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“Old” anticoagulants and renal insufficiency

Pirmin Schmid

Division of Hematology and Central Hematology Laboratory
Luzerner Kantonsspital, Luzern, Switzerland

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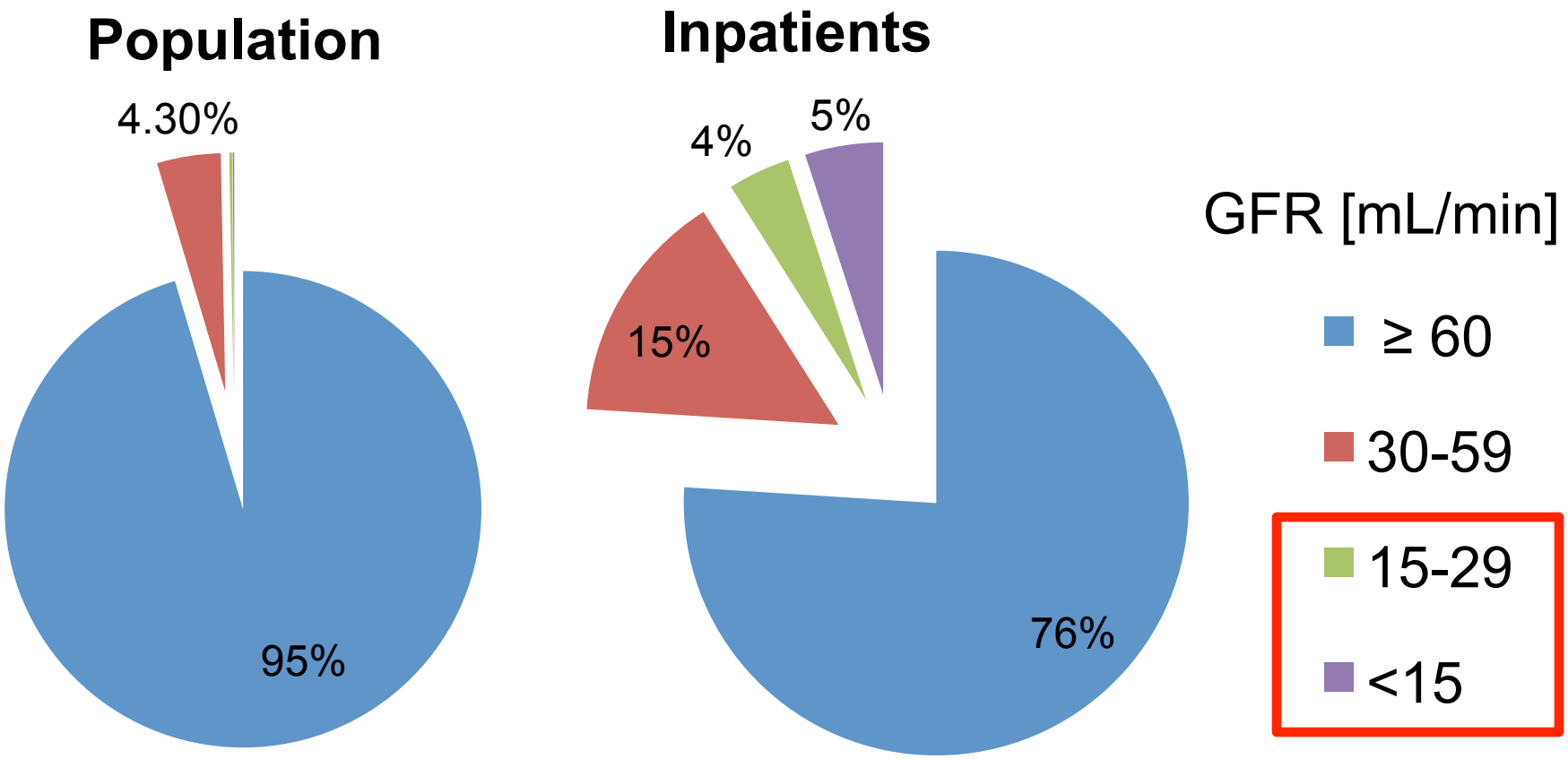
Disclosures

- Former investigator in a pharmacokinetic study on dalteparin in renal insufficiency, funded by Luzerner Kantonsspital
  and an unrestricted grant by Pfizer Switzerland

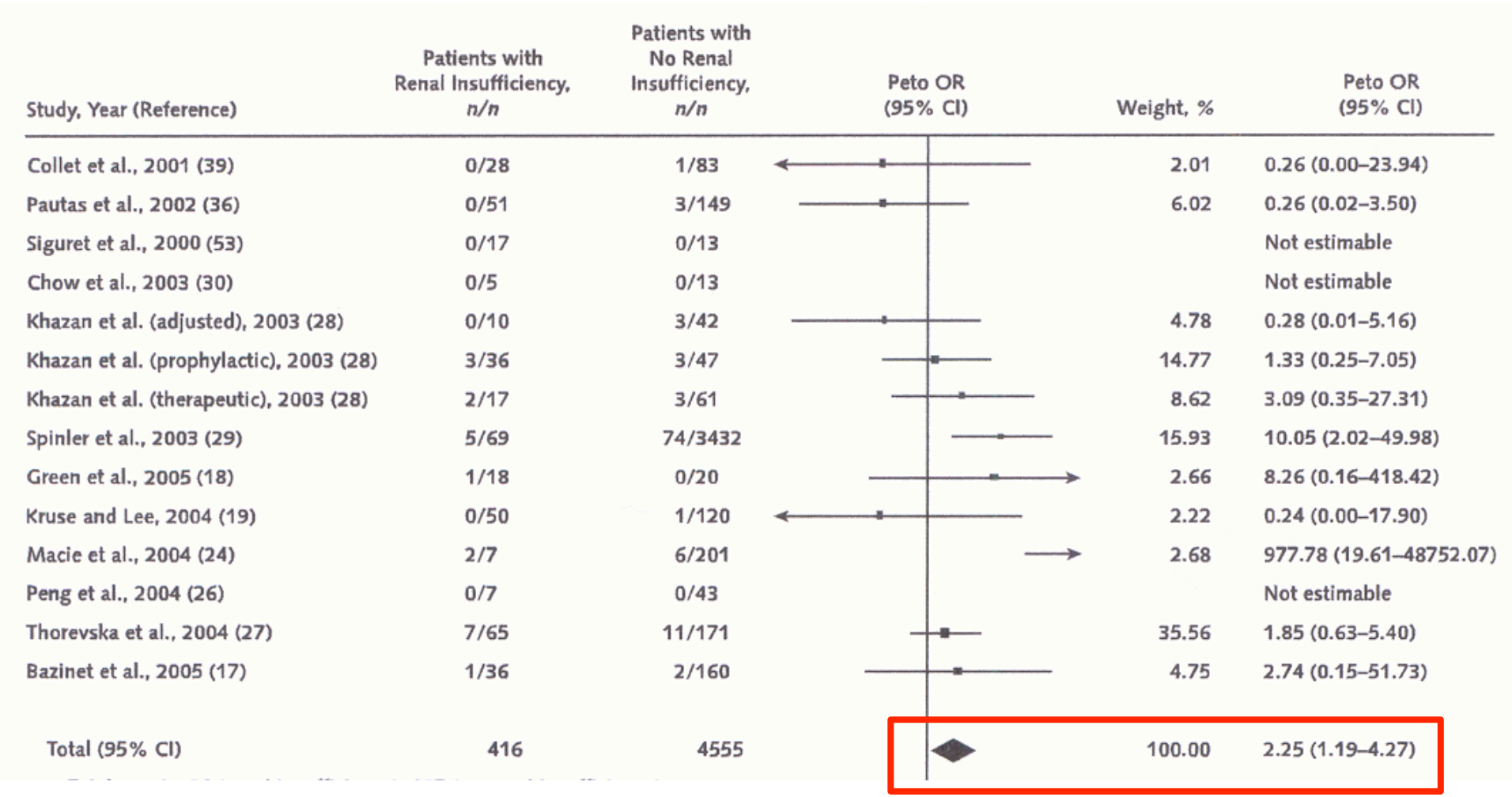
Agenda

- Introduction
- Vitamin K antagonists (VKA)
- Unfractionated heparins (UFH)
- Low-molecular-weight heparins (LMWH)
  - Pharmacokinetics
  - Clinical data
- Summary

