LOW MOLECULAR WEIGHT HEPARIN PROPHYLAXIS IN RENAL IMPAIRMENT

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Outline

- Pros and cons of low molecular weight heparin (LMWH)
- Review of existing literature
- Excretion of LMWHs and unfractionated heparin (UFH)
- NHS Lothian Venous thromboembolism (VTE) risk assessment
- VTE prophylaxis guideline in Edinburgh Renal Unit
- Evaluation of peak anti-factor Xa level - results
- Case studies
- Areas of concern

Pros and Cons of LMWH

- ↓ Dosing frequency
- Ease of administration
- ↓ Risk of HIT
- More predictable anticoagulation response
- Dose independent elimination
- More cost effective

- Risk of accumulation in renal impairment
- Not licensed in severe renal impairment
- Variation among different LMWHs in elimination, half-life and bioavailability

Eur J Clin Pharmacol (2015) 71:921–929
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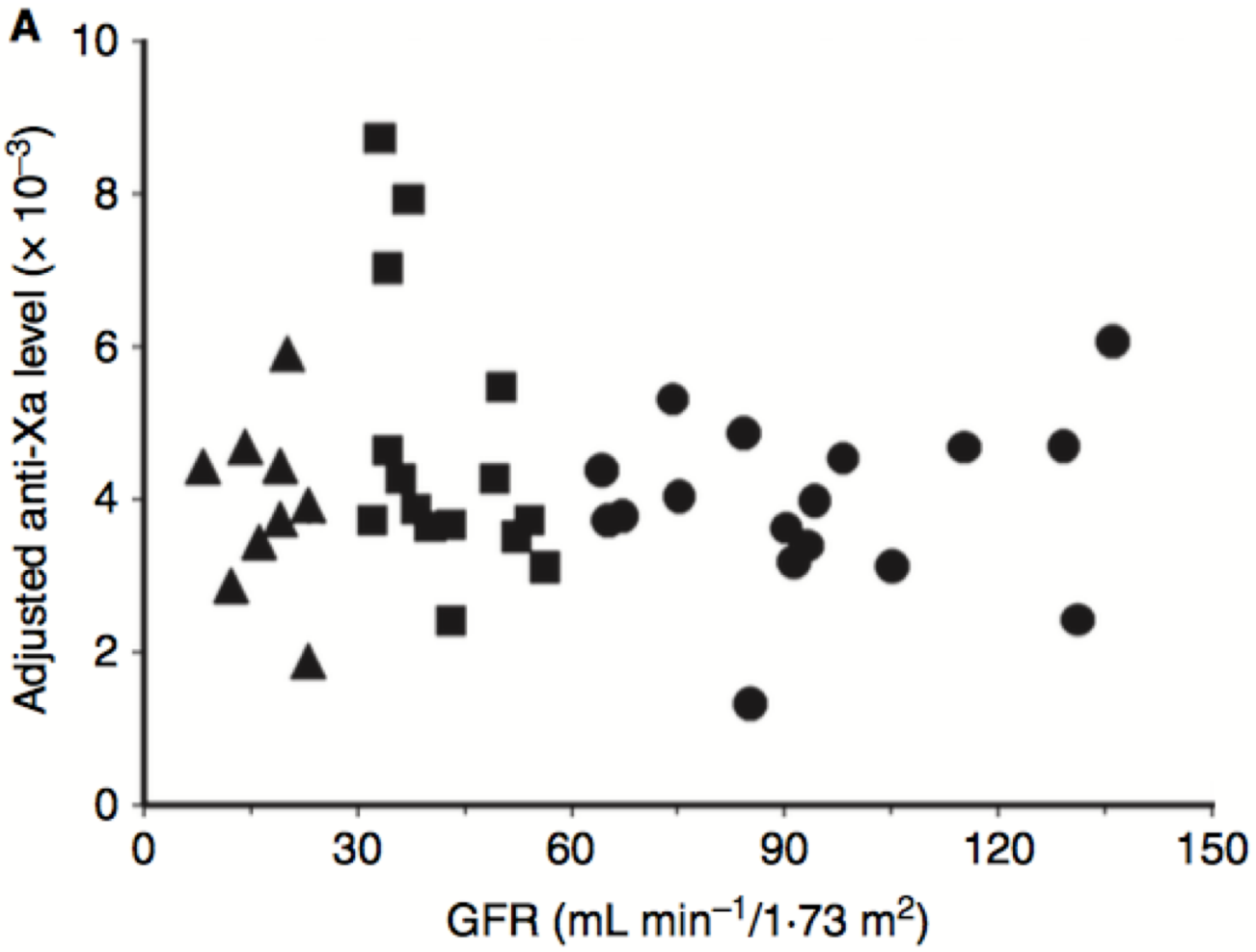
REVIEW ARTICLE

