Practical value of anti-xa activity in the evaluation of extracorporeal circuit anticoagulation during haemodialysis

Citation for published version (APA):

Coene, K. L. M., Dekker, M. J. E., Kerskes, M. C. H. M., Hengst, M., Schonck, M. J. M., Konings, C. J. A. M., & Scharnhorst, V. (2017). Practical value of anti-xa activity in the evaluation of extracorporeal circuit anticoagulation during haemodialysis: Results of a cross-sectional single-centre study. *Nephron*, 137(3), 205-211. <https://doi.org/10.1159/000479390>

DOI:

[10.1159/000479390](https://doi.org/10.1159/000479390)

Document status and date:

Published: 01/10/2017

Document Version:

Accepted manuscript including changes made at the peer-review stage

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.tue.nl/taverne

Take down policy

If you believe that this document breaches copyright please contact us at:

openaccess@tue.nl

providing details and we will investigate your claim.

Practical value of anti-Xa activity in the evaluation of extracorporeal circuit anticoagulation during haemodialysis: results of a cross-sectional single centre study.

Journal:	<i>Nephron</i>
Manuscript ID	201702016.R1
Manuscript Type:	Original Paper
Date Submitted by the Author:	n/a
Complete List of Authors:	Coene, Karlien; Catharina Ziekenhuis, Clinical Laboratory Dekker, Marijke; Catharina Ziekenhuis, Department of Internal Medicine Kerskes, Marieke; Catharina Ziekenhuis, Department of Clinical Pharmacy Hengst, Maaïke; Catharina Ziekenhuis, Department of Internal Medicine Schonck, Marc; Catharina Ziekenhuis, Department of Internal Medicine Konings, Stijn; Catharina Ziekenhuis, Department of Internal Medicine Scharnhorst, Volkher; Catharina Ziekenhuis, Clinical Laboratory; Technical University Eindhoven, Department of Biomedical Engineering
Keywords:	Haemodialysis, Low molecular weight heparin, Anti-factor Xa activity, Anticoagulation therapy

SCHOLARONE™
Manuscripts

Practical value of anti-Xa activity in the evaluation of extracorporeal circuit anticoagulation during haemodialysis: results of a cross-sectional single centre study.

Running title:

Anti-Xa activity in the evaluation of LMWH dosage during haemodialysis.

Karliën L.M. Coene¹, Marijke J.E. Dekker², Marieke C.H.M. Kerskes³, Maaïke Hengst², Marc J.M. Schonck², Constantijn J.A.M. Konings², Volkher Scharnhorst^{1,4}

- 1. Clinical Laboratory, Catharina Hospital Eindhoven, Eindhoven, The Netherlands
- 2. Department of Internal Medicine, Catharina Hospital Eindhoven, Eindhoven, The Netherlands
- 3. Department of Clinical Pharmacy, Catharina Hospital Eindhoven, Eindhoven, The Netherlands
- 4. Department of Biomedical Engineering, Technical University Eindhoven, Eindhoven, The Netherlands

Key words: Haemodialysis, anticoagulation therapy, anti-Xa activity.

Corresponding author:

Karliën L.M. Coene
Clinical Laboratory
Catharina Hospital Eindhoven
Michelangelolaan 2
5623 EJ Eindhoven
The Netherlands
0031 40 239 9111
coene.karliën@gmail.com

Abstract**Background/Aims:**

Anticoagulation of the extracorporeal circuit (ECC) is essential for adequate haemodialysis (HD). Low molecular weight heparins (LMWHs) are safe and sufficient towards this goal. In the Netherlands, dosage is based on bodyweight and adjusted based on clinical events. LMWH levels during dialysis can be quantified through measurement of the anti-Xa activity, and a target range of 0.5-1.0 IU/mL has been proposed. We aimed to evaluate the practical value of the anti-Xa activity to guide LMWH dosage in HD patients. Additionally, the value of the activated partial thromboplastin time (APTT) was investigated.