Renal Insufficiency - Prevalence



LMWH: Bleeding risk



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)

Lim et al. Ann Intern Med 2006:673

Risks: Bleeding / Thrombosis

- Balance the increased risks
  - bleeding
  - thromboembolic events
  - increased bleeding risk not dependent on used anticoagulant
  - TE events > bleeding

Vitamin K antagonists (VKA)

- since 1950s
- metabolism: hepatic

	$t_{½}$	renal fraction of final excretion
Warfarin	~ 40 h	~ 90%

Warfarin dose in RI

- moderate RI Δ dose - 9.5 %
- severe RI Δ dose - 19 %

→ adjust dose to INR

Vitamin K antagonists (VKA)

- since 1950s
- metabolism: hepatic

	$t_{½}$	renal fraction of final excretion
Acenocoumarol	~ 8-11 h	~ 60%
Warfarin	~ 40 h	~ 90%
Phenprocoumon	~ 160 h	~ 35%

"Warfarin related nephropathy"

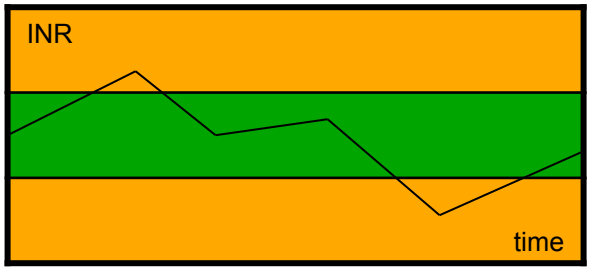
- over-anticoagulation (INR > 3.0)
  → renal function can decrease

- Cohort study, n=4006, 5 years
- WRN event: SC increased by 0.3 mg/dl
  within 1 week after INR > 3.0
- WRN in 20% (complete population),
  in 33% (patients with CKD)

- 1-year mortality with WRN 31%
  without WRN 19%

VKA: time in range

Meta-analysis	60%
Anticoagulation clinics or family doctor	32 - 77%
self-monitoring target range	72%
self-monitoring safety range 2.0 – 4.5	95%



Reynolds. Chest 2004:1938-45 / Heneghan. Lancet 2006:404-11 / Fritschi. Swiss Med Wkly 2007:252-8

VKA and severe RI

- adjust dose to target INR
- dose may be lower (20%)
- inter-individual variability
- **caution: over-anticoagulation**
  - bleeding risk
  - kidney damage

  → more frequent INR checks

  → patient education

Unfractionated heparin (UFH)

- discovered 1916, clinical trials 1935
- sulphated glycosaminoglycan, 12-15 kDa
- bound to plasma proteins
- Metabolism: RES, liver heparinases
- Excretion: renal, mostly inactive, depolymerized

- $t_{½}$ 30-120 min

→ continuously i.v.
→ frequently s.c. (bioavailability only 15-40%)

Unfractionated heparin (UFH)

- Liver function / kidney function
- Acute phase

- Monitoring: anti-Xa activity, aPTT, TT, PiCT

- **Adjust dose to target range**

- Advantages
  - short $t_{½}$
  - antagonist Protamine

LMWH

- depolymerized UFH
- in general more effective and safer than UFH

- known for renal clearance → accumulation

- intermittent use for hemodialysis

LMWH: Metabolism & Elimination

LMWH *

Radioactivity 100%

1. LMWH and Renal Clearance

Urine

Radioactivity 69%

LMWH: Metabolism & Elimination

LMWH *

Radioactivity 100%
Anti-Xa activity 100%

1. LMWH and Renal Clearance

Urine

Radioactivity 69%
Anti-Xa activity 10%

Palm & Mattsson. Thromb Haemost 1987:932-5 / Collignon. Thromb Haemost 1995:630-40 / Frydman. Haemostasis 1996;Suppl 2:24-38

LMWH: Metabolism & Elimination

LMWH *

Radioactivity 100%
Anti-Xa activity 100%

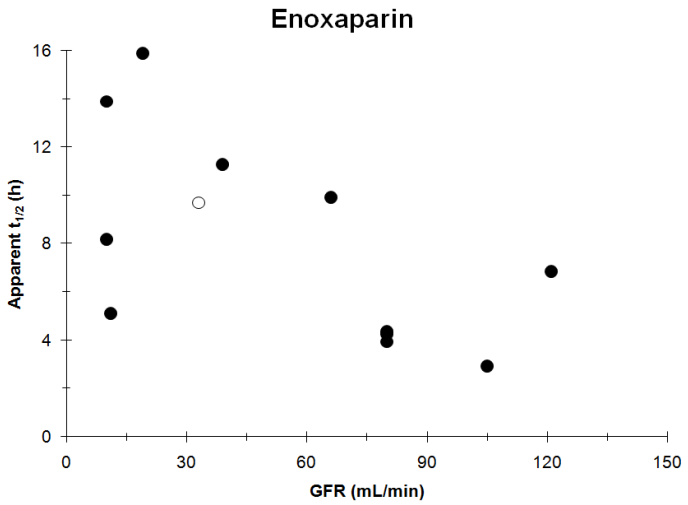
2. Various LMWH

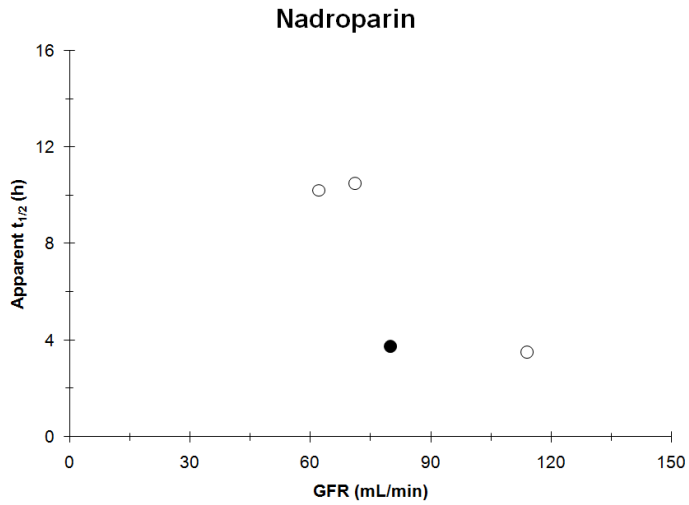
	Renal fraction of total drug clearance
Dalteparin	3%
Nadroparin	4%
Enoxaparin	6-8%

