Study of the Bioaccumulation of Tinzaparin in Renally Impaired Patients when Given at Prophylactic Doses - The STRIP study

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Running title: Prophylactic tinzaparin in severe renal disease

Highlights

- Accumulation of LMWH is a concern in severe chronic kidney disease (CKD)
- 28 subjects with severe CKD received prophylactic tinzaparin for up to 8 days
- All had undetectable trough anti-Xa levels; half had undetectable peak levels
- Prophylactic tinzaparin dosing did not incur clinically significant bioaccumulation

Keywords: Anticoagulant; Bioaccumulation; Kidney disease; Prophylaxis; Renal insufficiency; Venous thromboembolism

Abbreviations

Low-molecular-weight heparins (LMWHs),

Venous thromboembolism (VTE),

Severe chronic kidney disease (CKD),

Unfractionated heparin (UFH),

Estimated glomerular filtration rate (eGFR),

Limit of quantification (LOQ)

Body Mass Index (BMI)

Interquantile range (IQR)

Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI)

Dear Editors,

Low-molecular-weight heparins (LMWHs) are used for the prevention of venous thromboembolism (VTE) [1]. Compared to unfractionated heparin (UFH), they offer a number of advantages, including a simplified dosing schedule, improved adherence and decreased risk for heparin-induced thrombocytopenia [2, 3]. Severe chronic kidney disease (CKD) represents a high risk for VTE in hospitalised patients (1-3). Clinicians typically prefer UFH over LMWH for thromboprophylaxis in severe CKD because of concerns with bioaccumulation and possible increased risk for bleeding [4, 5]. However, data support the use of tinzaparin in patients with moderately impaired renal function [6, 7]. The aim of this observational study was to assess the severity of accumulation of tinzaparin when given at prophylactic doses in patients with severe CKD.

Methods

The STRIP study was a prospective observational study at the Maisonneuve-Rosemont Hospital between February and September 2016. The study protocol was approved by the local research ethics board and Health Canada, and was registered with ClinicalTrials.gov (NCT02719418). Informed consent was obtained. Local thromboprophylaxis guidelines recommend a fixed daily dose of subcutaneous tinzaparin of 3500 IU, with reduction to 2500 IU for patients with body weight <40 kg or an increase to 4500 IU for patients with a BMI ≥30 kg/m^2. This study included hospitalized patients>18 years of age, with estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73m^2, who were prescribed tinzaparin for prophylaxis (nonsurgical indication). The CKD-EPI formula was used to calculate the eGFR because of its ease of use and its improved accuracy to evaluate renal function compared to the Cockcroft-Gault equation [8]. Exclusion criteria were: body mass index (BMI) >50 kg/m^2, severe hepatic impairment (Child-Pugh C), acute kidney injury with mean baseline eGFR > 30 ml/min/1.73 m^2, anuria or current renal replacement therapy (ex. hemodialysis), and use of tinzaparin at a prophylactic dose for ≥72h before recruitment. Patients receiving the following anticoagulants were also excluded: argatroban or bivalirudin (< 24h), therapeutic UFH, LMWH or oral factor Xa inhibitors (< 48h), oral direct thrombin inhibitors, danaparoid, fondaparinux, or anti-vitamin K (< 7 days), prophylactic dose of LMWH other than tinzaparin (< 48h), prophylactic dose of UFH (< 12h).

The primary outcome was bioaccumulation, defined as a peak anti-Xa activity level >20% higher on day 5 as compared with day 2 [6, 9]. Secondary outcomes were bioaccumulation between days 2 and 8 and a trough anti-Xa level >0.40 IU/ml on day 5, which is indicative of excessive anticoagulation [10]. Peak anti-Xa levels were measured 4h after dosing on days 2, 5 and 8 and trough levels were obtained within 4h of the next dose on day 5. The medical staff and the project team were blinded to anti-Xa levels. Plasma anti-Xa activity (IU/ml) was determined with the STA®-Liquid Anti-Xa chromogenic assay (Stago, France; limit of quantification (LOQ), 0.1 IU/ml). A replacement approach (LOQ/$\sqrt{2}$) was used when anti-Xa levels were below the LOQ [11]. Statistical analysis was carried out with XlStat version 19. With a paired one-tailed t test, an alpha error of 0.05, a power of 90%, a minimum of 25 participants were required to detect an increase ≥ 20 % in anti-Xa activity between sampling on day 2 or 3 and day 5. The one-tailed Wilcoxon rank sum test was used for matched-paired samples of peak anti-Xa values on days 2 and 5 or 8. P-value > 0.05 was considered statistically significant.

