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A Retrospective Study of Anti-Xa Levels in Renally Impaired Patients Receiving Reduced or Non-Reduced Therapeutic Doses of Dalteparin

Katia Christina Pires[1,*], Lieke Mitrov-Winkelmolen[1,2,*], Hoang Lan Le[1], Rogier AM Quax[3], Rikje Ruiter[3,4], Marike Wabbijn[5], T Martijn Kuijper[6] and Tessa Maria Bosch[1,7]

[1]Department of Hospital Pharmacy, Maasstad Hospital, Rotterdam, The Netherlands

[2]Department of Hospital Pharmacy, Ikazia Hospital, Rotterdam, The Netherlands

[3]Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands

[4]Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands

[5]Department of Internal Medicine, Ikazia Hospital, Rotterdam, The Netherlands

[6]Maasstad Academy, Maasstad Hospital, Rotterdam, The Netherlands

[7]MaasstadLab Clinical Pharmacology & Toxicology, Maasstad Hospital, Rotterdam, The Netherlands

[*]**Corresponding Authors:** Lieke Mitrov-Winkelmolen, Department of Hospital Pharmacy, Maasstad Hospital, Rotterdam, The Netherlands, Tel.: 0630706275, E-mail: WinkelmolenL@maasstadziekenhuis.nl, ORCID ID: https://orcid.org/0000-0003-4133-2370

Katia Pires, Department of Hospital Pharmacy, Maasstad Hospital, Rotterdam, The Netherlands, E-mail: piresk@maasstadziekenhuis.nl, ORCID ID: https://orcid.org/0000-0002-9988-8198

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Abstract

Introduction: Dose reduction and anti-Xa monitoring of dalteparin is advised in current guidelines for renally impaired (RI) patients. However, due to a limited amount of evidence for this advice, there is a lack of consensus and a variety of dosing regimens are used in practice.

Method: We conducted a multicenter, retrospective observational study including intensive care-unit (ICU) and non-ICU patients (≥ 18 years) with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 or on dialysis, receiving ≥7500 IU of dalteparin daily. We compared anti-Xa levels with a 75% and 100% dalteparin weight-based dose and investigated the association between dose, anti-Xa levels and occurrence of bleeding and thrombotic events.

Results: In patients with an eGFR <30 ml/min/1.73m^2, the odds of reaching an adequate anti-Xa level were higher on a 100% weight-based dose than on a 75% weight-based dose (OR 3.59, 95% confidence interval (CI) 1.26-10.23, *p*-value

0.017). In dialysis patients, this did not differ significantly (OR 1.08, 95% CI 0.32-3.64, *p*-value 0.906). Eight bleeding events occurred during hospitalization, of which one minor bleeding event occurred in a patient with a supratherapeutic anti-Xa level.

Conclusion: In RI patients, 100% weight-based dose of dalteparin did not lead to overexposure in RI patients based on anti-Xa levels and increased the likelihood of adequate anti-Xa levels. Bleeding occurrences did not differ between 75% and 100% dosing. Thus, pre-emptive dose adjustments for in RI patients are likely unnecessary.

Keywords: dalteparin; dose adjustment; renal insufficiency; dialysis; and bleeding

Abbreviations: CI: Confidence interval; CDSS: Clinical Decisions Support System; CVVHD: continuous veno-venous hemodialysis; eGFR: estimated glomerular filtration rate; KNMP: Royal Dutch Pharmacists Association; ICU: Intensive Care Unit; IHD: Intermittent hemodialysis; IQR: interquartile range; IU: international units; LIMS: laboratory information management system; LMWH: Low-Molecular-weight Heparins; OR: odds ratio; RI: Renally impaired; SD: standard deviation

Introduction

Low-molecular-weight heparins (LMWHs), have largely replaced unfractionated heparins as anticoagulants because of the more predictable anticoagulant response, better side-effect profile and a greater ease of use [1–3].

LMWHs can be used in standardized doses based on body weight without the need for regular therapeutic drug monitoring. However, as LMWHs are primarily excreted by the kidneys, patients with renal insufficiency might face an increased potential to bio-accumulate LMWHs and consequently an increased risk of major bleeding [4–6]. Different LMWHs are available and each LMWH varies in pharmacokinetics properties, e.g. elimination half-life, clearance and bioavailability, because of differences in molecular weight [7,8]. Dalteparin has a high molecular weight (6000 Dalton) compared to enoxaparin and nadroparin, of which the molecular weight is 4500 Dalton and 4300 Dalton, respectively [9–11]. Tinzaparin has a higher molecular weight more similar to dalteparin, of 6500 Dalton [12]. For LMWHs with a higher molecular weight, the ratio of renal clearance to total drug clearance is lower, making the total clearance less dependent on renal function [13]. Indeed, for tinzaparin, an unadjusted dose in RI patients does not lead to a higher risk of bleeding, and dose reduction is not deemed necessary. It is therefore reasonable to expect a minimal tendency for dalteparin to accumulate in renally impaired (RI) patients [8,14,15]. However, previous studies on the adequate dosing of dalteparin in RI patients have been inconclusive. Some indeed have shown that therapeutically dosed Dalteparin does not bioaccumulate in RI patients, has a lower bleeding risk compared to heparin use and that pre-emptive dose reduction in RI patients leads to inadequate anti-Xa levels.[3,16,17] In contrast, Schmid *et al.* did observe an elevation of anti-Xa levels in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 [15]. The lack of consensus and insufficient evidence on dalteparin dosing strategies has resulted in conflicting recommendations in international and national (Dutch) guidelines and show substantial diversity in dalteparin treatment regimens in renally impaired patients [18].