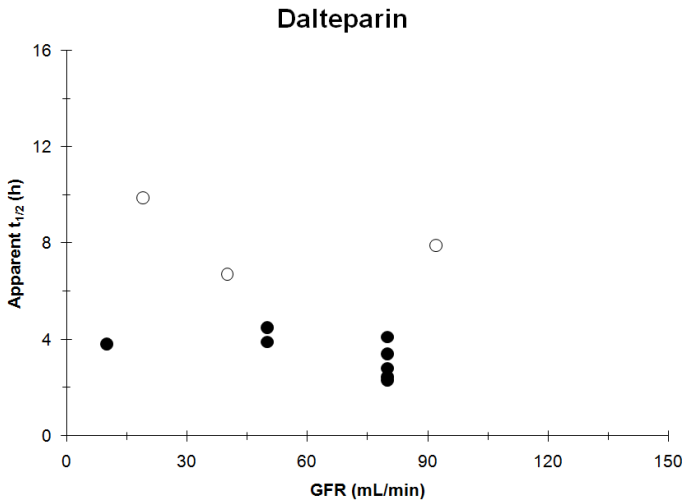
Urine

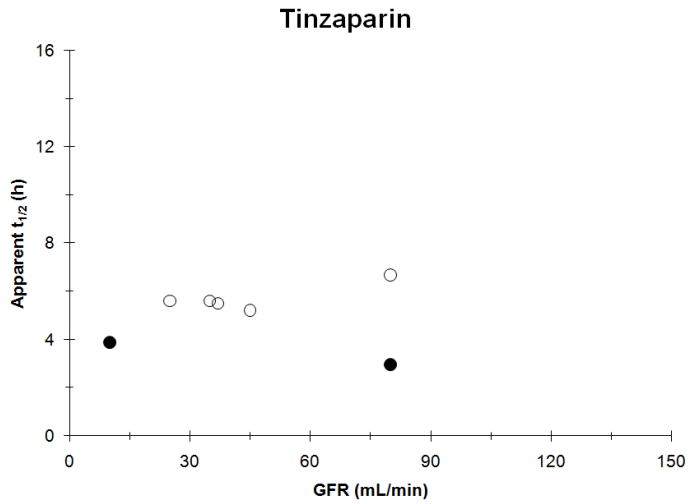
Radioactivity 69%
Anti-Xa activity 10%

Apparent $t_{1/2}$









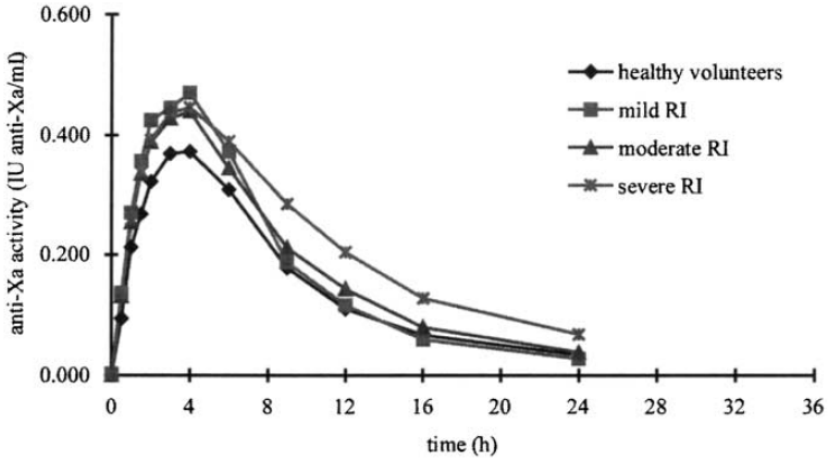
Schmid et al. Swiss Med Wkly 2009:438-52

Properties of LMWHs

		LMWH				
	UFH	Tinzaparin	Dalteparin	Enoxaparin	Nadroparin	Fondaparinux
MW (kDa)	15	6.5	6	4.5	4.3	1.7
anti-Xa : IIa	1.0	1.5-1.8	2.2-2.5	1.8-2.0	2.5-4.0	>30
Renal fraction of clearance						
Accumulation						