Results

A total of 39 patients were assessed for eligibility and 11 refused to participate. Of the 28 patients enrolled, 14 completed the study (3 were discharged from the hospital before day 5, 1 withdrew consent, 1 was switched to UFH, 3 had their treatment interrupted for a medical intervention, 2 missed samples and 4 had their eGFR rise above 30 ml/min/1.73m^2) (see supplementary Fig 1). Baseline characteristics are shown in Table 1. Most patients received a dose of 3500 IU daily (70%), whereas patients with a BMI ≥30 kg/m^2 were given 4500 IU daily, as per local guidelines. The median eGFR (IQR) was stable over the course of the study: 16 (12-25) (baseline), 18 (14-21) (day 5) and 16 (13-22) (day 8) ml/min/1.73m^2.

Table 1. Baseline characteristics of patients

Variables[1,2]	Recruited (n = 28)	Completed a 5 days course of treatment (n = 14)	Completed a 8 days course of treatment (n = 10)
Age in years	73 (69-85)	73 (67-86)	72 (66-84)
Male	17 (61 %)	9 (64 %)	6 (60%)
Caucasian	26 (93 %)	13 (93 %)	9 (90%)
African American	2 (7 %)	1 (7 %)	1 (10%)
Weight in kg	79 (66-91)	77 (63-91)	77 (66-86)
BMI in kg/m^2	30 (25-33)	28 (23-32)	28 (22-32)
eGFR [3] at baseline	20 (16-24)	16 (12-25)	19 (13-24)
Patients with eGFR at baseline ≤ 20 ml/min/1.73m^2	15 (54 %)	9 (64.3 %)	6 (60%)
Dose of tinzaparin in IU/kg	44 (42-54)	48 (42-56)	48 (44-55)
Patients with dose of 3500 IU	19 (68 %)	10 (71 %)	7 (70%)

[1] Continuous variables are given as median (interquartile range - IQR)

[2] Discrete variables are given as counts (%)

[3] eGFR = estimated glomerular filtration rate using CKD-EPI [8]

Median peak anti-Xa levels (range) measured at 4h on day 2 were 0.07 (0-0.24) IU/ml, 0.11 (0.07–0.25) IU/mL on day 5 and 0.09 (0.07–0.31) IU/ml on day 8. There was no statistically significant increase in peak anti-Xa levels over time between day 2 and day 5 (Figure 1). Ranges of peak anti-Xa levels were comparable to surgical patients with normal renal function receiving a 3500 IU dose of tinzaparin [12]. The difference between day 2 and day 8 was to the limit of statistical significance. Nevertheless, all anti-Xa values measured at peak or trough remained below 0.4 IU/ml (trough anti-Xa levels were undetectable), thus suggesting an absence of disproportionate anticoagulation. No patient experienced thrombotic complications or major bleeding events. One patient received two units of red blood cells on day 5 for symptomatic anemia not related to bleeding and anticoagulation was maintained.

Discussion

Our study shows that short-term tinzaparin in patients severe CKD is not associated with excessive anticoagulation, with peak anti-Xa levels below the therapeutic range and undetectable trough anti-Xa levels. Our findings are consistent with the study of Mahé et al. where a short course of fixed-dose prophylactic tinzaparin did not show clinically significant accumulation (peak, trough or area under the curve) in elderly patients mainly with moderate renal impairment [6]. Similarly, a low dependence of peaks anti-Xa ratio on baseline renal function was reported in elderly patients with renal impairment receiving therapeutic doses of tinzaparin [13].

Strengths of our study include prophylactic tinzaparin given exclusively to patients with severe CKD and median eGFR <20 ml/min/1.73m^2 over the whole course of the trial (as opposed to a majority of patients with moderate CKD in other studies), systematic assessment of bioaccumulation of tinzaparin using trough and peak anti-Xa levels and blinding of the clinical staff for the duration of the study.

Limitations of this observational single center study were the use of anti-Xa levels as a pharmacokinetic biomarker for bleeding risk, overall low anti-Xa blood levels and

most importantly sample size. Although we have enrolled 28 participants, half did not complete a 5-8-day tinzaparin course. This is reflective of the real-world trajectories of patients with severe CKD receiving prophylactic tinzaparin on medical wards. With 14 individuals in the final cohort, we had 85% power to detect a 20% difference with a 5% α error.

In summary, although caution should be used with LMWHs in severe CKD, a short course of tinzaparin for prevention of VTE in this high-risk population appears safe. It does not support lowering the prophylactic dose in severe CKD. Further clinical studies to assess the relative thrombotic efficacy versus bleeding risk of low-dose tinzaparin in this population would benefit from validation in a larger cohort, despite the feasibility challenge.