The Dutch Association Medical Professionals guideline for anticoagulation with LMWHs and the Royal Dutch Pharmacist Association (KNMP) recommend that in patients with an eGFR <30 mL/min/1.73m^2, after the initial full dose, dalteparin dose should be reduced by 50%, and in patients with an eGFR between 30 and 60 mL/min/1.73m^2 by 25% [8,19]. Additionally, anti-Xa levels should be monitored by determining anti-Xa peak levels at 4 hours after administration at steady state. These levels should be within the therapeutic ranges of 1.0-2.0 international units (IU)/mL or 0.6-1.0 IU/mL when dalteparin dosage frequency is, respectively, once or twice daily [8]. Supratherapeutic levels are considered to be associated with a higher bleeding risk [14,20]. The dalteparin weight-based dose should, if needed, be adjusted based on the measured anti-Xa levels [4,6,8]. Inter-

national guidelines recommend to avoid therapeutic doses of dalteparin in patients with an eGFR <30 mL/min/1.73m^2, to switch to an alternative anticoagulant that provides specific renal dose adjustments or that is less dependent on renal clearance, or to start with full dose and make dose adjustments according to anti-Xa level [8,21]. Dutch hospitals commonly reduce the dose of LMWH without anti-Xa monitoring when eGFR <50 ml/min, regardless of the LMWH type.

Based on known literature and clinical experience, the local protocol of our affiliated hospitals advises 25% dose reduction of dalteparin in patients with an eGFR <30 mL/min/1.73m^2 with anti-Xa monitoring, and no dose reduction for patients with an eGFR between 30 and 60 mL/min/1.73m^2 without anti-Xa monitoring. If the measured anti-Xa level is below the previously described ranges, dose of dalteparin is increased to 100% and a new anti-Xa level is measured in steady state. Moreover, in longer dalteparin use, anti-Xa levels are measured regularly to avoid undetected accumulation.

In the previously mentioned studies, dialysis patients were excluded from analysis, as could pose as a risk of bioaccumulation and consequently a bleeding when used in dialysis patients [22,23]. Data regarding the use of dalteparin in hemodialysis patients are very limited, but in clinical practice use of is sometimes unavoidable. Therefore, we included dialysis patients in our study as well.

The aim of this study was to assess the anti-Xa levels in a 75% versus 100% therapeutic dose in RI patients, including hemodialysis patients, to confirm or refute our dose regimen. Furthermore, we aimed to investigate the association between dose, anti-Xa levels and major bleeding and/or thrombosis.

Methods

Ethics

This study was approved by the Board of Directors of Maasstad Hospital and Ikazia Hospital, Rotterdam, the Netherlands On April 30, 2018, the Executive Board of the Review Committee Scientific Research Rotterdam gave permission to perform this study and concluded that this study does not fall under the Medical Research Involving Human Subjects Act. An informed consent was not required for this study. For personal data protection, all data were pseudonymized before analysis.

Study Design, Data Source and Collection

We conducted a multicenter, retrospective observational study in RI non-ICU and ICU patients who were given therapeutic doses of dalteparin in Maasstad Hospital and Ikazia Hospital, Rotterdam, The Netherlands. The patients were identified by a query of anti-Xa measurements from the laboratory information management system (LIMS) between February 13, 2017, and June 12, 2020. The measurements were stratified into two groups, distinguishing non-ICU and ICU patients, due to variations in pharmacokinetics and pharmacodynamics between both groups [24]. Clinical data collected from patient medical records included: initial dose of dalteparin, dose of dalteparin administrated before sampling, time of dalteparin administration, time of sampling, serum creatinine concentration, eGFR derived from the Chronic Kidney Disease Epidemiology Collaboration equation, thrombotic and bleeding events. The following baseline demographic characteristics were collected on each patient: gender, date of birth, and body weight.

Anti-Xa levels were eligible for inclusion when the levels were measured in adults (≥18 years) with an eGFR below 60 mL/min/1.73m2 who received therapeutic doses of dalteparin (≥7500 IU daily), and when anti-Xa levels were sampled at peak concentrations during steady state, defined as after at least three subcutaneous injections of dalteparin. Anti-Xa levels were only considered a peak concentration when the blood was sampled within 3-5 hours after a subcutaneous injection of dalteparin. Patients who were admitted due to Covid-19 were excluded as dose regimens for dalteparin in these patients in that period

were divergent from the standard dosing protocol. Furthermore, patients whose serum creatinine concentrations and/or body weight were not available in the medical records, were excluded from analysis.

The data were collected by one researcher and ultimately verified by another researcher. An independent third-party researcher assessed discrepancies and consensus was reached.

Dalteparin Dose and Available Dosages

The recommended dosage per subcutaneous injection is 200 IU/kg for once daily and 100 IU/kg for twice daily dalteparin. Since dalteparin is administered by using fixed dose syringes, the calculated recommended weight-based dose (both 75% and 100%) was rounded to the nearest available fixed dose [25].

Anti-Xa measurement

The anti-Xa levels was measured by a validated method in citrate plasma with the Sysmex CS2100i coagulation analyser in the ISO-15189 certified Clinical Chemical Laboratory of the MaasstadLab.

Clinical Endpoints: Bleeding and Thrombosis

Clinical endpoints of the study were the occurrence of bleeding events and thrombotic events (ischemic stroke, venous thrombosis including deep vein thrombosis or pulmonary embolism) during hospitalization after anti-Xa measurement. Events were classified into minor or major events, severity, and localization. If no event was reported in the medical file, it was assumed that no event had occurred.

Major bleeding events were collected from the patient medical records and evaluated following the classification of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis [26]. A major bleeding was defined as a fatal bleeding or a symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) or bleeding causing a fall in hemoglobin level of more than 20 g/L (1.24 mmol/L) or a bleeding event leading to transfusion of two or more units of red cells [26].

For each bleeding/thrombosis event that occurred during hospitalization, the measured anti-Xa level closest to the date of that event was included in the analysis. In case of no event, the last measured anti-Xa level was included.

Statistical Analysis

Continuous variables that were normally distributed were presented as mean and standard deviation (SD) and as median and interquartile range (IQR) otherwise. Categorical variables were presented as counts with corresponding percentages.

The association between the ratio of the weight-based dalteparin dose and anti-Xa levels was visually assessed by scatterplots. In addition, medians, and percentiles of anti-Xa levels, as well as the number of levels, below, within or above the therapeutic range, were calculated for the following strata: non-ICU / ICU, eGFR <30 mL/min/1.73m^2 / 30-60 mL/min/1.73m^2, dose frequency once / twice daily and 75% / 100% weight-based dose. For the subgroup of dialysis patients, similar analyses were performed. The number of bleeding events, type (major/minor) and description of the major events were evaluated according to ICU-status, dose ratio, measured anti-Xa levels and eGFR category.

