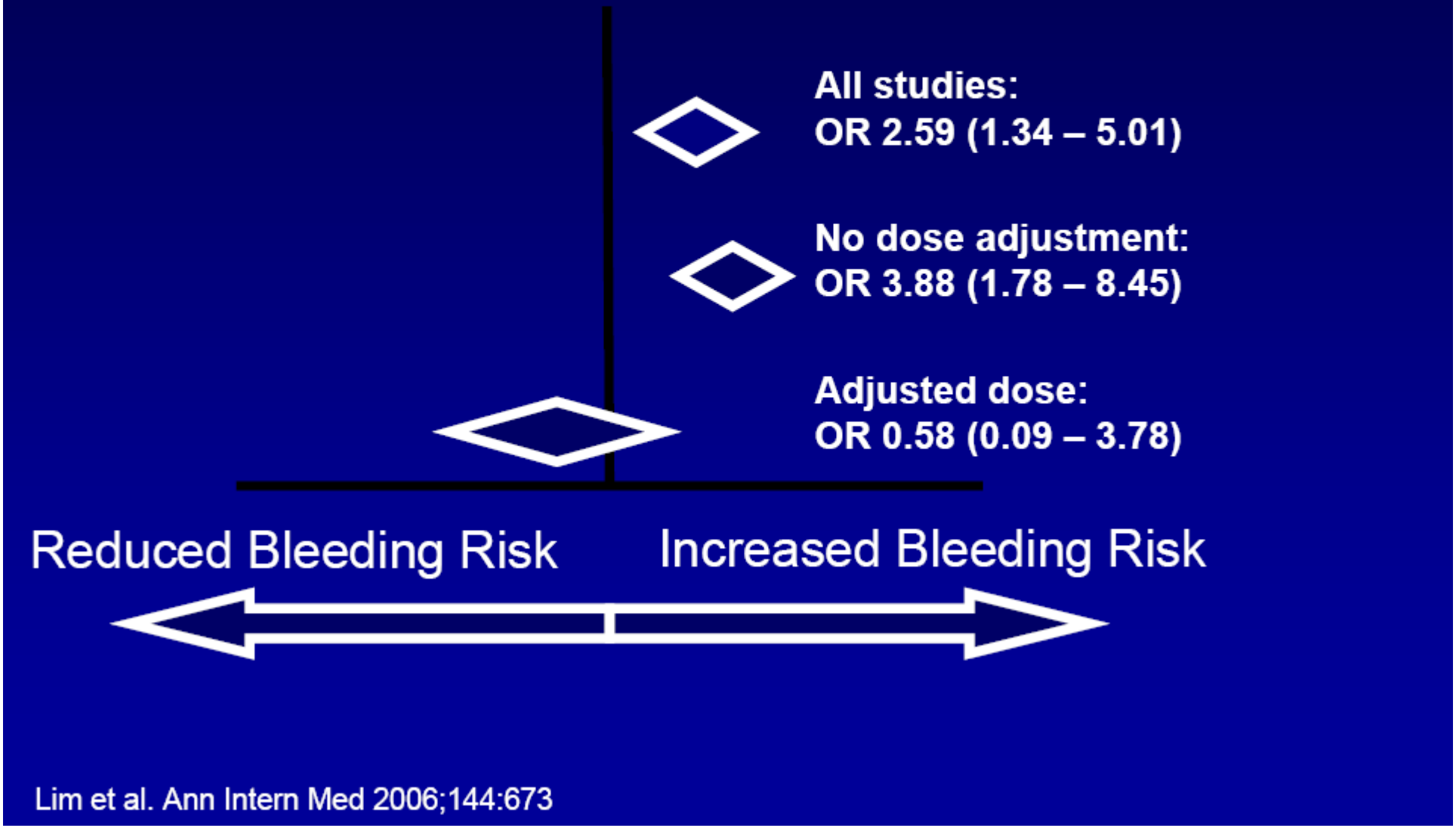


Figure 1. Linear correlation between antifactor Xa levels and creatinine clearance ($p < 0.0005$).