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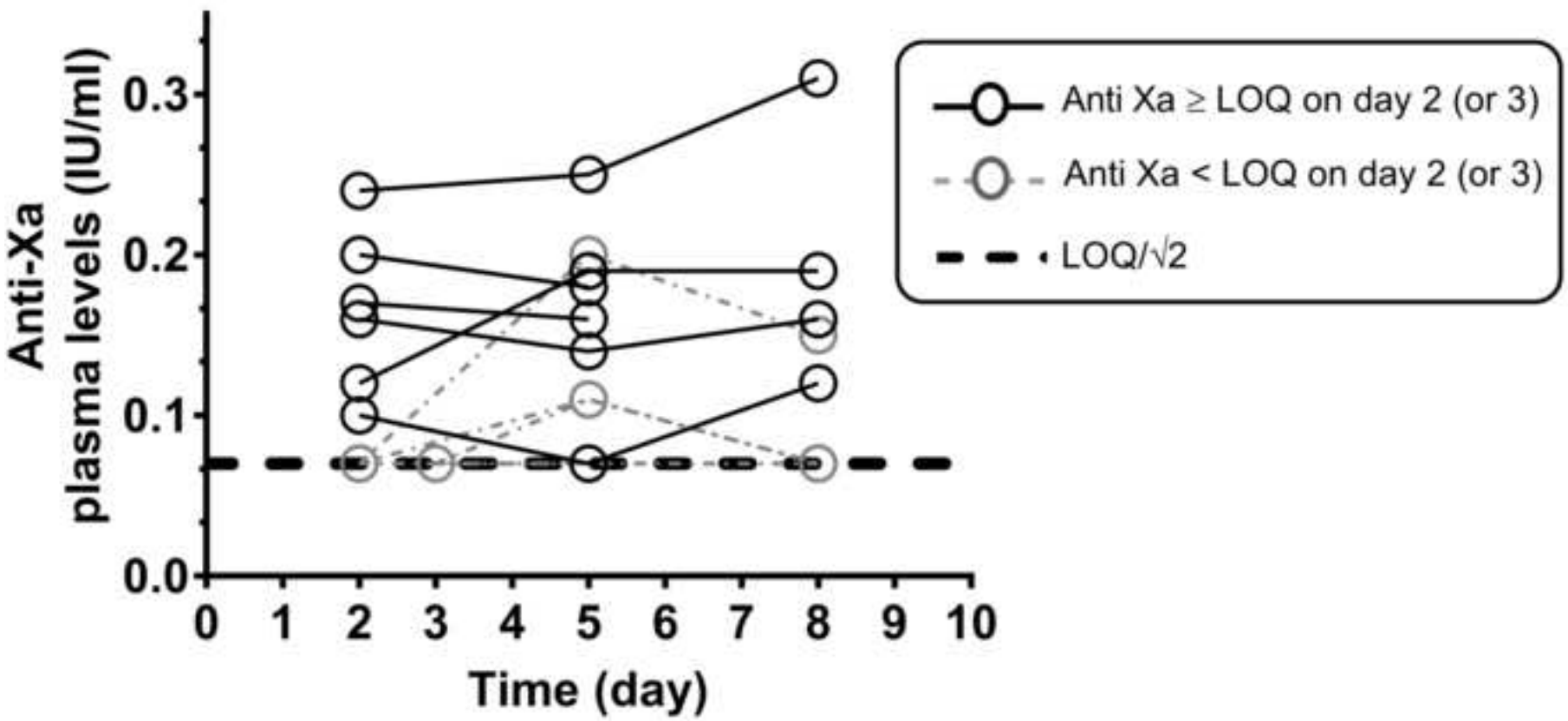
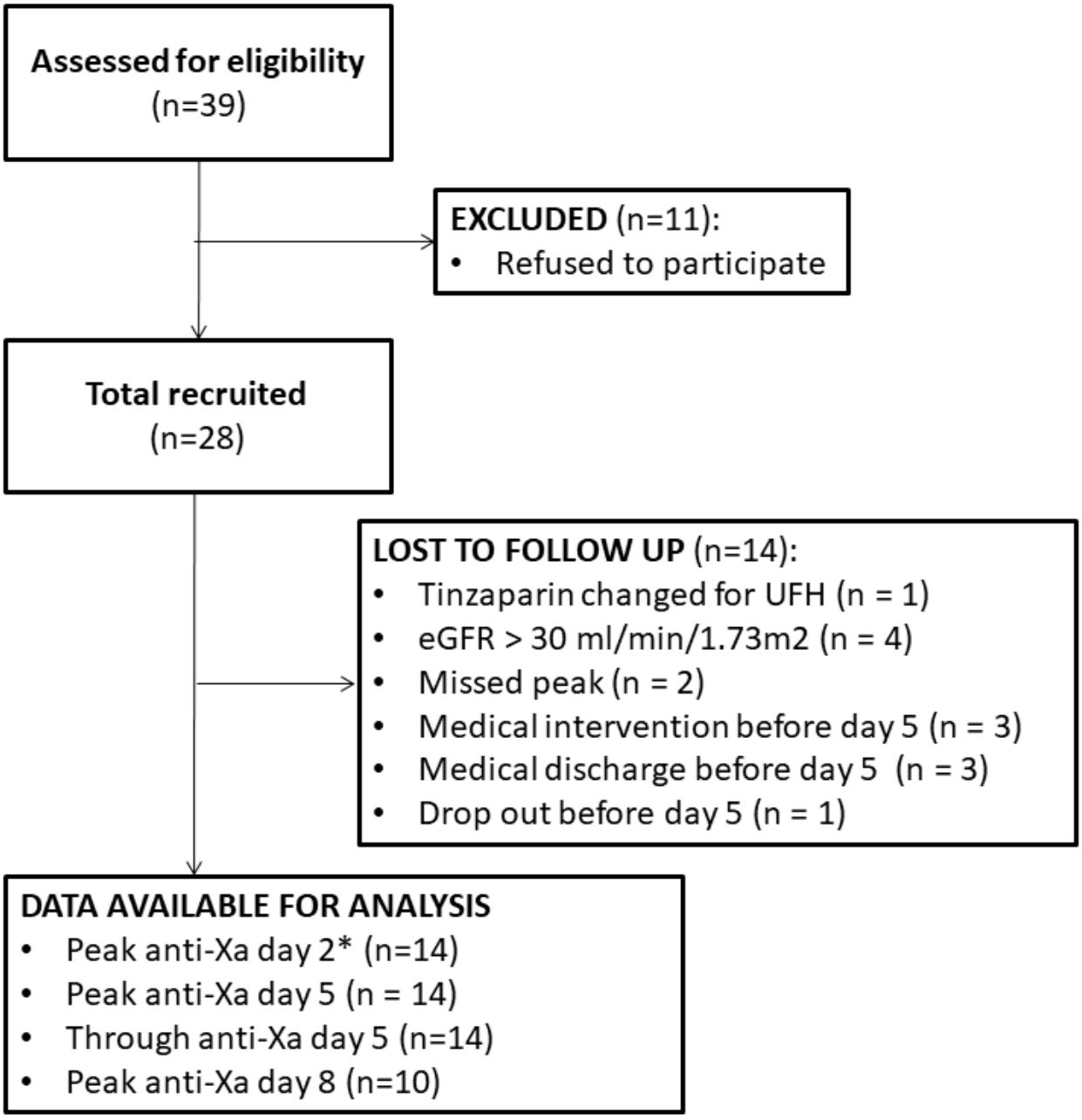
Figures Captions