A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency

Ferdows Atiq[1] · Patricia M.L.A. van den Bemt[1] · Frank W.G. Leebeek[2] · Teun van Gelder[1,3] · Jorie Versmissen[3]

***Lack of data for patients on chronic renal replacement therapy*

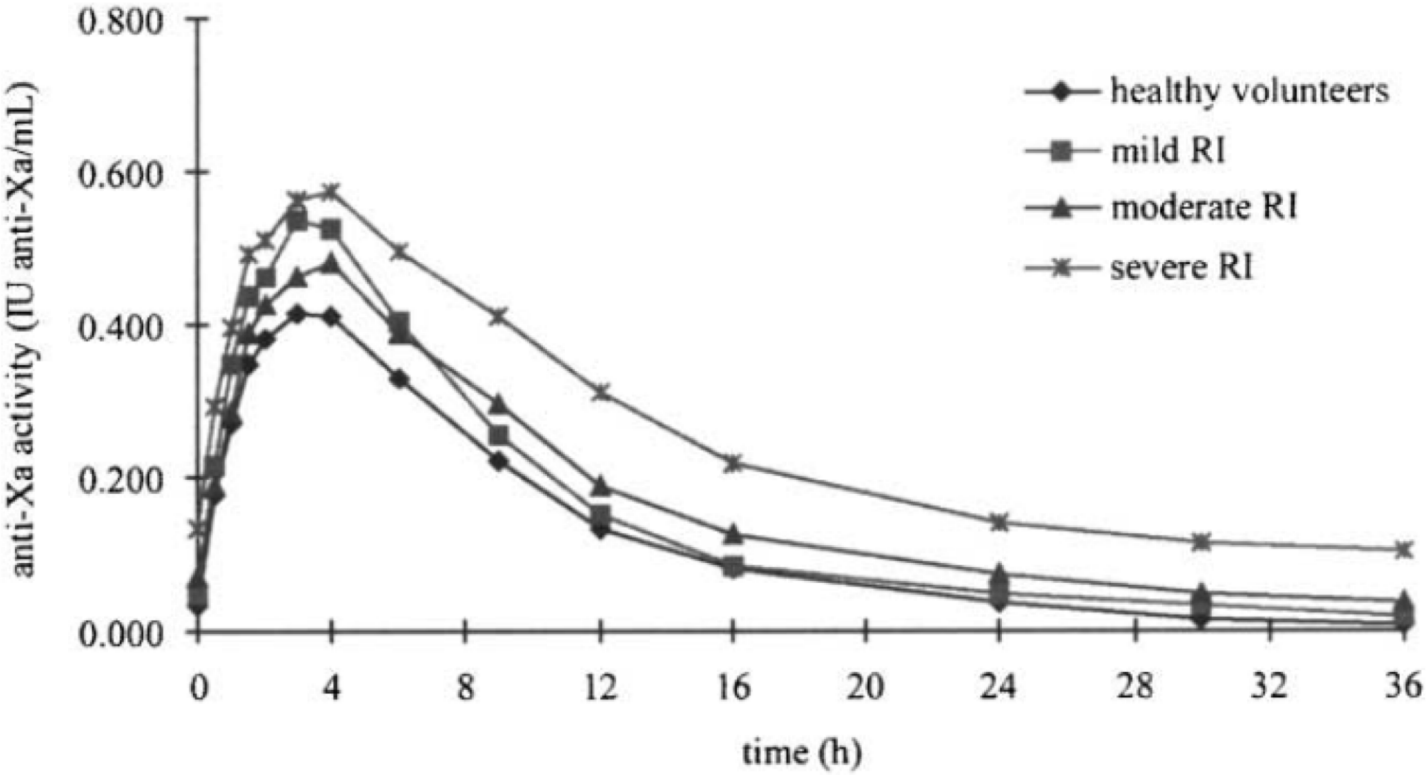


Schmid et al 2009 (n=42):
Compared peak anti-factor Xa levels in normal to mild to moderate and severe renal impairment on prophylactic dalteparin (dose adjusted with weight) in medical & surgical wards.