Chow SL et al. J Clin Pharmacol 2003;43:586-90

Enoxaparin and Bleeding Risk in Patients with CrCl < 30 mL/min Multivariate analysis of 15 studies



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

CPS Guidelines for Enoxaparin

Indication	**Cr Cl > 30mL/min**	**CrCl < 30mL/min**
Prophylaxis hip/knee GI Sx/Medical	 30mg q12h 40mg q24h	 30mg 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 RF (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

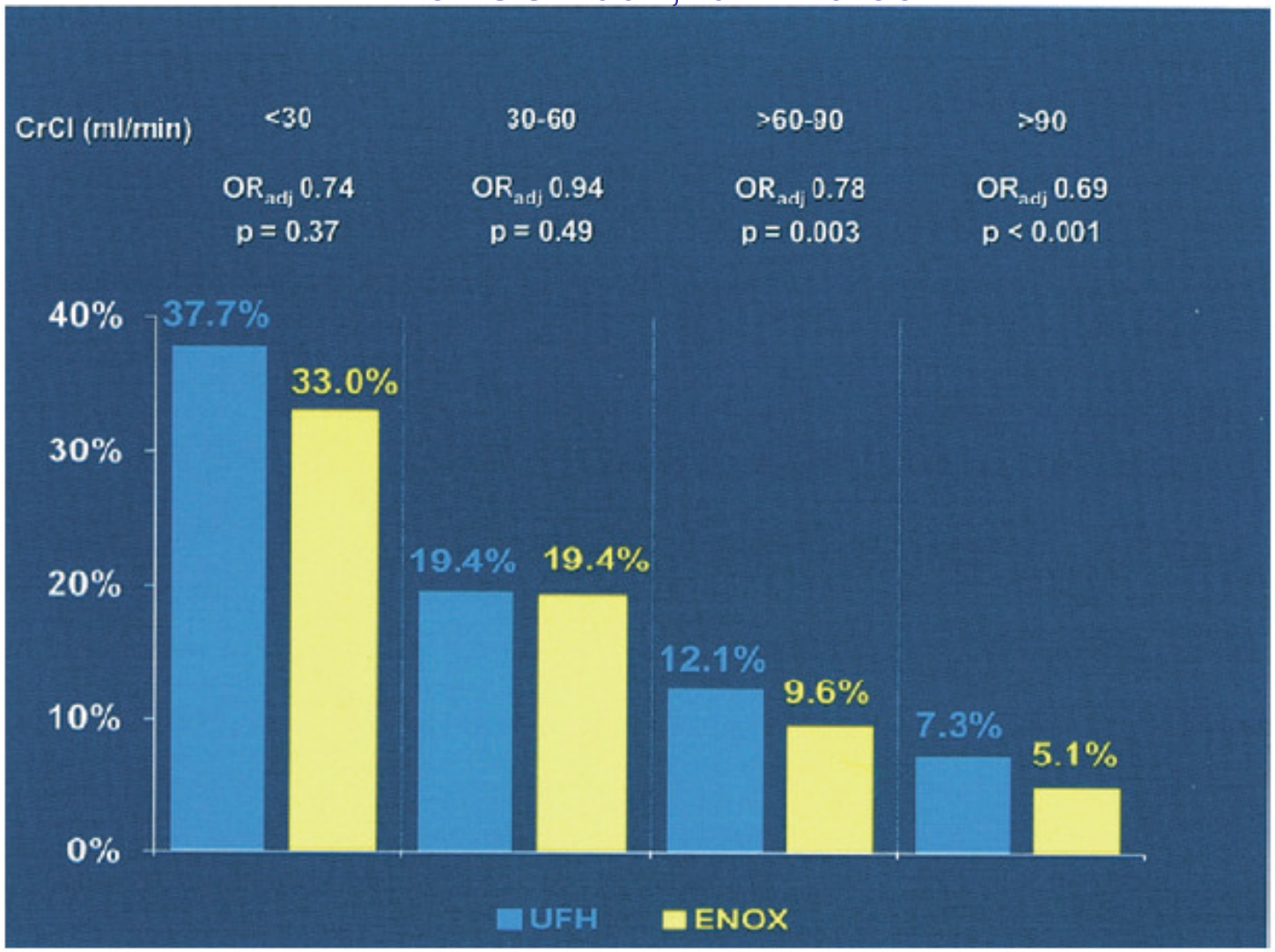


Figure 2 **Death or Nonfatal Recurrent MI at 30 Days in Strata of CrCl According to Treatment Assignment**