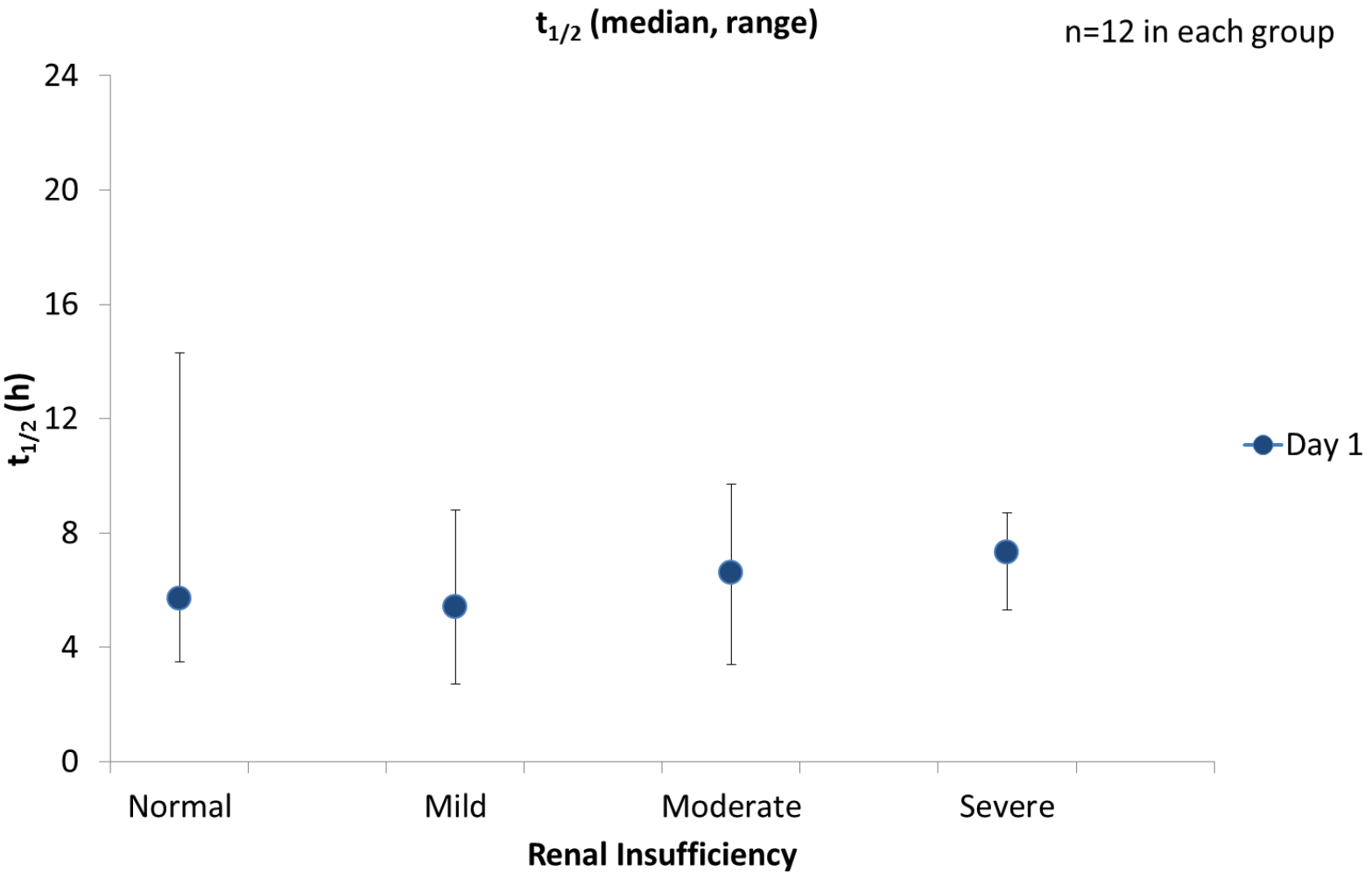
Observation time

- Enoxaparin 40 mg / d
- n=12 in each group
- Pharmacokinetic profiles



RI, renal impairment

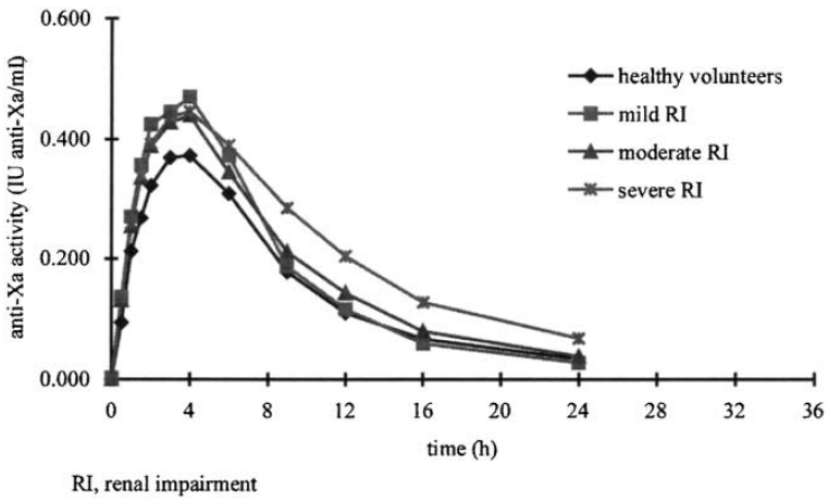
Observation time



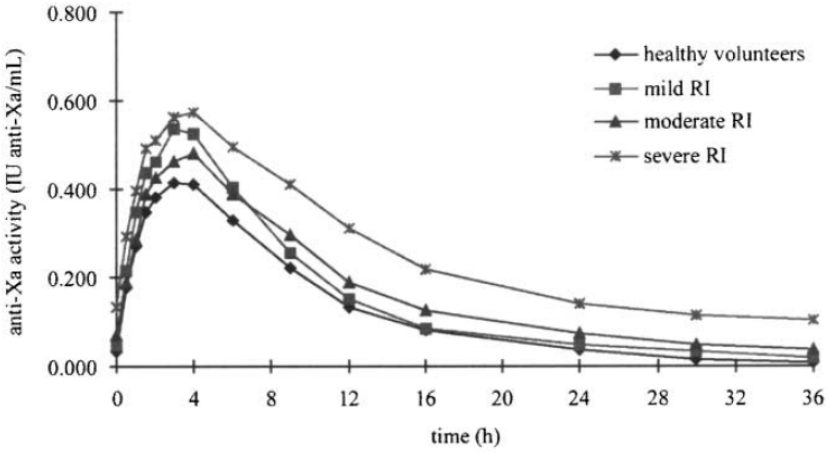
Data from Sanderink et al. Thromb Res 2002:225-31