Table 3. Serial Anti-Xa Levels at 0, 1, 2, 4, 8, 12, 20, and 24 Hours After a Targeted 3, 10, and 17 Days of Dalteparin Treatment[a]

Hours After Dalteparin Administration	Median (IQR) Anti-Factor Xa Levels		
	After 3 Days of Dalteparin Prophylaxis (n=102)	After 10 Days of Dalteparin Prophylaxis (n=46)	After 17 Days of Dalteparin Prophylaxis (n=15)
0 (Before treatment)	<0.06 (<0.06-<0.06)	<0.06 (<0.06-<0.06)	<0.06 (<0.06-0.08)
1	0.16 (0.10-0.26)	0.20 (0.11-0.29)	0.23 (0.19-0.25)
2	0.28 (0.19-0.40)	0.29 (0.18-0.39)	0.32 (0.25-0.38)
4	0.29 (0.20-0.42)	0.35 (0.24-0.43)	0.34 (0.27-0.45)
8	0.19 (0.11-0.30)	0.23 (0.09-0.31)	0.17 (0.10-0.27)
12	0.09 (<0.06-0.15)	0.11 (<0.06-0.18)	0.10 (<0.06-0.29)
20	<0.06 (<0.06-0.06)	<0.06 (<0.06-0.06)	<0.06 (<0.06-0.11)
24	<0.06 (<0.06-<0.06)	<0.06 (<0.06-<0.06)	<0.06 (<0.06-0.06)

Douketis et al 2009 (n=138) the DIRECT study:
Assessed peak and trough anti-factor Xa level after a dalteparin 5000units dose in critically ill patients in ITU with severe renal impairment.



RI, renal impairment

Fig. 2. Mean plasma anti-Xa activity in the four groups of study participants on Day 4.

Sanderink et al 2002 (n=48):

Compared peak anti-factor Xa levels in healthy volunteers with different renal function after enoxaparin 40mg daily