To test whether a 75% or 100% weight-based dose leads to a different percentage of anti-Xa levels within range, stratum adjusted odds ratios (OR) for anti-Xa levels being within range over the 2x2 strata were obtained by fitting logistic regression models including the 4 strata and weight-based dose (2 levels, 75% and 100%) as covariates. In addition, stratum specific odds ratios

were obtained by fitting a logistic regression model including the 2x2 strata and their interactions with dose. To account for multiple observations within patients, cluster robust standard errors were obtained using the sandwich estimator.

All analyses were conducted using STATA/SE statistical software version 14.2. A *p*-value <0.05 was used to indicate statistical significance.

Results

Patients and Baseline Characteristics

In total, 167 anti-Xa levels measurements were included in the study (figure 1 and table 1). Among these measurements, 87 anti-Xa levels belonged to non-ICU patients, including 21 anti-Xa levels from non-ICU dialysis patients. The remaining 80 anti-Xa levels were from ICU patients, with 37 anti-Xa levels from ICU dialysis patients. The mean dosage per dose for non-ICU patients was 170 IU/kg for once daily dalteparin and 87 IU/kg for twice daily dalteparin. For ICU patients the mean dosage per dose was 153 IU/kg for once daily dalteparin and 93 IU/kg for twice daily dalteparin. Nineteen anti-Xa levels belonged to patients who received dosages deviating from our dosage recommendations of 75% or 100% of the weight-based dose. (table 1).

The 148 levels from patients who did receive75% (N = 65 patients) and/or 100% (N = 83 patients) of the weight-based dose were analyzed in accordance with the predefined endpoints (table 1). Among these, 72 anti-Xa levels belonged to non-ICU patients, while 76 anti-Xa levels were from ICU patients (table 1).

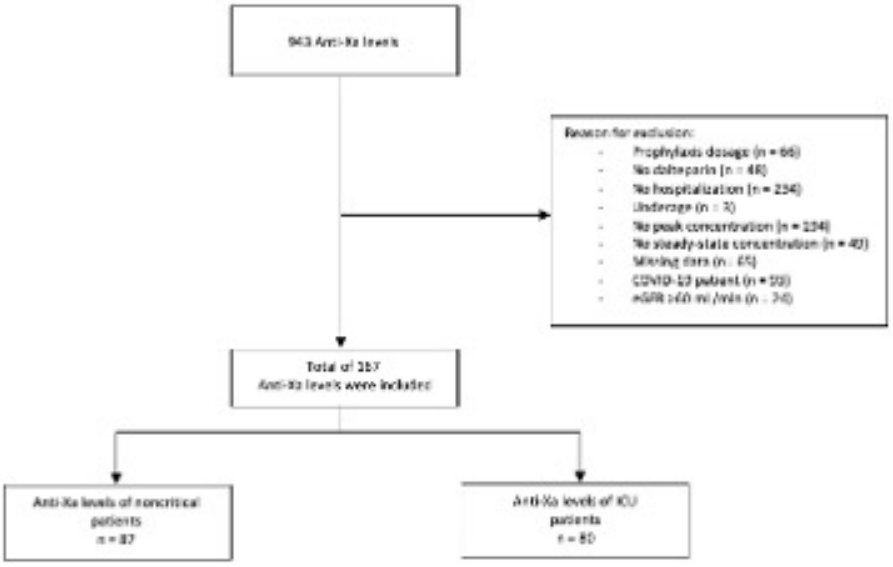

Figure 1: Study outline

Table 1: Baseline characteristics

characteristics		Non-ICU(n = 87)	ICU(n = 80)
Number of anti-Xa levels per patient, n (%)			
1	56 (80)	27 (61)	
2	6 (9)	11 (25)	
3	6 (9)	3 (7)	
4	1 (1)	2 (5)	
5	1 (1)	0 (0)	

6	0 (0)	1 (2)	
Age (years), median, (IQR)		76 (67 – 81)	70 (57 – 77)
Female, n (%)		47 (53)	24 (30)
Weight (kg), median (IQR)		80.4 (65 – 89.4)	85 (72 – 101)
eGFR (mL/min/1.73m2), median (IQR) (n),			
	<30 mL/min/1.73m2	18 (13 – 22) (74)	17 (12 – 22) (53)
	30 – 60 mL/min/1.73m2	37 (33 – 44) (13)	46 (33 – 51) (27)
Dialysis, n (%)			
CVVHD	N/A	27 (33.8)	
Intermittent HD	18 (20.7)	10 (12.5)	
HD Peritoneal§	3 (3.5)	N/A	
Dalteparin frequency, n (%)			
once daily	51 (58.6)	3 (3.8)	
twice daily	36 (41.4)	77 (96.3)	
Dosage per kg body weight per dose (IU), mean (sd)			
once daily	170 (44)	153 (30)	
twice daily	87 (20)	92 (16)	
Dosage expressed as % of full dose	once daily	85 (22)	77 (15)
	twice daily	87 (20)	92 (16)
Dose ratio, n (%)			
<75%	10 (11.5)	0 (0.0)	
75%	36 (41.4)	29 (36.3)	
75%-100%	0 (0.0)	3 (3.8)	
100%	36 (41.4)	47 (58.8)	
>100%	5 (5.8)	1 (1.3)	

n, total anti-Xa levels; IQR, interquartile range; eGFR, estimated glomerular filtration rate; CVVH, continuous veno-venous hemodialysis; HD, hemodialysis. N/A, not applicable §belonged to one patient

Anti-Xa Levels and Renal-Based Reduced and Non-Reduced Therapeutic Doses

In figures 2 and 3, anti-Xa levels are plotted against the ratio of the weight-based dose. Overall, the figures shows that the measured anti-Xa levels are highly scattered. Some (6%, 9 out of 148) exceed the upper therapeutic limits, while a majority of the anti-Xa levels (55%, 82 out of 148) are below the lower therapeutic limits (figures 2 and 3, table 2). In general, there seems to be a large variance in anti-Xa levels in patients at a specific percentage of a weight-based dose. Not all patients received dose adjustment according to our guideline. The dose recommendation of 75% or 100% was better adhered to in twice daily dosed patients (figure 2B/C, 3B/C).

