Tinzaparin and Bleeding Risk in CKD

Renal Pharmacists Network
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Sunnybrook HEALTH SCIENCES CENTRE when it matters MOST

Learning Objectives

By the end of the session participants will be able to:

- Summarize cases of advanced CKD patients with major bleeding on therapeutic tinzaparin
- Review the evidence and limitations for dosing of tinzaparin in CKD patients
- Discuss potential practice changes and approaches to mitigate bleeding risk with the use of tinzaparin in advanced CKD

CASE #1: HW

- 53F with stage 4 CKD secondary to IgA nephropathy followed in glomerulonephritis clinic

Medications
Irbesartan 225mg daily Hydrochlorothiazide 12.5mg daily prn Fish Oil 3 capsules daily

	June
Weight (kg)	93
Scr (umol/L)	213
GFR (mL/min)	22
Hgb (g/L)	113

- Developed a right MCA embolic stroke with isolated elevated anticardiolipin IgG
- Neurology recommended warfarin with tinzaparin bridging
- Plan: Start warfarin 5mg daily with Tinzaparin 16,000 units subQ daily (175units/kg subQ daily)

CASE #1 Continued

- 5 days later - INR 1.65
  - Patient reporting left sided hip pain limiting movement. No fever or chills; she denied weakness
  - Hip X-ray ordered but did not go for test
- 1 week after starting tinzaparin and warfarin
  - presented to ER with progressive worsening L hip pain with weakness of hip flexors
  - Hgb 111g/L (down from 113g/L), INR 1.8
  - Abdo/Pelvis CT - Intramuscular hematoma of the left iliacus and iliopsoas muscles. No active contrast extravasation

CASE #2: HS

- 72F with stage 5 CKD secondary to DM and HTN followed in MCKC
- PMHx: DM2, HTN, Dyslipidemia, Endometriosis, Ovarian cysts

Medications	
Eprex®	Clonidine
Ferrous fumarate	Terazosin
ECASA	Atorvastatin
Pantoprazole	Calcitriol
Linagliptin	Sodium bicarbonate

	Mar 31	ER Labs
Weight (kg)	68	
Scr (umol/L)	534	702
GFR (mL/min)	6	
Hgb (g/L)	103	68

- Diagnosed with DVT - initiated on Tinzaparin 10,000 units subQ daily
- 6 days later -Developed acute right flank pain & presented to ER
- CT abdo/pelvis – large right kidney subcapsular hematoma
- Required blood transfusion & IVC filter insertion

CASE Reflections & Questions

- Was tinzaparin the most appropriate anticoagulant?
- Was the dosing of tinzaparin appropriate for advanced stage 4/5 CKD?

Low Molecular Weight Heparin Kinetic Characteristics

	Enoxaparin	Dalteparin	Tinzaparin
Molecular weight (Da)	4500	6000	6500
$T_{1/2}$ (hr)	4.5	3-5	3-4
Bioavailability (%)	100	90	86.7
Time to peak anti-Xa activity (hr)	3-5	4	4-5
Anti-Xa/anti-IIa ratio	3.6	2.5	1.8
Cmax	1.2 ± 0.17	0.59 ± 0.25	0.87 ± 0.15
Elimination	Renal	Renal	Renal Reticuloendothelial system

Helfer et al. Am J Cardiovasc Drugs 2020

LMWH Dosing Considerations per CPS

Use in Patients with Renal Impairment

- All patients with renal impairment treated with LMWHs should be monitored carefully.
- Renal function should be assessed using a formula based on serum creatinine to estimate creatinine clearance (CrCl) level.
- Administration of LMWHs to patients with renal impairment has been shown to result in prolongation of anti-Xa activity, especially in those with severe renal impairment (CrCl <30 mL/min), leading to increased risk of bleeding.

Tinzaparin

Dosing per CPS Monograph

- Available evidence for tinzaparin demonstrates no accumulation in patients with CrCl levels down to 20 mL/minute, however, caution is recommended when treating patients with severe renal impairment. There is limited data available in patients with an estimated CrCl level below 20 mL/minute.
- Consideration of dosage adjustment in patients with severe renal impairment should be undertaken.

Therapeutic Dosing per Micromedex:

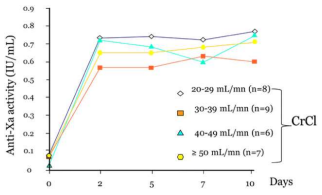
- CrCl as low as 20 mL/min: 175 units/kg subQ once daily based on total body weight

Sunnybrook Renal Insufficiency & Anticoagulant Recommendations

enoxaparin for treatment	• **CrCl <30 mL/min + patients not on dialysis:** ▪ Suggest tinzaparin as (175 units/kg SC once daily). ▪ If tinzaparin unavailable: ○ < 36 kg – consult TE Service ○ 36 - 50 kg – enoxaparin 40 mg SC once daily ○ 51 - 70 kg – enoxaparin 60 mg SC once daily ○ 71 - 90 kg – enoxaparin 80 mg SC once daily ○ 91 - 110 kg – enoxaparin 100 mg SC once daily ○ 111 - 135 kg – enoxaparin 120 mg SC once daily ○ 136 - 160 kg – enoxaparin 150 mg SC once daily ○ > 160 kg – consult TE Service ○ Consider obtaining anti-Xa level 2-4 hrs after injection (generally aim for 0.75-1.25 U/mL)

Elderly patients treated with Tinzaparin

- Prospective observational study (n=30)
- Elderly patients with mean Clcr 40.6mL/min (range 20-72) treated with tinzaparin 175U/kg/day



Siguret et al. Thromb Haemost 2000; 84(5):800-4.