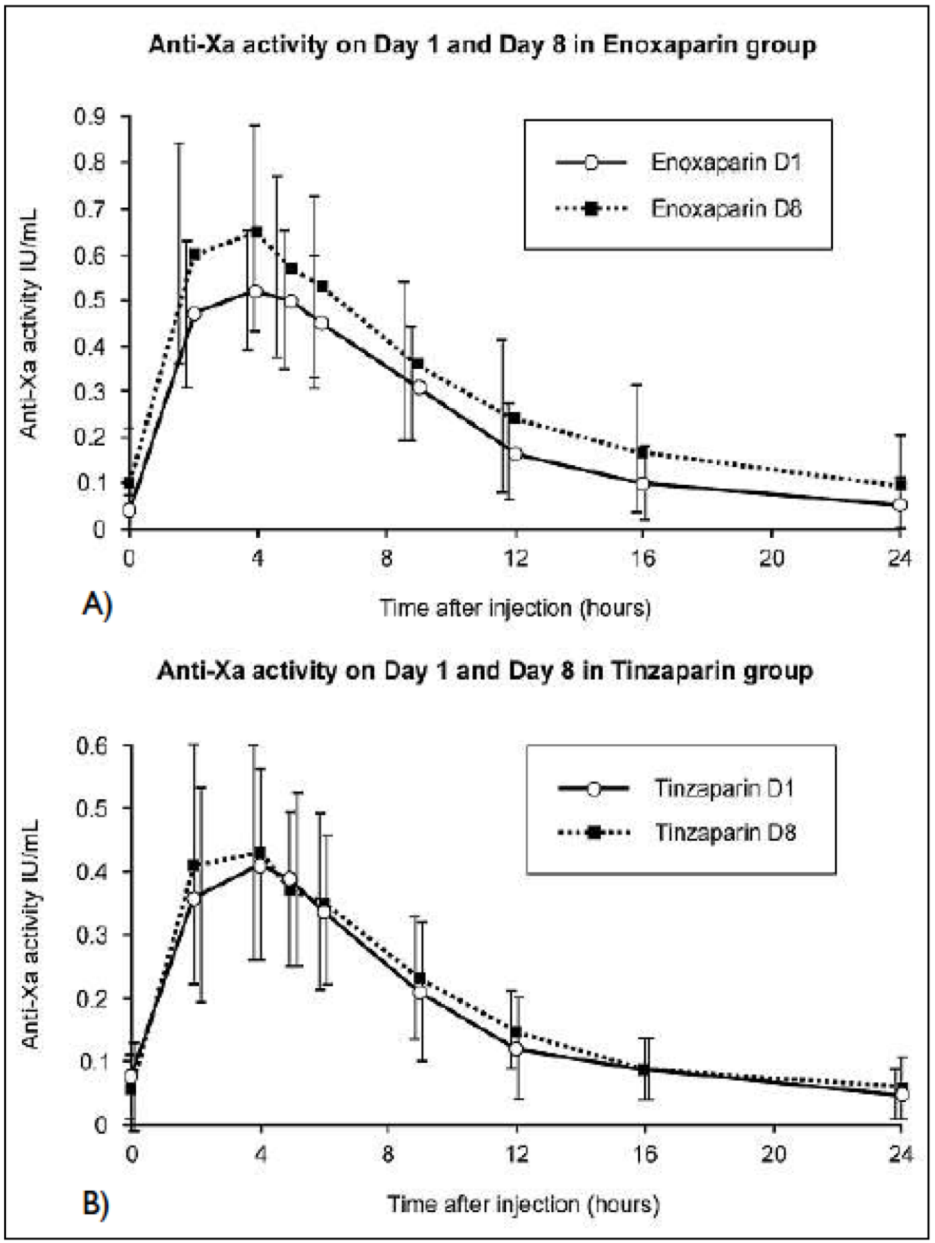


Figure 1: Comparative curves of pharmacokinetic data from patients receiving a thromboprophylaxis by enoxaparin (A) or tinzaparin (B) at day 1 and day 8 (n=50).

Mahe et al 2007 (n=50):

Compared anti-factor Xa activity between prophylactic enoxaparin and tinzaparin in patients aged ≥75years with CrCl 20-50ml/min and body weight <65kg.

Excretion of LMWHs and UFH

Cellular elimination

	MW (Da)	$T_{1/2}$ (hours)
UFH	15,000	0.5 to 1.5
Tinzaparin	6,500	1.5
Dalteparin	6,000	3.5 to 4
Enoxaparin	4,400	5 to 7

Dependence on renal elimination

VTE Risk Assessment

Risk Factors

VTE Prophylaxis

Bleeding Risk

- Age >60 years
- BMI ≥ 40
- Recent surgical procedure
- Chronic conditions (COPD, CCF, Diabetes)
- Critical care admission
- Haematological disorders
- Dehydration
- Nephrotic syndrome
- COC/HRT or tamoxifen
- Acute infection
- Immobility due to hospital admission
- Active cancer or chemotherapy
- Personal/family history of VTE
- Recent cardiac event or stroke

- Severe renal disease
- Planned procedure within 6 hours
- Active bacterial endocarditis
- Platelets <70 x 10^9/l
- Post-surgery or biopsy
- Severe hepatic disease
- Recent bleeding episode
- Major trauma
- Low dry weight (<46kg)