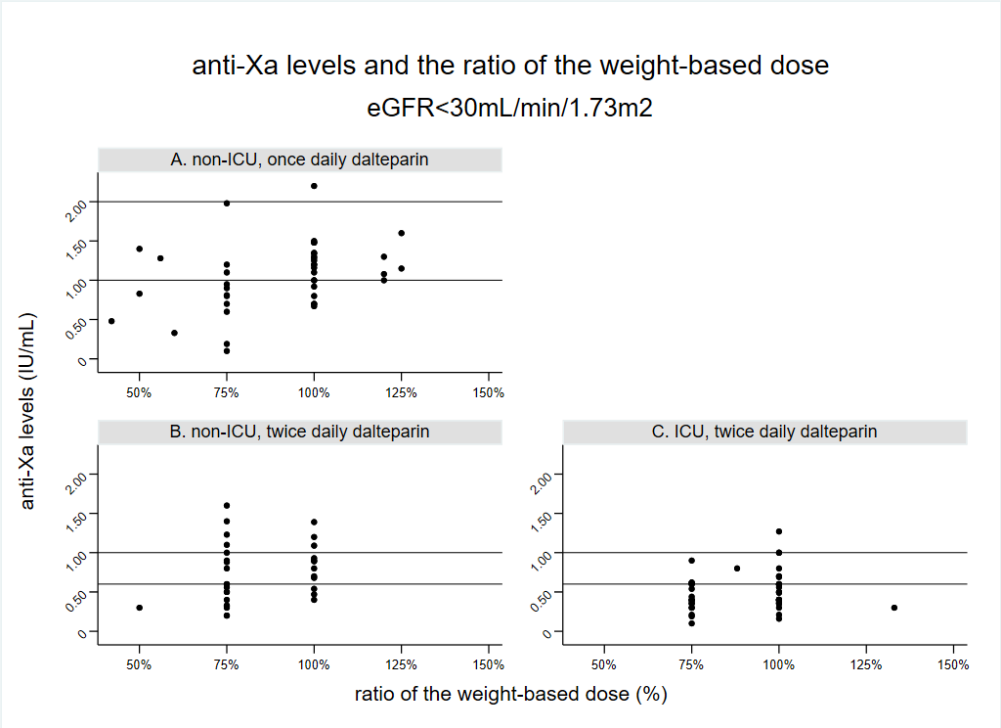

Figure 2: Scatterplot anti-Xa levels of non-ICU and ICU patients with an eGFR <30 mL/min/1.73m^2 plotted against the ratio of the weight-based dose. Therapeutic ranges 1.0-2.0 IU/mL for once daily dalteparin or 0.6-1.0 IU/mL for twice daily are represented by the solid black lines in the graphs.

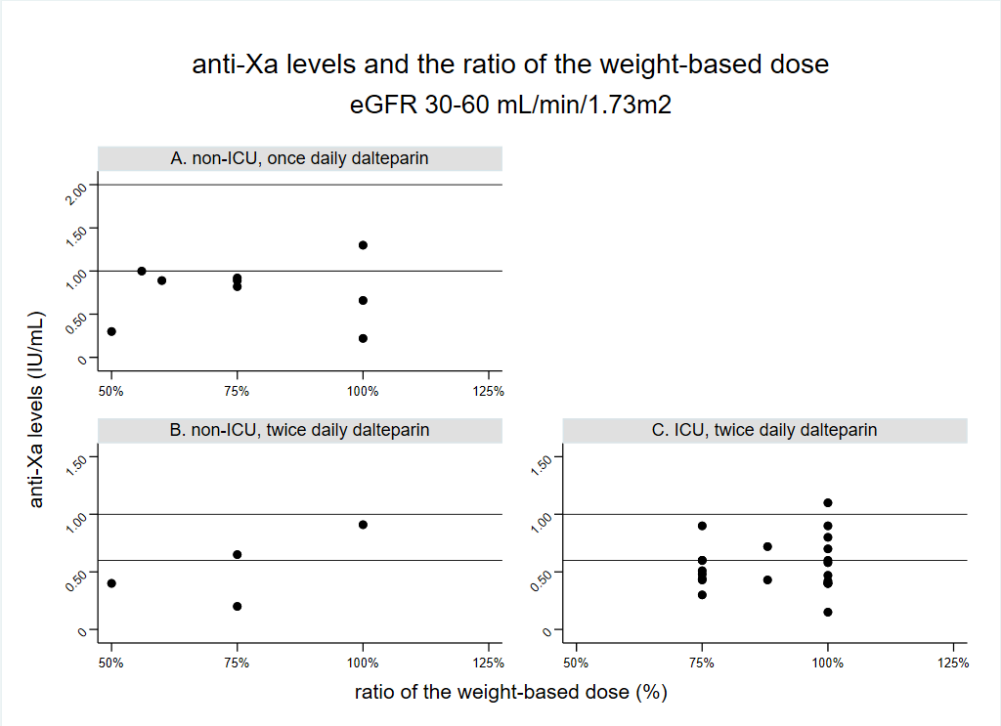

Figure 3: Scatterplot of the anti-Xa levels of non-ICU and ICU patients with an eGFR 30 - 60 mL/min/1.73m^2 plotted against the ratio of the normal dose. Therapeutic ranges 1.0-2.0 IU/mL for once daily dalteparin or 0.6-1.0 IU/mL for twice daily are represented by the solid black lines in the graphs.