Enoxaparin Once Daily (Pharmacotherapy 2007;27:1347-52

- P, NR, CKD stage 4 (n=18) and 5 (n=1) using dosing strategy of 1 mg/kg Q24H
  - ACS: n=12; PE: n=3; A Fib: n=2; Valve: n=2
- Peak/trough levels at 2nd and 3rd dose
- **Results:** no adverse outcomes

Level	Anti-Xa Level (U/mL)	% sub
Peak Levels (post 2nd/3rd)	0.67 (0.39-0.9)	5/19 (26%) (< 0.5)
Trough Level (before 2nd/3rd)	0.12 (0-0.5)	5/19 (26%) (<0.05)

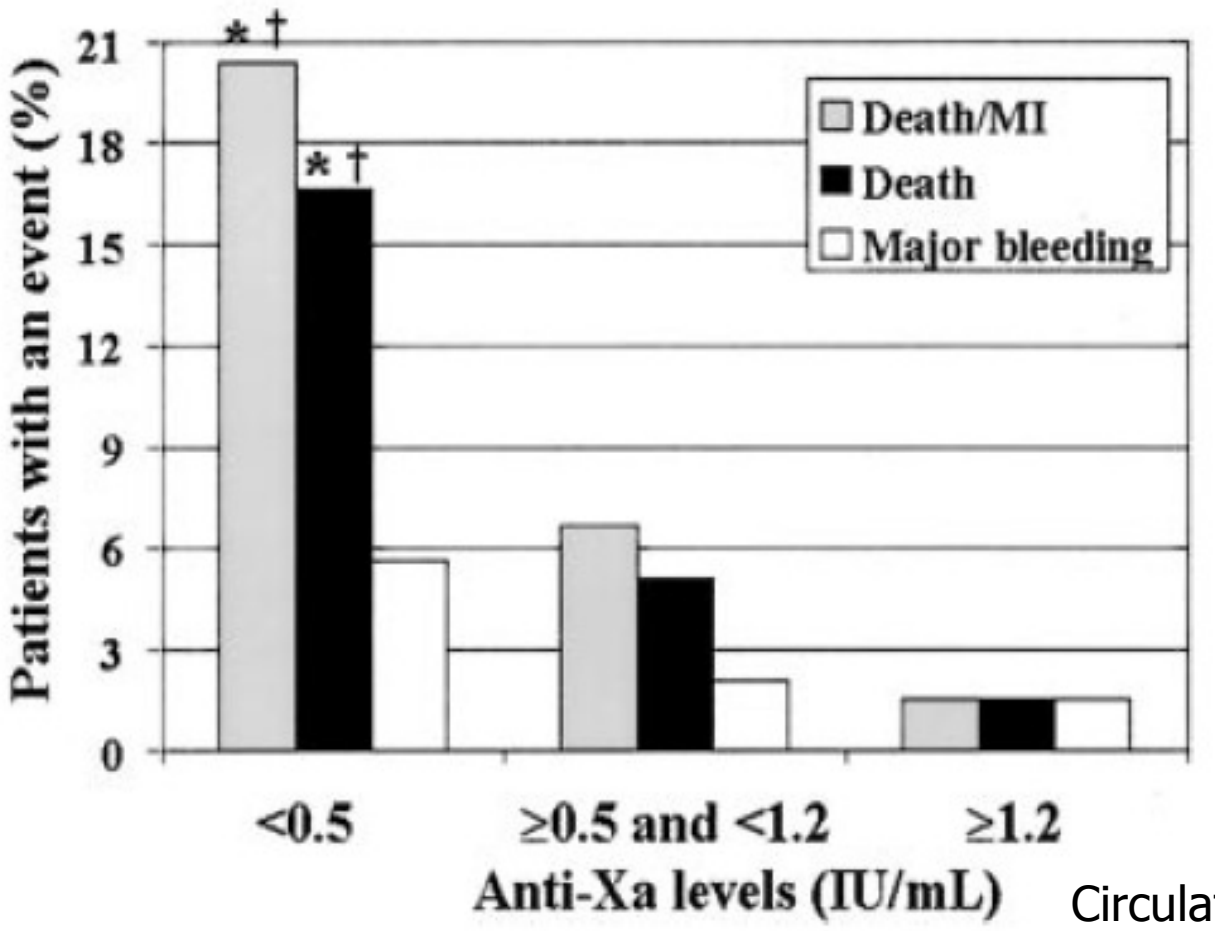
BID Dose Adjustments

(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 $\leq$ 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