Observation time

- Enoxaparin 40 mg / d
- n=12 in each group
- Pharmacokinetic profiles

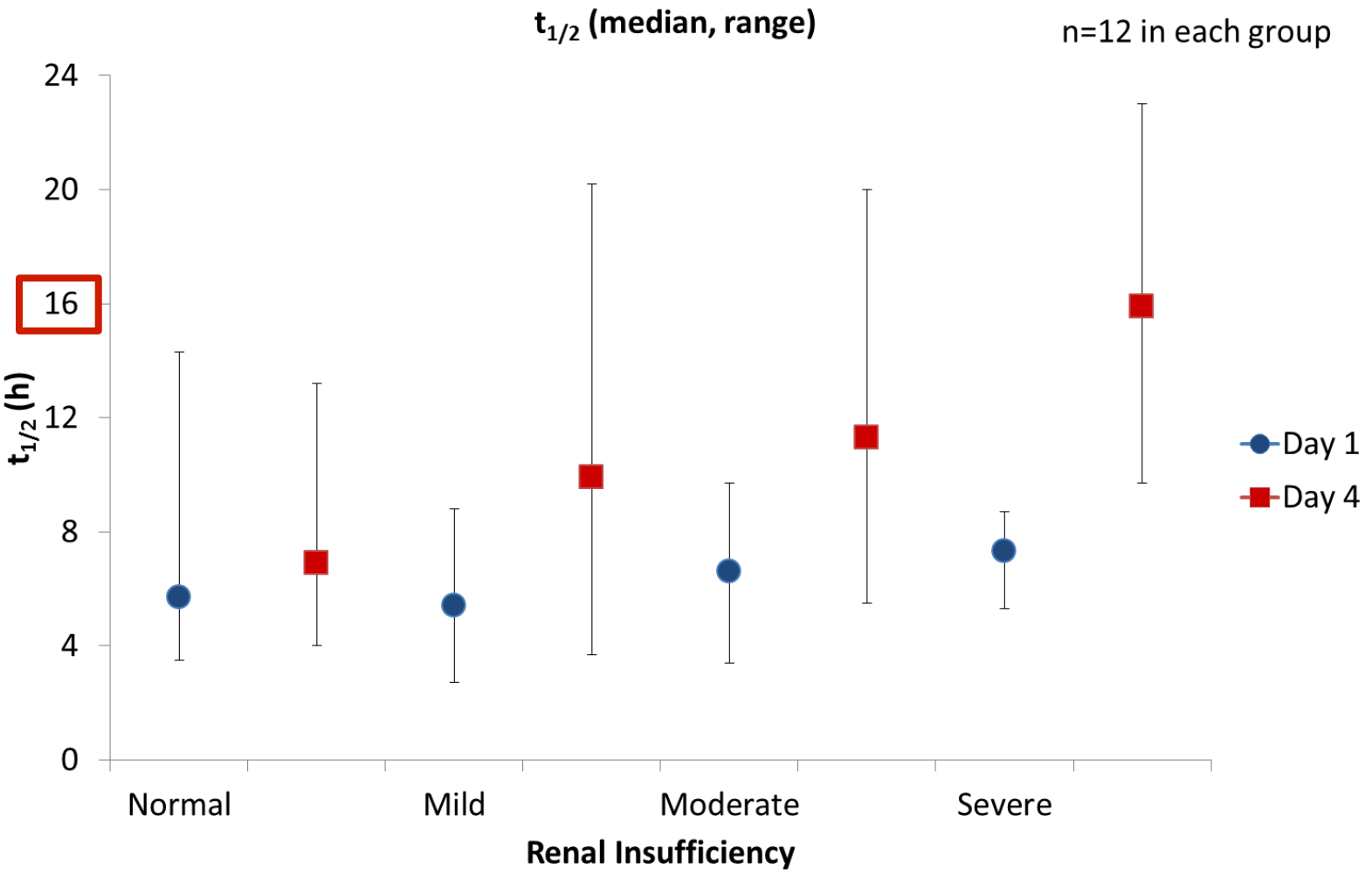


RI, renal impairment



RI, renal impairment

Observation time



Data from Sanderink et al. Thromb Res 2002:225-31

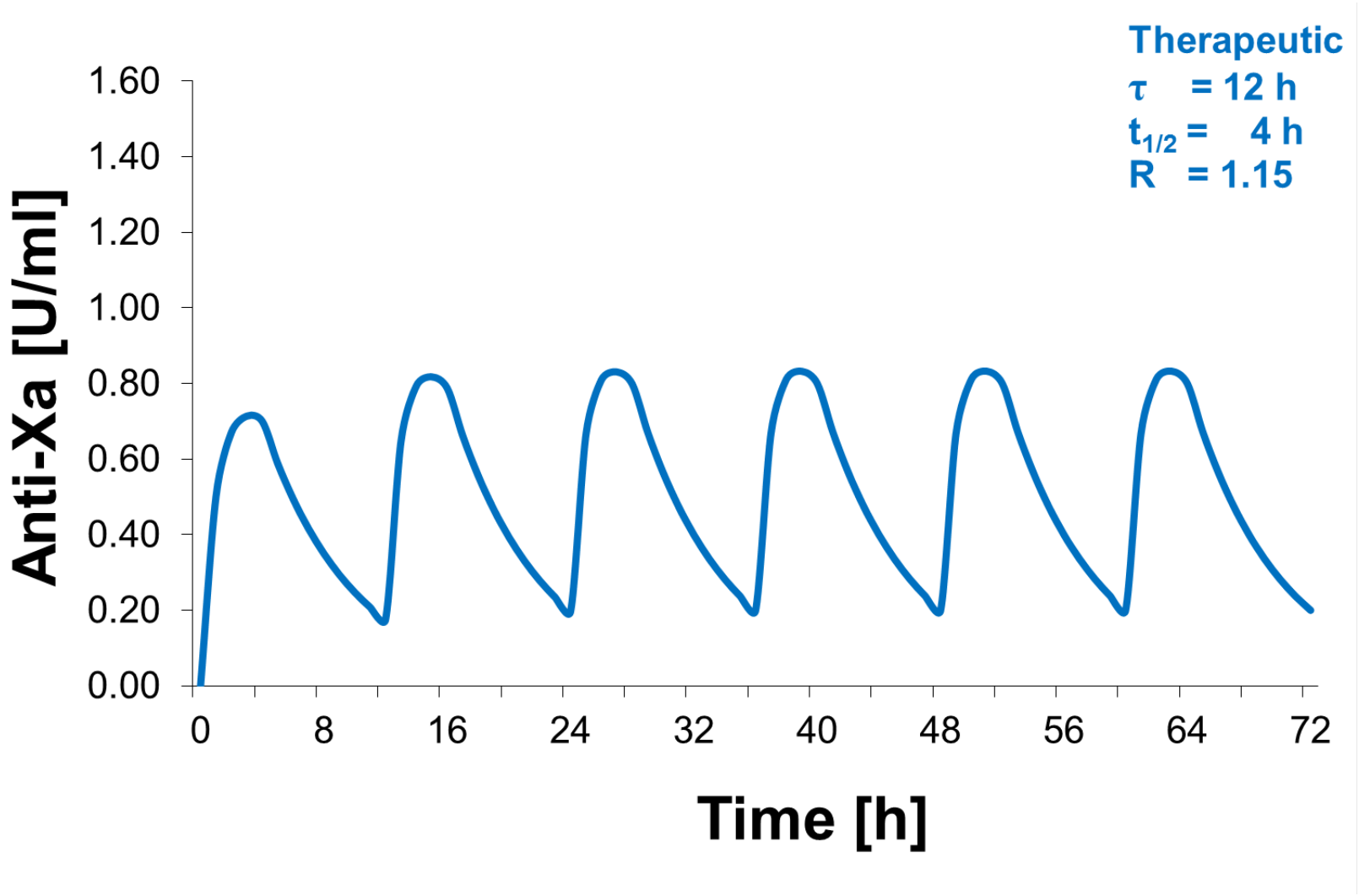
$t_{1/2}$ vs. τ

- Bioaccumulation related to ratio of $t_{1/2}$ and τ

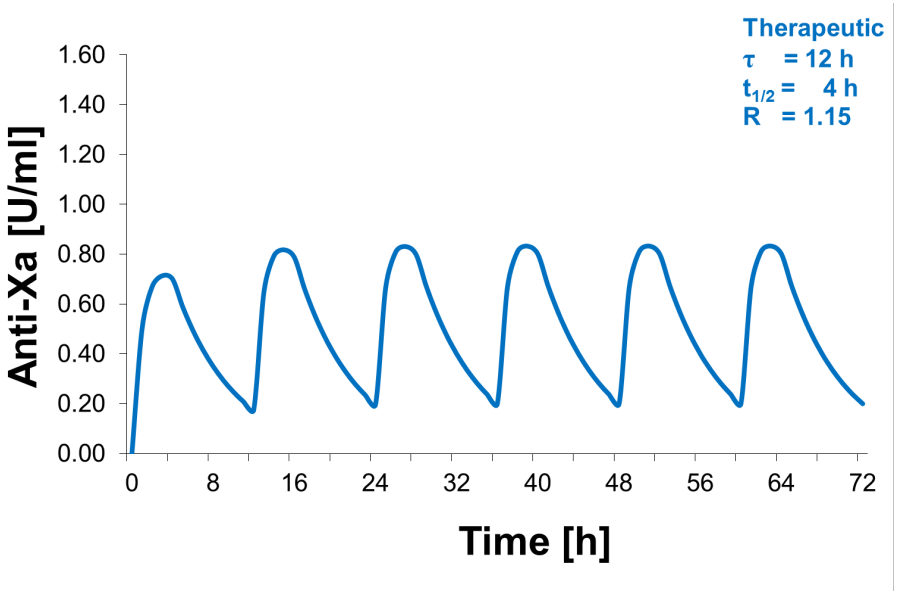
- LMWH $t_{1/2}$ 3-4 h
- Prophylaxis τ 24 h
- Therapeutic τ 12 h (or high dose / 24 h)

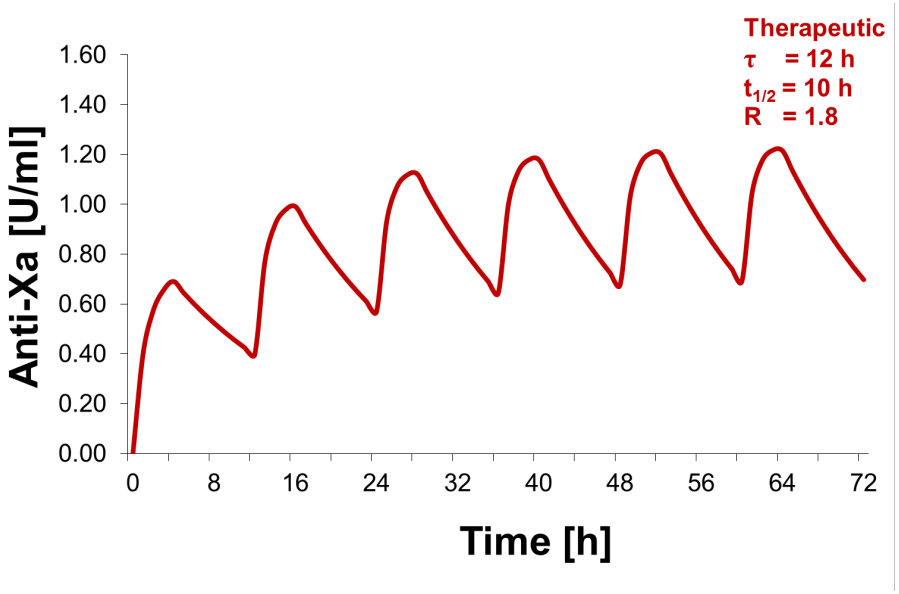
- Consequence: Recommendations for prophylaxis (may) differ from therapy

$t_{1/2}$ vs. τ

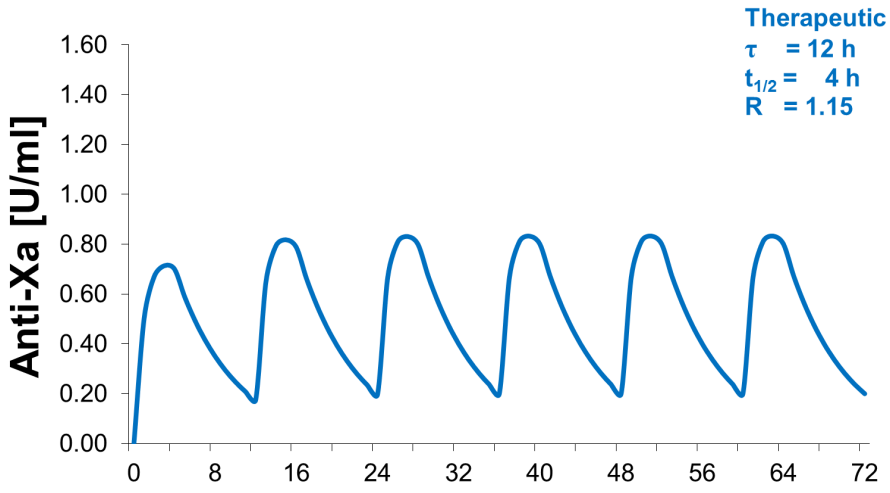

Therapeutic
τ = 12 h
t1/2 = 4 h
R = 1.15
Anti-Xa [U/ml]
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72
Time [h]