Methods:

All prevalent adult HD patients of our dialysis clinic were included. APTT and anti-Xa activity were measured before, during and after two dialysis sessions. Clinical and dialysis characteristics, including LMWH dosage, were derived from digital patient charts.

Results:

Our final study cohort consisted of 83 patients. LMWH dosage during dialysis was appropriate for bodyweight in 61% of cases, of which 50% reached an anti-Xa activity within the putative target range of 0.5-1.0 IU/mL. 46% of patients had an anti-Xa activity >1.0 IU/mL. Anti-Xa levels during and after dialysis were significantly correlated ($r=0.803$, $P<0.01$). No thrombotic or haemorrhagic complications were observed in this study. Correlation of APTT with anti-Xa activity was poor.

Conclusion:

Anti-Xa activity measurements during dialysis can identify patients in whom LMWH dosage should be lowered in a subsequent dialysis session. If such an intervention leads to a decrease in haemorrhagic complications needs to be evaluated in prospective studies.

Introduction

In prevalent haemodialysis (HD) patients, clotting of the extracorporeal circuit (ECC) is still a major inconvenience for patients and dialysis staff and reduces HD efficacy. To prevent coagulation of the ECC, in the Netherlands, as in other countries in Europe, low molecular weight heparins (LMWHs) are administered at the start of the HD session [1,2]. LMWHs have been established as a safe and effective alternative to unfractionated heparin (UFH) during HD [3,4]. The advantage of LMWHs over UFH is that, in most cases, a single bolus at the start of the HD session is sufficient for appropriate anticoagulation and a lower bleeding complication rate has been reported in several studies [5].

However, literature on the optimal LMWH dosage for ECC clotting prevention is scarce and available studies do not agree on a standardized dosing protocol [5–8]. In current clinical practice in the Netherlands, the initial LMWH dose is based on patient bodyweight, consistent with national guidelines, which were based on the European Best Practice guidelines [2,9]. Patients with a weight below 50 kg receive 2500 IU LMWH at the start of dialysis, while patients heavier than 50 kg receive a dosage of 5000 IU. The nephrologist re-evaluates this LMWH dosage every HD session and adjusts the dosage based upon occurrence of thrombotic or haemorrhagic events. The goal of this approach is to administer the lowest possible dose of LMWH to achieve optimal anticoagulation while preventing haemorrhagic complications [9]. Ideally, an uneventful previous dialysis session should therefore trigger the clinical nephrologist to consider a decrease in LMWH dosage.

To tailor the LMWH dosage for the individual patient, it may be useful to objectively monitor LMWH effectiveness during dialysis. With the development of automated assays to directly measure the factor Xa inhibiting effect of LMWHs, a tool for monitoring LMWH therapy during dialysis is readily available [10]. However, guidelines on how to use the anti-Xa activity for this purpose are lacking and no consensus has been reached on the target range nor on the optimal time point for measurement of the anti-Xa activity during dialysis [7,11]. The summary of product characteristics (SMPC) of the LMWH Dalteparin advises an anti-Xa target range of 0.5-1.0 IU/ml during dialysis [12]. However, all putative anti-Xa target ranges described in literature have not been validated for the prevention of ECC clotting through randomized control trials, making their clinical relevance and applicability unclear. As LMWHs are administered with the sole purpose to prevent coagulation of the ECC, anti-Xa activity levels should be undetectable or at least below the target range after dialysis to prevent increased haemorrhagic risks for patients. Also anti-Xa target values at the end of the dialysis session have been previously reported, for example an anti-Xa activity <0.4 IU/ml by Sridharan et al [7].

In this study, we retrospectively evaluated our HD cohort for concurrence of the administered dose of the LMWH Dalteparin with the dose advised in the national guideline [9]. By measuring anti-Xa activity levels before, during and after HD, we aimed to gain more insight in the value of objective laboratory monitoring of LMWH. Because of the still limited availability of the anti-Xa activity assay in

hospital laboratories, we performed a sub-analysis to assess the activated partial thromboplastin time (APTT) as an alternative parameter to gain insight in overall coagulation status in prevalent HD patients.