Table 2: Median anti-Xa levels and percentages below, within and above the designated anti-Xa therapeutic range of the non-ICU and ICU patients who received 75% and 100% weight-based dose dalteparin

Patient	Dialysis	Dose(n)	Anti-Xa level (IU/ml)Median (IQR)	Therapeutic range§(n)	
non-ICU patients, eGFR <30 mL/min/1.73m2 once daily					
	No	75% (9)	0.81 (0.70 - 0.95)	Below lower limit	7 (78%)
				Within rangeAbove upper limit	2 (22%)0 (0%)
		100% (14)	1.2 (0.70 - 1.35)	Below lower limit	4 (29%)
				Within range	9 (64%)
				Above upper limit	1 (7%)
	Yes	75% (2)	1.04 (0.10 - 1.98)	Below lower limit	1 (50%)
				Within rangeAbove upper limit	1 (50%)0 (0%)
		100% (7)	1.16 (0.92 - 1.34)	Below lower limit	2 (29%)
				Within range Above upper limit	5 (71%)0 (0%)
Non-ICU patients, eGFR <30 mL/min/1.73m2, twice daily					
	No	75% (15)	0.60 (0.33 - 1.10)	Below lower limit	6 (40%)
				Within range	5 (33%)
				Above upper limit	4 (27%)
		100% (8)	0.90 (0.75 - 1.01)	Below lower limitWithin range	0 (0%)6 (75%)
				Above upper limit	2 (25%)
	Yes	75% (4)	0.53 (0.41 - 0.72)	Below lower limit	3 (75%)
				Within range Above upper limit	1 (25%)0 (0%)
		100% (4)	0.51 (0.44 - 0.97)	Below lower limit	3 (75%)
				Within range Above upper limit	1 (25%)0 (0%)
non-ICU patients, eGFR 30-60 mL/min/1.73m2, once daily					

	No	75% (4)	0.89 (0.86 - 0.91)	Below lower limitWithin rangeAbove upper limit	4 (100%)0 (0%)0 (0%)
		100% (2)	0.98 (0.66 - 1.30)	Below lower limit	1 (50%)
				Within range Above upper limit	1 (50%)0 (0%)
	Yes	75% (0)	N/A	N/A	N/A
		100% (0)	N/A	N/A	N/A
Non-ICU patients, eGFR 30-60 mL/min/1.73m2, twice daily					
	No	75% (2)	0.43 (0.20 - 0.65)	Below lower limit	1 (50.0%)
				Within range Above upper limit	1 (50.0%)0 (0%)
		100% (1)	(N/A)	Below lower limitWithin range Above upper limit	0 (0%)1 (100%)0 (0%)
	Yes	75% (0)	N/A	N/A	N/A
		100% (0)	N/A	N/A	N/A
ICU patients, eGFR <30 mL/min/1.73m2, once daily					
	No	75% (1)	(N/A)	Below lower limitWithin rangeAbove upper limit	1 (100%)0 (0%)0 (0%)
		100% (0)	N/A	N/A	N/A
	Yes	75% (0)	N/A	N/A	N/A
		100% (1)	N/A	Below lower limitWithin rangeAbove upper limit	1 (100%)0 (0%)0 (0%)
ICU patients, eGFR <30 mL/min/1.73m2, twice daily					
	No	75% (10)	0.38 (0.30 - 0.40)	Below lower limit	8 (80%)
				Within range Above upper limit	2 (20%)0 (0%)
		100% (18)	0.48 (0.40 - 0.69)	Below lower limit	10 (55%)
				Within range	7 (39%)
				Above upper limit	1 (6%)
	Yes	75% (8)	0.49 (0.31 - 0.61)	Below lower limit	5 (62%)
				Within range Above upper limit	3 (38%)0 (0%)

		100% (13)	0.49 (0.38 - 0.59)	Below lower limit	10 (77%)
				Within range Above upper limit	3 (23%)0 (0%)
ICU patients, eGFR 30-60 mL/min/1.73m2, once daily					
	No	75% (0)	N/A	N/A	N/A
		100% (0)	N/A	N/A	N/A
	Yes	75% (1)	N/A	Below lower limitWithin rangeAbove upper limit	1 (100%)0 (0%)0 (0%)
		100% (0)	N/A	N/A	N/A
ICU patients, eGFR 30-60 mL/min/1.73m2, twice daily					
	No	75% (5)	0.51 (0.48 – 0.60)	Below lower limit	3 (60%)
				Within range Above upper limit	2 (40%)0 (0%)
		100% (7)	0.47 (0.40 – 0.70)	Below lower limit	4 (57%)
				Within range Above upper limit	3 (43%)0 (0%)
	Yes	75% (4)	0.42 (0.35 – 0.67)	Below lower limit	3 (75%)
				Within range Above upper limit	1 (25%)0 (0%)
		100% (8)	0.59 (0.40 – 0.80)	Below lower limit	4 (50%)
				Within range	3 (37%)
				Above upper limit	1 (13%)

ICU, Intensive care unit; N/A, not applicable, eGFR, estimated glomerular filtration rate, IQR interquartile range

§ Therapeutic ranges are 1.0-2.0 IU/mL for once daily dalteparin or 0.6-1.0 IU/mL for twice daily dalteparin.

The median anti-Xa levels of patients who received a 100% weight-based dose were below or close to the lower limits of the therapeutic ranges, while the median anti-Xa levels in patients with a 75% weight-based dose were mostly below the lower limits (table 2). In all patients, the probability that anti-Xa levels fell within the therapeutic range was higher for patients who received a 100% weight-based dose compared to patients who received a 75% weight-based dose (stratum adjusted OR 2.66, 95% CI 1.24-5.70, *p*-value 0.012)) (table 3). Considering the stratum specific OR, a significantly higher probability for an anti-Xa level within therapeutic range when receiving 100% compared to 75% dosed patients was observed in the stratum of non-ICU patients with eGFR <30 mL/min/1.73m^2: OR 3.59, 95% CI 1.32-9.79, p-value 0.017. Odds ratios for the other strata were not significant (table 4). We repeated the analysis for the subgroups of non-dialysis and dialysis patients. In non-dialysis patients the stratum adjusted OR was significantly higher in 100% weight-based dosed patients compared to 75% weight-based dosed patients: 4.48 (95% CI 1.79-11.20, p-value 0.001). For the dialysis patients the OR was 1.08 (95% CI 0.30-3.90, *p*-value 0.911) (table 3).