Enoxaparin Summary

- Accumulates in renal failure – ↓ dose
- Primarily studied for ACS
- Controversy once daily dosing (per CPS) vs lower dose BID dosing
  - Low peaks associated with ↑ mortality in ACS
  - Loss of superiority of enoxaparin over UFH for STEMI in patients with CrCl < 60 mL/min

Dalteparin

- **Case report**: Dalteparin 200 U/kg SC daily for DVT in 84 yo female with CrCL 26 mL/min
  - hematoma developed on day 4, Hg ↓ 119 to 55 g/L

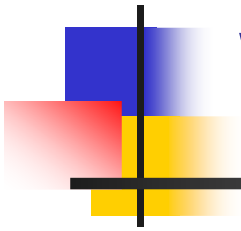
(Pharmacotherapy 2005;25:881-5)

- **OL study** of 11 pts with CrCl < 40 mL/min (range 16-38 mL/min)
  - Dalteparin 100 U/kg SC BID
  - Indication: VTE (n=6), A fib (n=3), and unstable angina (n=2)
  - Peak anti-Xa levels 3-5 h after 5 or 6th dose: 0.1-1 U/mL (mean 0.47 U/mL)

(Pharmacotherapy 2005;25:817-22)

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



What About Prophylactic Dosing

Dalteparin Prophylaxis Trial: DIRECT (Arch Intern Med 2008;168:1805-12)

- 138 ICU patients with CrCl< 30mL/min
  - mean CrCl 18.9 mL/min; 9.4% on dialysis
- Dalteparin 5000 units SC daily $\leq$ 30 days (IQR 4-12 days)
- Trough anti-Xa levels measured on days 3, 10, 17

Results:

- All trough anti-Xa levels < 0.4 units/mL
  - Median trough level – undetectable (<0.1 units/mL)
  - Peak levels 0.29-0.34 units/mL
- No evidence of accumulation
- DVT 7/138 pts (5.1%)
- Major bleeding 10/138 (7.2%)
  - all had trough anti-Xa levels < 0.18 units/mL
  - ASA use and ↑ INR risk factors for bleed

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 $\leq$ 30mL/min

Enox vs. Tinza 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	P value
Enoxaparin	0.55 (day 1) 0.67 (day 8)	0.06 (day 1) 0.11 (day 8)	P<0.0001 (peak) P=0.027 (trough)
Tinzaparin	0.44 (day 1) 0.46 (day 8)	0.06 (day 1) 0.06 (day 1)	NS (peak) NS (trough)

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"
  - LMWHs with a higher molecular weight may be less prone to accumulation and bleeding.

    (Lim W Intern Emerg Med 2008;83:319-23)

- Tinzaparin (< 10 days) 175 U/kg/day appears safe with minimal accumulation
  - Efficacy and safety data (small studies; 1° 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 (BC)

Summary: LMWH and RF Therapeutic Dose

- Enoxaparin accumulates in RF; needs dosage adjustment
  - Dose adjustments in CPS – daily dosing
    - 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° outcomes with CrCl < 60mL/min; more bleeding in enoxaparin group
  - VGH: UFH used in CCU/Cath for CrCl < 30mL/min
- Dalteparin – minimal data

Summary: LMWH and RF Anti-Xa Levels

- Guidelines recommend to follow anti-Xa levels for therapeutic doses of LMWH
  - Twice daily: 4H peak 0.6-1 units/mL
  - Once daily: 4-5h peak 0.6-1.5 units/mL
  - ?Trough < 0.5 units/mL
- Turnaround time (SPH) ~2-4 days

- Heparin (full dose) still preferred agent esp. if anti-Xa levels not available