Figure 1. Dot plot comparing the detectable peak anti-Xa plasma levels of individual patients on day 2, day 5 and day 8. LOQ = limit of quantification. A substitution approach (LOQ / √2) was applied when anti-Xa levels were below LOQ. Two patients had peak anti-Xa on day 3 instead of day 2. For these subjects, all anti-Xa levels, including day 5 and 8 were below 0.1 IU/ml. Differences between day 2 and day 5 or day 8 were not considered clinically significant ($p = 0.22$ and $p=0.05$, one-tailed Wilcoxon rank sum test on matched pairs).

Figure 1


Anti-Xa plasma levels (IU/ml)
0.0
0.1
0.2
0.3
0 1 2 3 4 5 6 7 8 9 10
Time (day)
Anti Xa ≥ LOQ on day 2 (or 3)
Anti Xa < LOQ on day 2 (or 3)
LOQ/√2

Flow Chart


Assessed for eligibility
(n=39)
EXCLUDED (n=11):
• Refused to participate
Total recruited
(n=28)
LOST TO FOLLOW UP (n=14):
• Tinzaparin changed for UFH (n = 1)
• eGFR > 30 ml/min/1.73m2 (n = 4)
• Missed peak (n = 2)
• Medical intervention before day 5 (n = 3)
• Medical discharge before day 5 (n = 3)
• Drop out before day 5 (n = 1)
DATA AVAILABLE FOR ANALYSIS
• Peak anti-Xa day 2* (n=14)
• Peak anti-Xa day 5 (n = 14)
• Through anti-Xa day 5 (n=14)
• Peak anti-Xa day 8 (n=10)