Table 3: Stratum adjusted analyses (all patients, dialysis non-dialysis patients) and stratum specific analyses (all patients)

Patient	Dose 75% vs. 100%odds ratio	95% CI	p-value
Stratum adjusted analysis§			
All patients	2.66	1.24-5.70	0.012
non-dialysis patients	4.48	1.79-11.20	0.001
dialysis patients	1.08	0.30-3.90	0.911
Stratum specific analysis¥ (all patients)			
Non-ICU, eGFR <30 mL/min/1.73m2	3.59	1.32-9.79	0.017
Non-ICU, eGFR 30-60 mL/min/1.73m2	10.00	0.39-254.51	0.161
ICU, eGFR <30 mL/min/1.73m2	1.27	0.38-4.22	0.709
ICU, eGFR 30-60 mL/min/1.73m2	2.67	0.48-14.75	0.302

ICU, Intensive care unit; eGFR, estimated glomerular filtration rate; CI, confidence interval § Adjusted for stratum intercept, assuming a common odds ratio over strata ¥ Adjusted for stratum intercept, allowing for different odds ratios over strata

Table 4: Median anti-Xa levels of IHD and CVVHD dialysis patients. The frequencies of anti-Xa levels below, within and above the designated anti-Xa range are shown

Group	Type dialysis	Dose (n)	Anti-Xa level (IU/mlMedian (IQR)	Therapeutic range[§] (n) (%)	
non-ICU patients, once daily					
	Intermittent HD	75% (2)	1.04 (0.10 – 1.98)	Below lower limit	1 (50%)
				Within range Above upper limit	1 (50%)0 (0%)
		100% (5)	1.25 (1.16 – 1.34)	Below lower limit	1 (20%)
				Within range Above upper limit	4 (80%)0 (0%)
	PD	75% (0)	N/A	N/A	N/A
		100% (2)	0.9 (0.8 – 1.00)	Below lower limit	1 (50%)
				Within range Above upper limt	1 (50%)0 (0%)
non-ICU patients,twice daily					
	Intermittent HD	75% (4)	0.53 (0.41- 0.72)	Below lower limit	3 (75%)
				Within rangeAbove upper limit	1 (25%)0 (0%)

		100% (3)	0.47 (0.40 – 1.39)	Below lower limitWithin range	2 (67%)0 (0%)
				Above upper limit	1 (33%)
	PD	100 % (1)	N/A	Below lower limit Within rangeAbove upper limit	1 (100%)0 (0%)0 (0%)
ICU patients, once daily					
	CVVHD	75% (1)	N/A	Below lower limitWithin rangeAbove upper limit	1 (100%)0 (0%)0 (0%)
	Intermittent HD	100% (1)	N/A	Below lower limitWithin rangeAbove upper limit	1 (100%)0 (0%)0 (0%)
ICU patients, twice daily					
	CVVHD	75% (8)	0.36 (0.30 – 0.52)	Below lower limit	6 (75%)
				Within range Above upper limit	2 (25%)0 (0%)
		100% (16)	0.54 (0.40 – 0.75)	Below lower limit	9 (56%)
				Within range	6 (38%)
				Above upper limit	1 (6%)
	Intermittent HD	75% (4)	0.58 (0.49 – 0.62)	Below lower limit	2 (50%)
				Within range Above upper limit	2 (50%)0 (0%)
		100% (5)	0.38 (0.36 – 0.49)	Below lower limit Within rangeAbove upper limit	5 (100%)0 (0%)0 (0%)

ICU, Intensive care unit; HD, hemodialysis; CVVHD, continuous veno-venous hemodialysis; PD, peritoneal dialysis; N/A, not applicable. § Therapeutic ranges are 1.0-2.0 IU/mL for once daily dalteparin or 0.6-1.0 IU/mL for twice daily dalteparin.

In total, of 148 anti-Xa levels, only nine (6.0%) levels were above the upper therapeutic limits; four out of these nine elevated anti-Xa levels were observed in patients with an eGFR <30 mL/min/1.73m^2 who received 100% weight-based dose, four in patients with an eGFR <30 mL/min/1.73m^2 who received a 75% weight-based dose and one in a patient with an eGFR of 30-60 mL/min/1.73m^2 who received a 100% weight-based dose (table 2).

Dialysis

The median anti-Xa levels of the non-ICU intermittent hemodialysis (HD) patients who received 100% dose were 1.25 IU/mL (95% CI 1.16-1.34) for once daily and 0.47 IU/mL (95% CI 0.40-1.39) for twice daily (table 4). The median anti-Xa of the ICU continuous veno-venous HD (CVVHD) and intermittent HD patients who received twice daily 100% weight-based dose were, respectively, 0.54 IU/mL (95% CI 0.40-0.75) and 0.38 IU/mL (95% CI 0.36-0.49) (table 3). Only the median anti-Xa levels of non-ICU intermittent HD patients who received once daily 75% and 100% weight-based dose were within range, whereas the other median anti-Xa levels were below the lower therapeutic limit.

Two anti-Xa levels, one of a non-ICU intermittent HD patient and one of an ICU CVVHD patient, exceeded the upper therapeutic limits. Both patients received the 100% weight-based dose.

Bleeding and Thrombosis

A total of eight bleeding events occurred during hospitalization, of which five bleeding events were major and three events were minor. Table 5 depicts the occurrence of bleeding events, corresponding anti-Xa levels and patient and dose characteristics. Bleeding events occurred in both the 75% and 100% weight-based dosed groups, and anti-Xa levels were below range in 4 (44%) patients, within range in 3 (37.5%) patients and above range in 1 (12.5%) patient. Notable is that five of the eight bleeding events (62.5%) occurred in patients on dialysis.

Table 5: Bleeding events in RI patients who received 75% or 100% of the normal dose dalteparin.