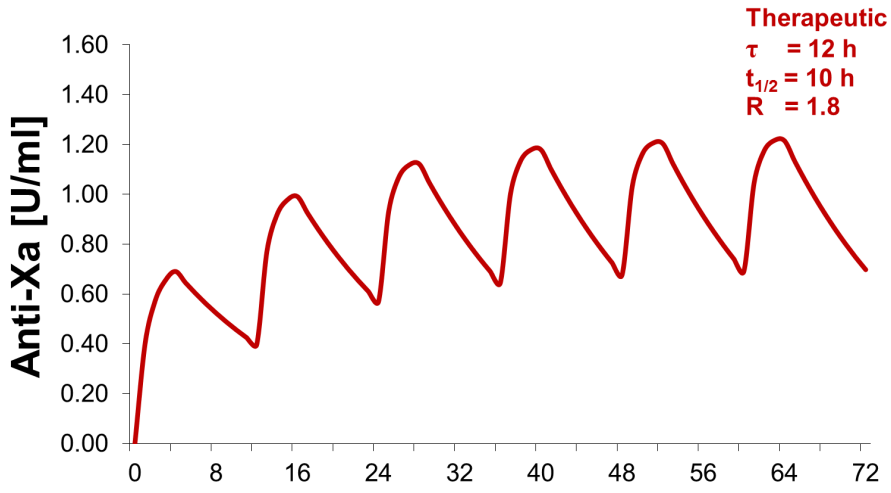
$t_{1/2}$ vs. τ

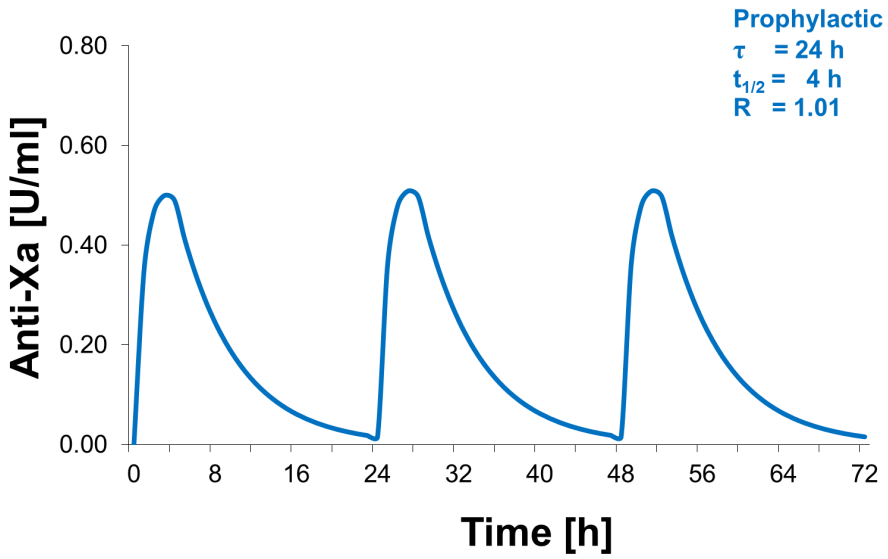

Therapeutic
τ = 12 h
t1/2 = 4 h
R = 1.15
Anti-Xa [U/ml]
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72
Time [h]

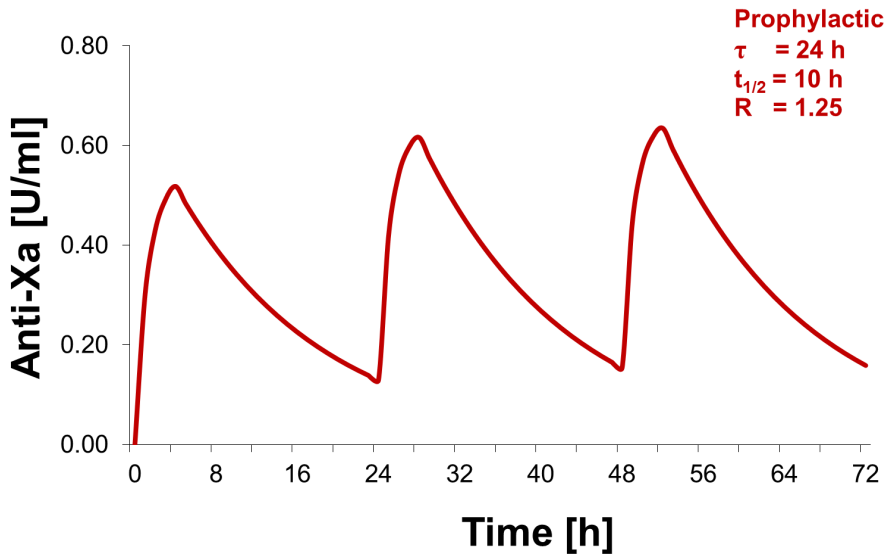

Therapeutic
τ = 12 h
t1/2 = 10 h
R = 1.8
Anti-Xa [U/ml]
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72
Time [h]

$t_{1/2}$ vs. τ


Therapeutic
τ = 12 h
t1/2 = 4 h
R = 1.15
Anti-Xa [U/ml]
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72


Therapeutic
τ = 12 h
t1/2 = 10 h
R = 1.8
Anti-Xa [U/ml]
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72


Prophylactic
τ = 24 h
t1/2 = 4 h
R = 1.01
Anti-Xa [U/ml]
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72
Time [h]


Prophylactic
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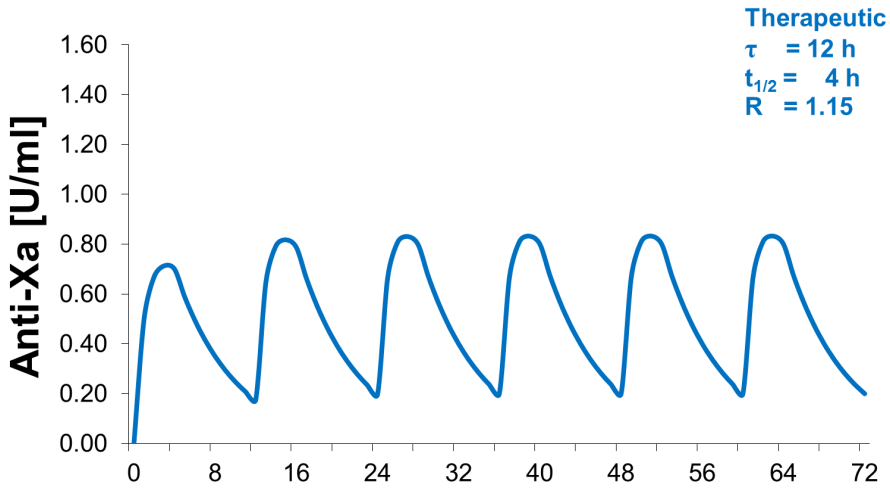
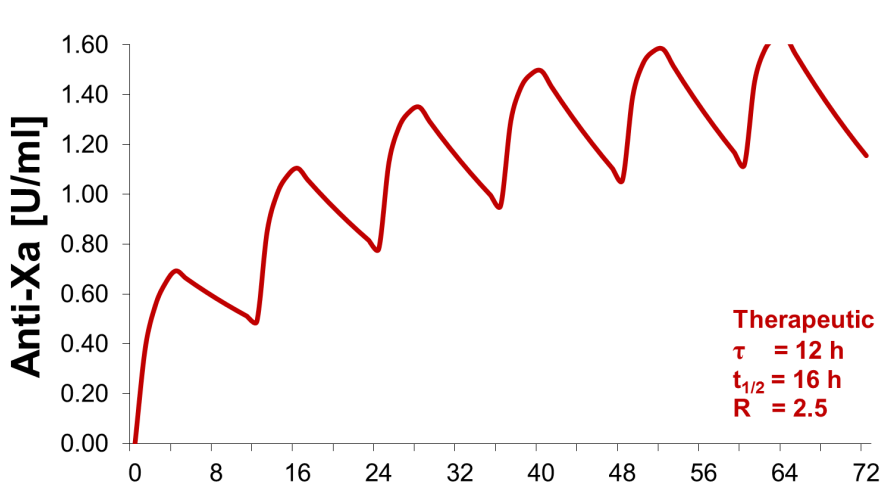
t1/2 = 10 h
R = 1.25
Anti-Xa [U/ml]
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72
Time [h]

$t_{1/2}$ vs. τ


Therapeutic
τ = 12 h
t1/2 = 4 h
R = 1.15
Anti-Xa [U/ml]
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72