Patients and Methods

Study protocol

In this single centre, open-label, cross-sectional study, we included all prevalent in-centre HD and haemodiafiltration (HdF) patients of the Catharina Hospital Eindhoven, who received the LMWH Dalteparin as anticoagulant. **Patients gave informed consent for participation in this study.** Exclusion criteria were age below 18 years, pregnancy, hypersensitivity to LMWHs, history of heparin-induced thrombocytopenia, major trauma or surgery within the two weeks prior to enrolment or withdrawal of consent. **Use of anticoagulants, such as vitamin K antagonists, was not considered an exclusion criterion. We chose this strategy to reflect the real-time situation in our dialysis clinic, in which patients are dosed with LMWH during dialysis regardless of concomitant use of other anticoagulants.** The study was approved by the Hospital Board and conducted following the Good Clinical Practice Guidelines.

Blood for determination of anti-Xa activity, prothrombin time (PT), INR and APTT was drawn from the inlet lines of the dialysis machine at the start of dialysis, 15 minutes after LMWH administration, corresponding to the peak anti-Xa activity [11] and at the end of dialysis. **Standard duration of dialysis was 4 hours.** Sampling was performed during two dialysis sessions with an interval of one month. **The results for the anti-Xa activity were evaluated retrospectively and did not influence the decision of the attending nephrologist on the LMWH dosage administered.**

Before the start of dialysis, patients received an initial bolus of LMWH intravenously, which ranged from 1250 IU to 7500 IU. According to the national guidelines, dosage was initially based on pre-dialysis weight, and was adapted over time based either on thrombotic events, or on uneventful dialysis [9]. Dialysis was started immediately after application of the first LMWH bolus. During and after the dialysis treatment, the extracorporeal circuit was checked for fibrin deposition and clot formation. When the time of compression necessary to stop bleeding from the puncture exceeded 15 minutes, it was noted in the patient chart as prolonged. Individual patient characteristics and dialysis and clinical parameters were derived from digital patients charts. The anti-Xa activity target range of 0.5-1.0 IU/L was based on the SMPC of the LMWH Dalteparin [12].

Laboratory tests

Samples for analysis of anti-Xa activity were collected in 0.109M sodium citrate tubes (Vacutainer, Beckton Dickinson, Breda, the Netherlands), which were centrifuged within 30 minutes after blood draw at 2500 RCF for 15 minutes. The anti-Xa activity was assessed on an automated STA-R platform with the STA liquid anti-Xa reagent, which was calibrated using the MultiHep calibrator (both from Diagnostica Stago, Asnières, France) and to which no antithrombin was supplemented. Samples for analysis of APTT and PT/INR were also collected in 0.109M sodium citrate tubes (Vacutainer, Beckton Dickinson, Breda, the Netherlands), but were centrifuged within 30 minutes after blood draw at 2600 RCF for 5 minutes. PT/INR was analysed with Neoplastin Plus reagent, which neutralizes LMWHs levels up to 1.5 IU/ml anti-Xa activity. APTT was analysed with STA APTT reagent (reference interval 31-40 seconds), both on an automated STA-R platform (all from Diagnostica Stago, Asnières, France).

Statistical analysis

We used T-Tests and Mann-Whitney U-tests, with $P < 0.05$ as a threshold for statistical significance, to compare clinical and laboratory parameters, depending on their distribution. To analyse potential differences between the anti-Xa activity measurements at the two time points, we used a Wilcoxon Signed Rank test before pooling the sample results. All analyses were performed with SPSS version 23.0 (IBM SPSS Statistics for Windows, version 23.0, Armonk, NY, USA).

Results

Study cohort and LMWH dosage

Out of the 106 eligible patients that gave consent to participate in the study, the complete set of blood samples of both dialysis sessions could be obtained for 83 patients. Reasons for exclusion were intercurrent illness ($N=3$) or unavailability of the complete blood set of anti-Xa activity measurements in month 1 ($N=14$) or month 2 ($N=9$) (**Figure 1**).