Assessed individually on a case-by-case basis

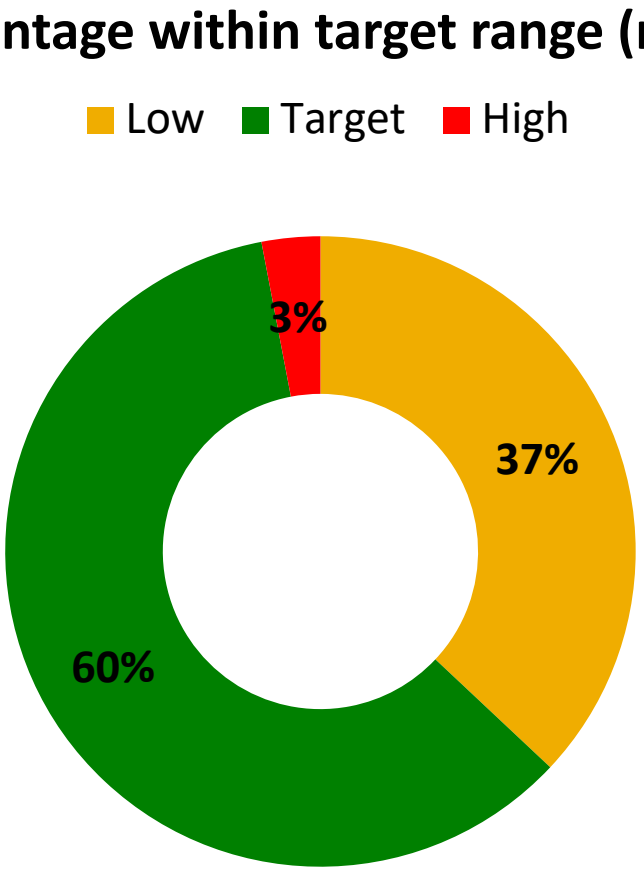
VTE Prophylaxis in Renal Unit

If **low risk,** encourage mobility or consider mechanical thromboprophylaxis

eGFR > 30 ml/min/1.73m^2	SC dalteparin 5000 units daily
eGFR 10-30 ml/min/1.73m^2	SC dalteparin 2500 units daily If very high thrombotic risk, consult specialist registrar or consultant – may consider 5000 units daily. Monitor anti-factor Xa level **after 10 days**.
eGFR < 10 ml/min/1.73m^2 or patients on renal replacement therapy/conservative management	No heparin for thromboprophylaxis unless high risk. If high risk use SC dalteparin 2500 units daily. Monitor anti-factor Xa level **after 10 days**.

- Target anti-factor Xa peak range is 0.1-0.4units/ml
- For patients requiring biopsy/surgical procedure, withhold evening dose of dalteparin and take a trough anti-factor Xa level at the same time