Therapeutic
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t1/2 = 16 h
R = 2.5
Anti-Xa [U/ml]
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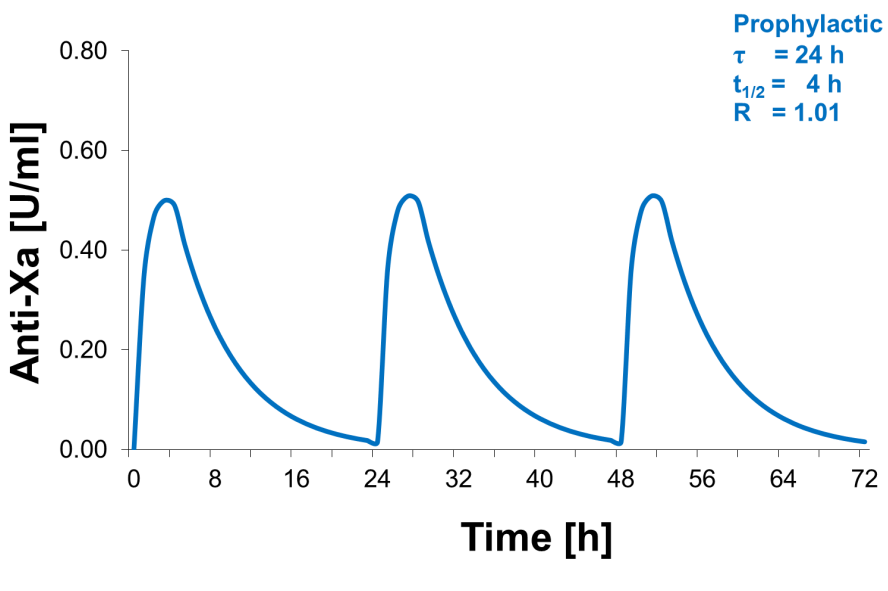
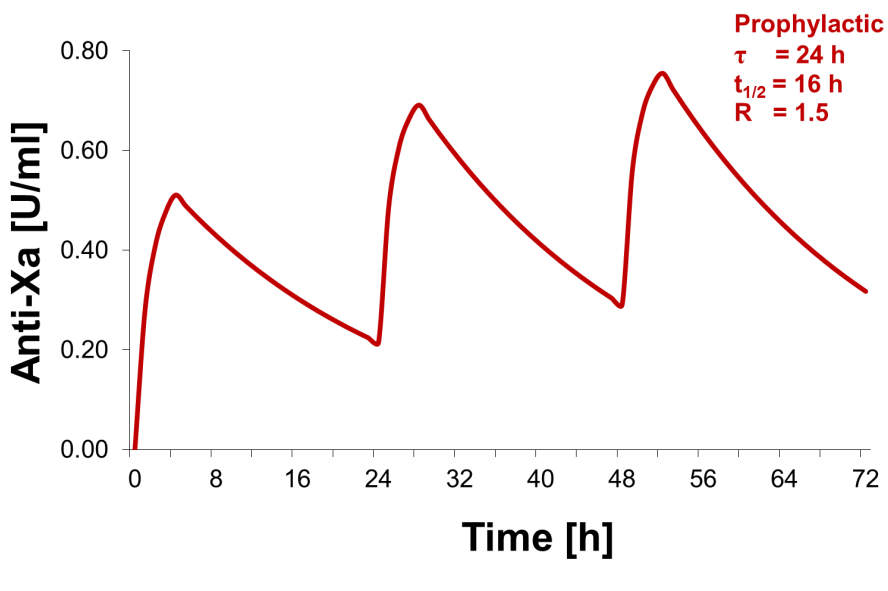
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72


Prophylactic
τ = 24 h
t1/2 = 4 h
R = 1.01
Anti-Xa [U/ml]
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72
Time [h]


Prophylactic
τ = 24 h
t1/2 = 16 h
R = 1.5
Anti-Xa [U/ml]
0.80
0.60
0.40
0.20
0.00
0
8
16
24
32
40
48
56
64
72
Time [h]

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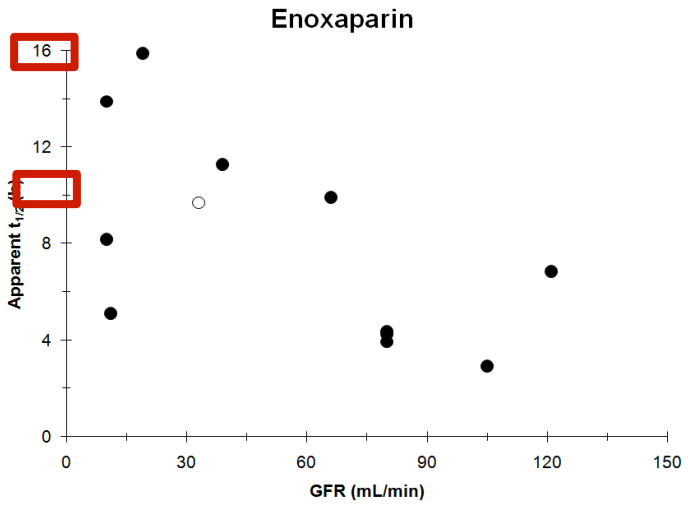
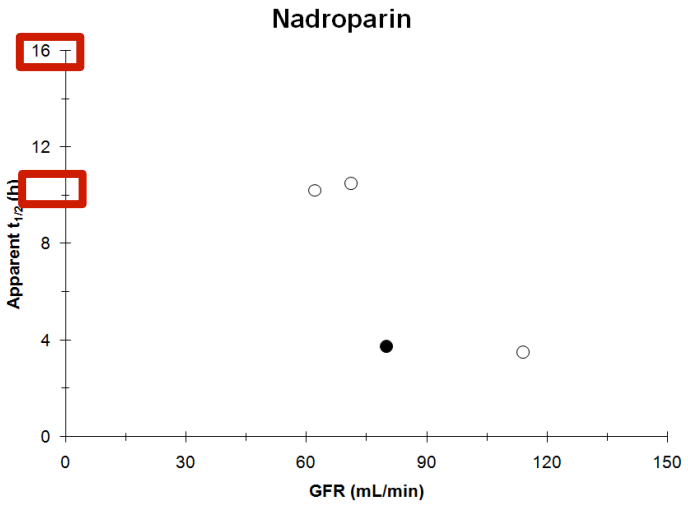
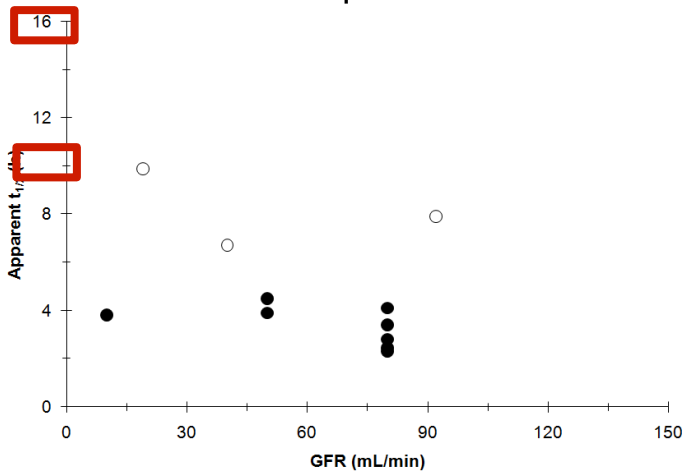
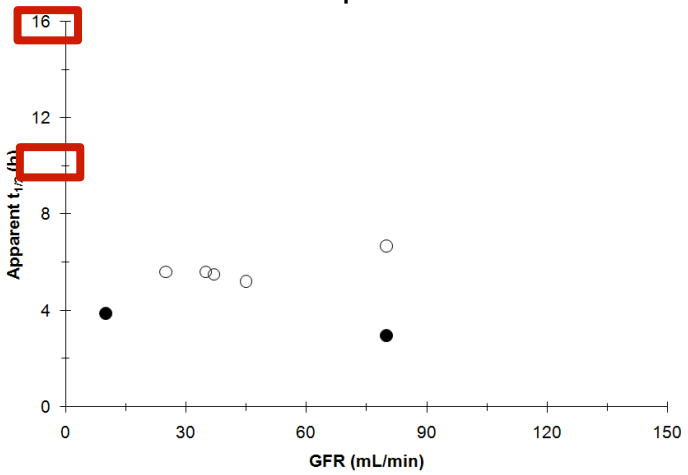
Apparent $t_{1/2}$









LMWH

- various LMWH
  →different properties
  →different pharmacokinetics
- Different setting: Prophylaxis – Therapy
  – Recommendations (may) differ
- Long-term data needed for proper PK data
- Clinical end points

Enoxaparin

- Most data: pharmacokinetic and clinical
- Lots of data on acute coronary syndrome
- Dosing suggestion for severe RI in drug monograph

Enoxaparin

- Therapeutic
  - ACS, severe RI (post-hoc analysis)
    TE event 26% compared to no RI 17% (trend)
    Bleeding 6.6% compared to no RI 1.1% (sig.)
    Bleeding: No difference whether UFH-LMWH
  - Dosing scheme deduced and prospectively validated
    severe RI: use 65% of dose
    adjust to target peak anti-Xa 0.5 – 1.0 U/ml

Enoxaparin

- Therapeutic
  - ACCP & product monograph: dose reduction to 50%

- Prophylactic
  - ACCP & product monograph: dose reduction to 50%
  - USA: 2x 30 mg/d → 1x 30 mg/d
  - Europe: 1x 40 mg/d → 1x 20 mg/d

  - risk of under-dosage?