TRIVET Study

OBJECTIVE	Assess tinzaparin accumulation at varying degrees of renal impairment via anti-Xa levels
DESIGN	Prospective MC (5 Centres) cohort study of patients with objectively confirmed VTE treated with tinzaparin Tinzaparin 175 IU/kg was administered subcut once daily for up to 7 days Trough anti-Xa levels were measured twice, prior to the 3rd - 5th dose and prior to the 5th - 7thdose of tinzaparin
PATIENTS	148 CKD patients stratified into 4 groups with CrCl (ml/min): >60, 30-60, <30 and HD-dependent
OUTCOME	Accumulation: defined as anti-Xa trough >0.5 IU/mL (resulted in a predefined dose reduction) Bleeding and recurrent thrombotic events were recorded.

Lim et al. J Thromb Haemost 2016;14(Supp 1): 1-168.

TRIVET Study

Table 1

CrCl (ml/min)	Patients, n*	Mean anti-Xa level (IU/L)	
		1st measurement (Day 3-5), SD	2nd measurement (Day 5-7), SD
>60	56/56	0.17 (0.12)	0.15 (0.12)
30 – 60	35/34	0.23 (0.22)	0.17 (0.09)
<30	29/26	0.29 (0.23)	0.29 (0.19)
20-29	22/19	0.25 (0.19)	0.29 (0.18)
<20	7/7	0.41 (0.32)	0.30 (0.24)
HD-dependent	25/20	0.35 (0.34)	0.33 (0.20)

*Number of patients included for 1st measurement/2nd measurement

- 5 major bleeding events occurred within 7 days (none with anti-Xa >0.5IU/mL)

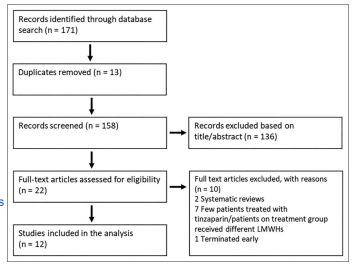
CONCLUSIONS

- Higher mean anti-Xa trough with Clcr<30 and HD-dependent
- Major bleeding events more frequent in patients with Clcr<30 (not correlated to trough levels)

Lim et al. J Thomb Haemost 2016;14(Supp 1): 1-168.

Tinzaparin Safety in Patients with Cancer & Renal Impairment: Systematic Review

- Prospective clinical trials with ≥ 20 patients assessing safety of prophylactic or therapeutic administration of tinzaparin for VTE in patients with cancer &/or renal impairment
  - administration on consecutive days and measurement of anti-Xa levels
- Primary Outcome:
  - # of patients with at least 1 bleeding event
  - Bioaccumulation measured by anti-Xa levels



Vathiotis et al. Clin App Thomb/Haemost 2021;27: 1-7.

Prospective Trials in Patients with Renal Impairment

Study (Year)	Patients	N	Mean Clcr (mL/min)	Tinzaparin Dose	Accumulation	Major Bleeding (%)
Mahe et al (2007)	>75 yrs, Clcr 20-50	55	34.7	Prophylactic	No	NA
Projean et al (2018)	eGFR <30	28	20	Prophylactic	No	0
Pautas et al (2002)	>70 yrs, Clcr >20	200	51.2	Therapeutic	No	1.5
Lim et al (2016)	<70 yrs	148	NA	Therapeutic	No	3.4
Siguret et al (2011)	>75 yrs	87	40.8	Therapeutic	No	2.3
Siguret et al (2000)	>70 yrs, hospitalized	30	40.8	Therapeutic	No	0
Bauersachs et al (2018)	Cancer pt, eGFR <60	131	*<60*	Therapeutic	No	4.3
Yeung et al (2020)	Cancer pt, Clcr 20-50	20	*20-50*	Therapeutic	No	10

Lessons Learned & Implications for Practice

- Evidence suggests discordance between anti-Xa trough levels and bleeding risk
- Major bleeding events occur more frequently with Clcr <30mL/min
- Limited data for patients with Clcr <20mL/min

- Dosing considerations for tinzaparin in stage 4 & 5
  - Full dose (175 units/kg) tinzaparin may not be safe for stage 4/5 and HD patients
  - Sunnybrook LMWH dosing: Clcr or eGFR < 30 mL/min, reduce enoxaparin dose by approx. 50% → what should be done for tinzaparin?
  - Renal Drug Handbook: "Some units routinely use a dose of 125 units/kg with GFR <20mL/min requiring full anticoagulation."
  - Need to develop specific renal dosing guidance