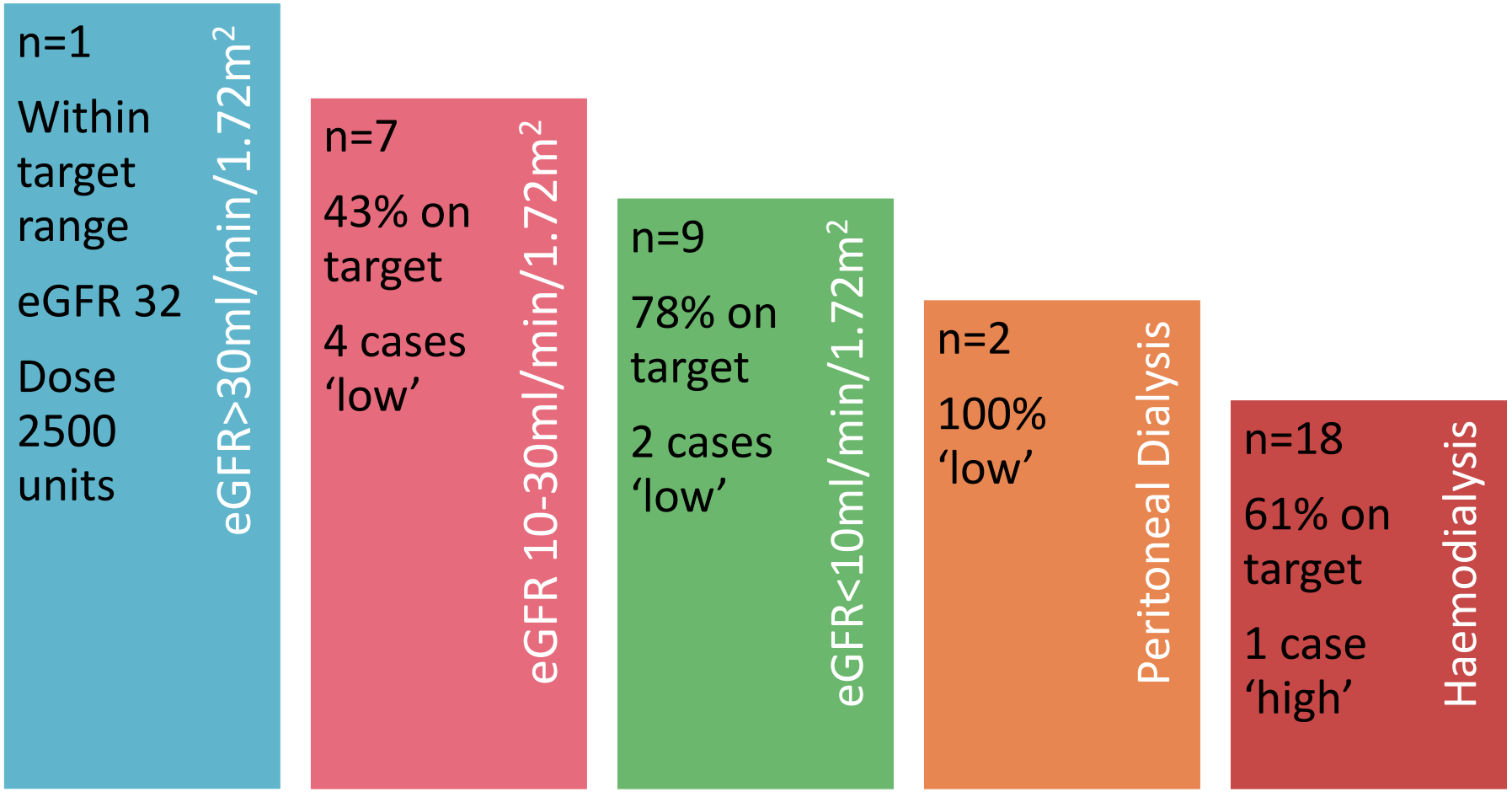
Results – Peak Anti-Factor Xa level



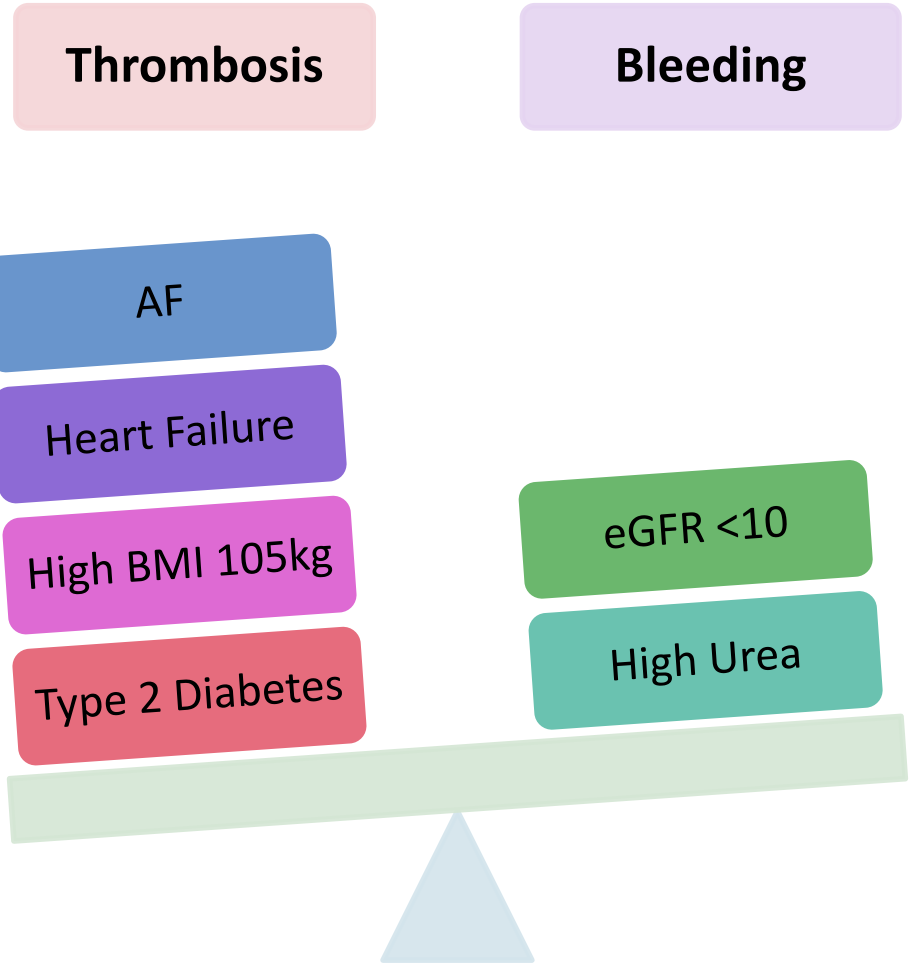
*Feb 2017 to March 2018

- SC dalteparin 2500units were used in all cases except 1 very high thrombosis risk
- No dose increase for cases with low levels except high thrombotic risk
- No related bleeding or thrombosis events reported