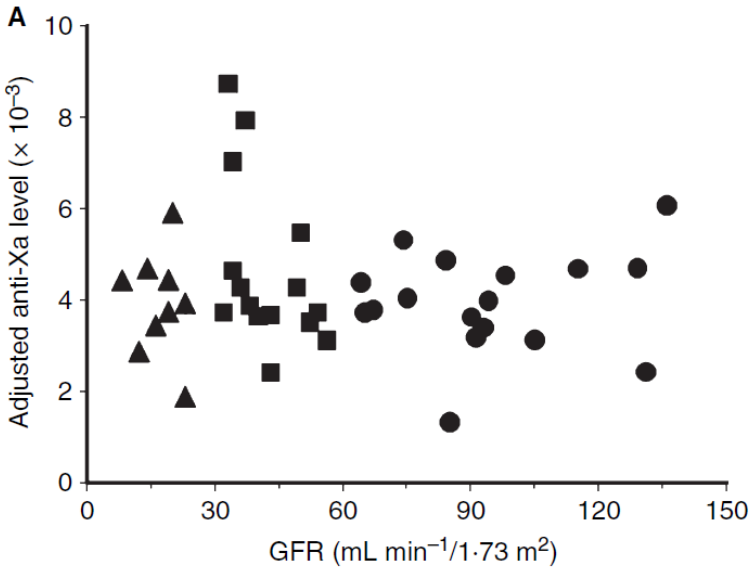
Nadroparin

- Therapeutic
  - significant increase in peak anti-Xa already with mild RI
  - calculated $t_{½}$: 10 h with GFR 60 ml/min

Dalteparin

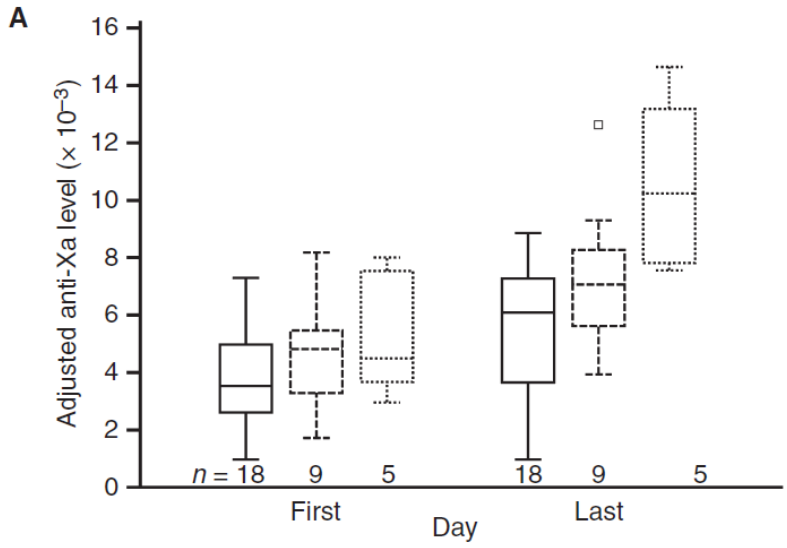
- Prophylactic
  - ICU: n=138, CrCl 19 ± 7 ml/min
    anti-Xa in range 0.29 – 0.34 U/ml
    for median 7 days (IQR 4-12)
  - general ward: pharmacokinetics
    no bioaccumulation > 30%
    for median 10 days (4-13)

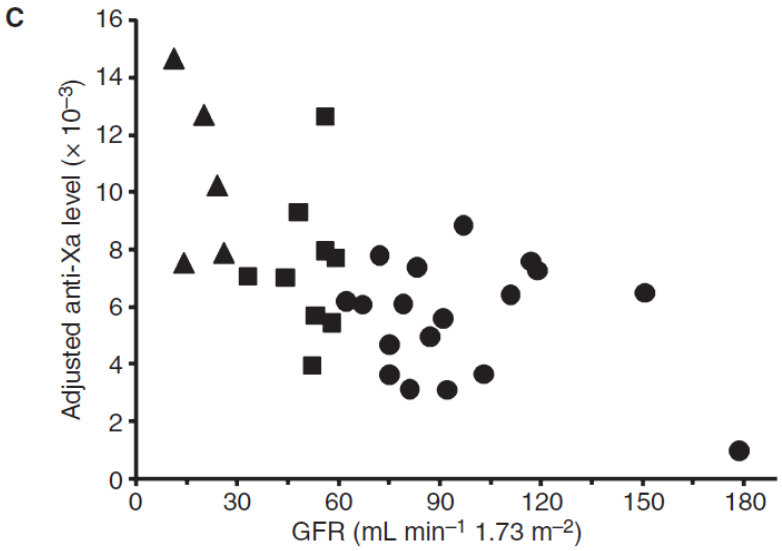
$$\text{adjusted anti-Xa}\,[\text{kg mL}^{-1}] = \frac{\text{anti-Xa}\,[\text{U mL}^{-1}] \cdot \text{weight}\,[\text{kg}]}{\text{dose}\,[\text{U}]}$$



Dalteparin

- Therapeutic
  - general ward: pharmacokinetics for median 6 days (IQR 4-10)





Tinzaparin

- Therapy without dose adjustment
  - 10 days in 8 patients
    CrCl 20-29 ml/min
    no bioaccumulation

- Prophylaxis
  - 8 days in 27 elderly patients
    CrCl 37 ± 13 ml/min
    no significant bioaccumulation

Tinzaparin

- IRIS: Therapy of VTE, RCT, 25% with CrCl ≤ 30 ml/min
- Evaluation on day 90 of treatment
- stopped after interim analysis

	unadjusted Tinzaparin 175 U/kg/d VKA (overlap)	UFH adjusted by aPTT VKA (overlap)	RR (95% CI)
n	269	268	
CrCl	39.9 ± 12.2 ml/min	39.8 ± 11.9 ml/min	
Mean Exposure	7.9 d	7.5 d	
Recurrent VTE	5.9%	3.4%	1.8 (0.8–3.9)
Bleeding (s.c. period)	6.7%	5.6%	1.2 (0.6–2.3)
Death any cause	11.5%	6.3%	1.8 (1.03-3.2)

Certoparin

- Prophylaxis
- sub-group analysis CERTIFY
- GFR ≤ 30 ml/min/1.73 m^2

	Certoparin 3000 U/d	UFH 5000 U 3x/d	OR (95% CI)
n	97	92	
Exposure	9.5 ± 3.9 d	9.1 ± 3.5 d	
comb. TE events	6.5%	2.6%	2.60 (0.49 – 13.9)
Bleeding events	5%	14%	0.33 (0.11 – 0.97)
Death any cause	5.4%	5.8%	0.92 (0.26 – 3.30)

Summary I

- Evaluate renal function, may change
- VKA
  - adjust dose to INR target value
  - expect ~20% lower dose
  - avoid INR > 3
- UFH
  - Adjust dose to monitoring

Summary II: LMWH & severe RI

- Evaluate bleeding and thrombosis risk → UFH?
- Monitor anti-Xa activity

LMWH *	Prophylaxis	Therapy
Certoparin	3000 U/d	?
Dalteparin	5000 U/d	? adjust to anti-Xa
Enoxaparin	50%: 20mg/d ?	~50%: detailed scheme
Nadroparin	?	?
Tinzaparin	4500 U/d	? 1x 175 U/ kg / d
* alphabetically listed; summarizing table – evidence varies for each drug		

"Old" anticoagulants

- "well-known" anticoagulants
  - clinical experience
  - rare side effects

- Severe RI: evidence by clinical end-points still limited for several anticoagulants

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