Patient	Dose	Bleeding event (n)	Type bleeding event (n)	Defined major/minor bleeding event	Anti-Xa(IU/mL)	Dalteparinfrequency	Within rangea?	Dialysis patient (yes or no, and type)
Non-ICU, eGFR <30 mL/min/1.73m2								
	75%	1	Major (1)	Renal hemorrhage	0.80	1dd	Below	No
	100%	2	Minor (1)	Nosebleed	1.09	2dd	Above	No
			Major (1)	Hematuria	1.25	1dd	Within	Yes, IHD
Non-ICU, eGFR 30-60 mL/min/1.73m2								
	75%	1	Minor (1)	Hematoma in old ICD pocket	0.65	2dd	Within	No
	100%	0	N/A	N/A	N/A	N/A	N/A	N/A
ICU, eGFR <30 mL/min/1.73m2								
	75%	1	Major (1)	retroperitoneal hematoma	0.32	2dd	Below	Yes, CVVHD
	100%	2	Minor (1)	rectal bleeding following procedure	0.16	2dd	Below	Yes, IHD
			Major (1)	melena with >1.24 mmol/L Hb drop	0.30	2dd	Below	Yes, CVVHD
ICU, eGFR 30-60mL/min/1.73m2								
	75%	1	Major (1)	hyper acute cerebral hemorrhage	0.90	2dd	Within	Yes, CVVHD
	100%	0	N/A	N/A	N/A		N/A	N/A

ICU, Intensive care unit; eGFR, estimated glomerular filtration rate; IHD, intermittent hemodialysis; CVVHD, continuous veno-venous hemodialysis; Hb, hemoglobin; ICD, implantable cardioverter-defibrillator; N/A, not applicable.

aTherapeutic ranges are 1.0-2.0 IU/mL for once daily dalteparin or 0.6-1.0 IU/mL for twice daily dalteparin.

A total of two thrombotic events occurred during the use of dalteparin during hospitalization. Both events occurred in ICU patients with an eGFR <30 mL/min/1.73m^2 who received twice daily 100% weight-based dose. The anti-Xa levels were once within therapeutic range in a non-dialysis patient (0.60 IU/mL) and once below the lower limit in a CVVHD patient (0.5 IU/mL).

Discussion

Our data shows that 100% dosing of dalteparin in RI patients does not lead to supratherapeutic anti-Xa levels. Moreover, we showed that bleeding does not occur more frequently in RI patients when dosed a 100% weight-based dose of dalteparin and bleeding events occur regardless of anti-Xa level or dose regimen. This further debates the necessity of pre-emptive dose adjustment based on kidney function for dalteparin. Dose adjustment to 75% of weight-based dose resulted in lower anti-Xa levels in all strata, with medians close to or below the lower therapeutic limits. Most (94%) of the anti-Xa levels of patients receiving a 100% weight-based dose of dalteparin did not exceed the upper therapeutic limits. Furthermore, in non-ICU patients with eGFR <30 mL/min/1.73m^2 and in non-dialysis RI patients, a 100% weight-based dose led to a higher probability of anti-Xa levels being within the therapeutic range.

For the ICU patients in comparison to non-ICU patients, more patients receiving the 100% weight-based dose had anti-Xa levels below range. A possible explanation is the increased volume of distribution for hydrophilic drugs in ICU patients due to fluid resuscitation leading to lower anti-Xa levels in ICU patients [27].

Minor and major bleeding events (N = 8) occurred in both the 75% and 100% weight-based dose groups and thrombotic events (N = 2) were registered in patients who received 100% of the weight-based dose. In the patients with bleeding events, only one of the anti-Xa levels exceeded the upper therapeutic limit and in the patients with thrombosis, anti-Xa levels were at or below the lower therapeutic limit.

Previously, Hornung *et al.* also concluded that pre-emptive dose adjustment of therapeutic dalteparin and nadroparin in patients with an eGFR <60 mL/min/1.73m^2 leads to a high proportion of inadequate anti-Xa levels. There were large differences in the proportion of patients within the therapeutic ranges for dalteparin and nadroparin use and used doses, and no association was found between anti-Xa levels and bleeding or thrombosis in this study [16]. Shprecher *et al.* did not find a significant difference in anti-Xa levels between RI patients and patients with a normal renal function, all of whom received 100% of the weight-based dose of dalteparin. The mean anti-Xa levels were below the lower therapeutic limit. The authors suggest to perform no dose adjustments in RI patients who are not receiving dialysis [3]. Park *et al.* showed that dalteparin at therapeutic doses does not result in increased occurrence of clinically significant bleeding in RI patients and they suggested that RI patients can be administered therapeutic doses of dalteparin in in-hospital settings [17]. Our findings are in agreement with the results of the above mentioned studies. A plausible explanation for the inadequate anti-Xa levels in patients with pre-emptive dose adjustments is that there is no strong correlation between dalteparin elimination and renal clearance [28]. Larger LMWHs, such as dalteparin, show more dependency on non-renal clearance than small LMWHs such as enoxaparin, therefore different LMWHs have various levels of bioaccumulation [15,28,29]. Nevertheless, in the current Dutch guidelines, LMWHs are treated as a class of drugs with similar general characteristics, so for every LMWH the advice is a one-size-fits all. The exception in this guideline is the dose recommendation for tinzaparin, like dalteparin, a large LMWH with a molecular weight of 6500 Dalton. For tinzaparin, no dose reduction is recommended [8,19].

This study is the largest study so far to observe and compare the anti-Xa levels between patients with renal insufficiency using 75% and 100% doses of dalteparin. Shprecher *et al.* and Schmid *et al.* are smaller observational studies (N = 22 and N = 32, respectively) [3,15]. Hornung *et al.* analyzed a larger number of anti-Xa levels in 445 dalteparin users, but information about the time of LMWH administration and time of blood sampling were not available [16]. Therefore, they could not exclude the possibility of incorrect blood sampling, making the results harder to interpret. As shown in figure 1, in our study, many anti-Xa levels were excluded due to wrong timing of sampling. This is in accordance with what we observe in daily clinical practice and therefore we consider this to be information bias in other studies, where adequate timing of sampling has not been confirmed. Accurate sampling is important to be in compliance with the recommendations of the guideline [5]. In addition, we investigated the association between anti-Xa levels within range and dalteparin for unadjusted and adjusted dosages in RI patients. So far, no study has investigated this association.