Assessment Based on Renal Function



Case 1

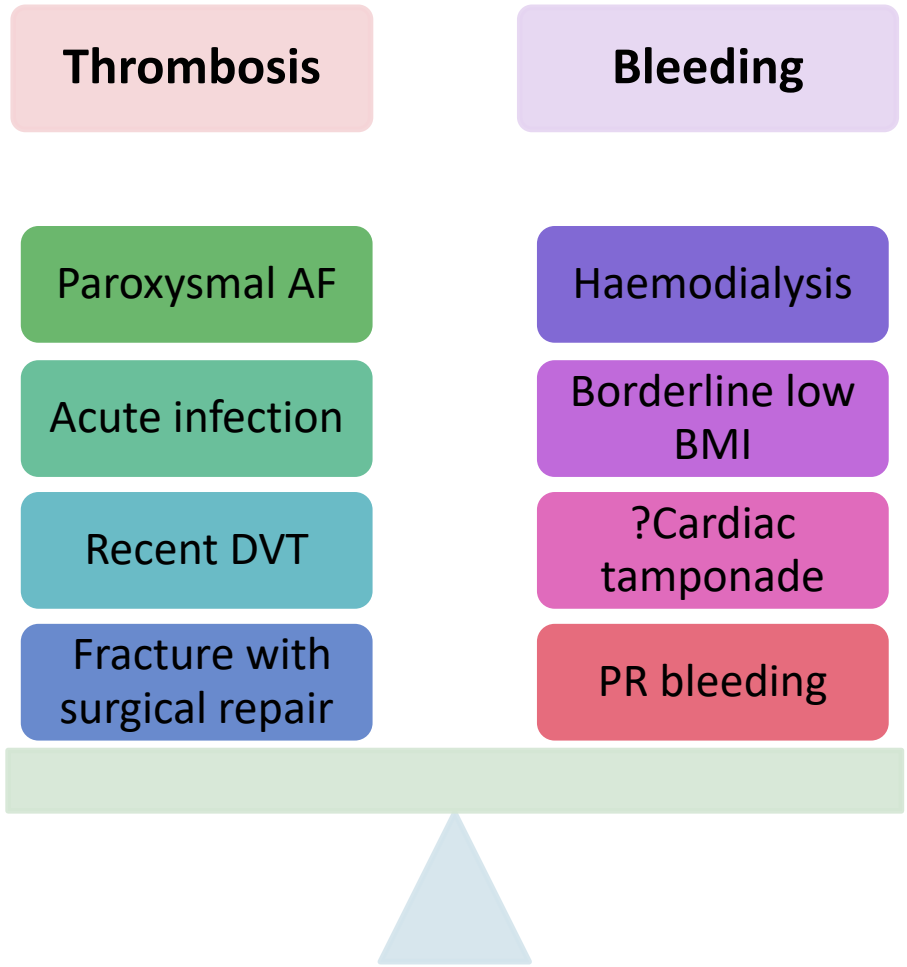


71 years
Diabetic nephropathy

- Admitted for intensive diuresis for fluid overload
- 12 day admission

- SC dalteparin 2500units – low anti-factor Xa level (0.02units/ml)
- Dose increased to 5000units due to high thrombosis risk
- Low anti-factor Xa level may be attributed to
  - Reasonable residual urine output
  - High body weight

Case 2



72 years
Polycystic kidney disease

- Admitted for acute start of HD
- 30 day admission
- Warfarin stopped due to bleeding events

- SC dalteparin 5000units – high anti-factor Xa level (0.59units/ml)
- Dose reduced to 2500units due to high bleeding risk – repeated anti-factor Xa level within range
- Withheld during bleeding episodes
- High anti-factor Xa level may be attributed to
  - Low dry weight
  - No urine output

Areas of Concern

- In the immediate transplant period where biopsy is urgent and unpredictable
- Patients who require spinal anaesthesia
- Patients with extreme low body weight
- Patients requiring surgical intervention or invasive procedures

Conclusion

- Prophylactic LMWHs can be used in severe renal impairment including patients on renal replacement therapy
- Routine anti-factor Xa monitoring is useful to determine accumulation but should be interpreted with clinical observation
- Larger studies required to further establish its safety and efficacy

Thank You