Previous studies considered dialysis as an exclusion criterion because of evidence-based information about the use of LMWHs in dialysis patients was deemed insufficient [3,15–17]. In the current guidelines it is assumed that LMWHs are not removed from plasma during hemodialysis or continuous veno-venous hemofiltration and therefore pose a risk of bioaccumulation and bleeding when used repeatedly in patients on hemodialysis [22]. Our study, in which hemodialysis patients were included, suggests that while bleeding events do occur in hemodialysis patients using dalteparin, this occurred in both 75% and 100% dosed patients and was unrelated to measured anti-Xa levels. Based on the median anti-Xa levels of ICU dialysis patients and non-ICU intermittent HD patients who received 100% weight-based dose, which were below the lower limits, one would expect no high risk of bioaccumulation. A possible explanation is that hemodialysis does have a potential for drug clearance, as suggested by other authors [30]. Another theory is that dalteparin hepatic clearance could be increased in hemodialysis patients to compensate for the absence of renal clearance, although LMWHs have a minimal hepatic clearance under normal circumstances [31]. We did observe five bleeding events in dialysis patients, of which four where major (table 4), however, the anti-Xa levels remained within acceptable limits. In a subgroup analysis of the Protect trial, dalteparin or UFH use in VTE did not result in a difference in major bleeding; however, this was at a prophylactic dose [32]. In a small RCT studying bridging of oral anticoagulation with therapeutic tinzaparin and dalteparin in hemodialysis patients, both LMWHs accumulated to anti-Xa levels >0.2 IU/mL 20-24 hours after administration [32]. No bleeding events occurred in the dalteparin group [33]. However, no peak anti-Xa levels were reported, making this data hard to compare with the results of our study. Further research evaluating bleeding risk using therapeutic doses of dalteparin and the correlation with anti-Xa levels in dialysis patients is necessary.

As mentioned above, only few bleeding events occurred in our study. The five major bleeding events occurred in both the 75% and 100% dose groups, none of these patients had a supratherapeutic anti-Xa level. Only one patient with a (minor) bleeding event had a supratherapeutic anti-Xa level. Our results suggest that a 100% dalteparin dose is not associated with an increased risk of bleeding in non-dialysis patients. In another study in which RI patients were administered a 100% weight-based dose of dalteparin, the researchers did not observe serious adverse events, and no patients were withdrawn from the study [3]. Our results are also in accordance with Hornung *et al.*, who did not find an association between the anti-Xa level and risk of bleeding and thrombosis [16]. Gómez *et al.* reported a much higher incidence of minor bleeding events in 87 patients with both renal insufficiency and normal renal function using therapeutic dalteparin of 26.8% and 8.7%, respectively, but no major bleeding events were reported [34]. A possible explanation for the high number of reported bleeding events was the high number of surgical patients included in the study.

Our findings question the hypothesis that anti-Xa levels, acting as a surrogate marker for bioaccumulation, are the best clinical predictors of risk of both bleeding and thrombotic events. Indeed, this has been questioned before. Van den Broek suggests in a critical appraisal that anti-Xa levels should not be monitored in patients with renal insufficiency, as use of an upper limit as a marker for bleeding risk is not supported by data [35]. Previous studies have identified multiple other risk factors for in-hospital risk of bleeding and thrombosis, regardless of the use of anticoagulants/LMWHs, including age, gender, presence of cancer,

hepatic failure, critical illness or low platelet count [36]. Indeed, in our study, four out of eight bleeding events (2 minor, 2 major) occurred in ICU patients, but their anti-Xa levels were below or within therapeutic range.

Our study has its limitations, one of which is the retrospective nature of the study. We primarily identified patients based on measured anti-Xa levels, which could mean we did not include all patients with RI and dalteparin if anti-Xa levels were not measured. However, the hospitals works with a Clinical Decisions Support System (CDSS) that identifies all patients using dalteparin and RI. As a result, the pharmacist will always have advised the physician to measure anti-Xa levels in these patients, according to hospital protocol. In our experience, adherence to these advices is high and we do not expect to have missed many patients in our analysis. Another limitation is the large amount of excluded data. Despite the large amount of data we collected, most anti-Xa levels were not suitable for analysis. Many of the collected data were excluded because the blood sampling did not occur on time and/or blood was not drawn when steady state was reached. However, being able to use only the anti-Xa levels drawn conform current guidelines could also be seen as a strength.

Our findings are relevant to clinical practice as they further elaborate on the premise of previous smaller studies that dalteparin dosage should not pre-emptively be adjusted in RI patients. We believe that our findings should be further investigated in a prospective trial to provide conclusive evidence in order to improve patient care. Also, more research on the association between anti-Xa levels and thrombosis and bleeding risk is desirable, as we could not find a correlation between these parameters.

Conclusion

Unadjusted (100%) weight-based dalteparin therapy in RI patients resulted in a higher probability of anti-Xa levels within range, without increasing the risk of clinically relevant bioaccumulation. Bleeding incidence was low, and there were no differences in the occurrence of bleeding when dosed 75% vs. 100% in RI patients. Therefore, we conclude that it is likely that preemptive dose adjustment of dalteparin is not necessitated in RI patients. Nonetheless, preventing bleeding events still requires monitoring in these patients and risk of bleeding should always be considered while using dalteparin in a therapeutic dose, especially if other risk factors for bleeding are present.

Statements and Declarations

Contributions of Authors statement

K.C. Pires and H.L. Le designed the method and collected the data. K.C. Pires, L. Mitrov-Winkelmolen, R.A.M. Quax, M. Wabbijn and T.M. Bosch verified the collected data. K.C. Pires, L. Mitrov-Winkelmolen and T.M. Kuijper analyzed the results. K.C. Pires and L. Mitrov-Winkelmolen wrote the manuscript. T.M. Kuijper performed the statistical analysis, wrote the method of the statistical analysis, and contributed to writing the results. R.A.M. Quax, R. Ruiter, M. Wabbijn, T.M Kuijper and T.M Bosch critically reviewed and edited the manuscript

Ethics Approval Statement

This study was approved by the Board of Directors of Maasstad Hospital and Ikazia Hospital, Rotterdam, The Netherlands. The Executive Board of the Review Committee Scientific Research Rotterdam gave permission to perform this study and concluded that this study does not fall under the Medical Research Involving Human Subjects Act. For personal data protection, all data were anonymized before analysis.

Patient Consent Statement

Patients were not involved in the plans for design, conduct, reporting or dissemination of the research

Permission to Reproduce Material from other Sources

For this study, no material from other sources has been reproduced

Conflict of Interest

Nothing to declare

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated during the current study

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