Patients' characteristics of the total cohort, the study cohort and the excluded cohort are presented in **Table 1**. Patients in the final study cohort had a lower prevalence of diabetes mellitus (28.9% versus 34.0%, $P=0.02$) and vitamin K antagonist usage (26.5% versus 56.5%, $P=0.01$) than patients in the excluded study cohort (**Table 1**). The administered Dalteparin dosage was slightly, but significantly lower in the excluded patient cohort compared to the study cohort (4345 U/mL versus 4512 U/mL, $P=0.02$) (**Table 1**). The majority of patients received either 5000 IU or 2500 IU Dalteparin prior to dialysis (**Supplemental Table 1**). Artificial kidneys that were used in the eligible patient cohort were Polyflux 210 H (55.7%), Polyflux 17L (40.5%) and Hospal Nephral (3.8%).

Anti-Xa activity before, during and after dialysis

After confirmation that the anti-Xa activity levels did not significantly differ between the two study months, all measurements from the 83 included patients were pooled (**Table 2**). Anti-Xa activity at the start of the dialysis session was undetectable in 91% patients (median 0.0 (25th and 75th interval 0-0) **Table 2**). Post-dialysis median anti-Xa activity was 0.32 IU/mL (25th and 75th percentile 0.24-0.48) in the first study month (**Table 2**). Anti-Xa activity during dialysis significantly correlated to anti-Xa activity post-dialysis (Pearson correlation coefficient 0.803, $P < 0.01$).

In 61% of all cases, Dalteparin dosage was correct for patient body weight. Within this category, in exactly 50% of cases, an anti-Xa activity within the range of 0.5-1.0 IU/mL was achieved 15 minutes after Dalteparin administration, while in 46% of cases, anti-Xa activity exceeded 1.0 IU/mL (**Table 3**). All patients with a Dalteparin dosage above the dosage advised by the guideline based on their bodyweight (10% of all cases) achieved an anti-Xa activity above 0.5 IU/mL during dialysis, with the majority (65% within group) having an anti-Xa activity of > 1.0 IU/mL. Out of the patients for whom Dalteparin dosage was lower than the recommended dosage for bodyweight (29% of all cases), two third reached an anti-Xa activity range above 0.5 IU/mL during dialysis (out of which 54% fell within the range of 0.5-1.0 IU/mL), while one third had an anti-Xa activity of < 0.5 IU/mL. After dialysis, an anti-Xa activity level < 0.5 IU/L was found in 75% of cases. During this study, no coagulation problems of the ECC occurred. Only minimally prolonged bleeding time (< 5 additional minutes) was observed in 4 patients.

Analysis of APTT during dialysis

Because of the still limited availability of the anti-Xa activity assay in hospital laboratories, we assessed to what extent the APTT assay might provide insight in Dalteparin dosage in dialysis patients. Taking all patient results into account, we found poor correlation between the anti-Xa activity and the APTT with an R^2 value of 0.269 (**Figure 2**). However, it was apparent that an APTT longer than 175 seconds always corresponded to anti-Xa level exceeding 1.0 IU/mL.

Discussion

We measured anti-Xa activity to objectively evaluate the LMWH dosage regime in our HD patient cohort. Anti-Xa activity levels before start of dialysis were < 0.5 IU/ml, confirming previous findings that LMWHs do not accumulate in HD patients [11]. The median (25th-75th percentile) anti-Xa activity levels during dialysis in this study, 0.82 IU/mL (0.60-1.11) for the first and 0.77 IU/mL (0.60-1.05) for the second month, are lower than the peak anti-Xa level during dialysis described by Nigten et al., where in 9 HD patients an overall range of 0.71-1.24 IU/mL anti-Xa activity was found [11]. Apart from the larger patient cohort analysed in this study, a possible explanation for the lower anti-Xa activity found during dialysis could be the different anti-Xa reagent used. An important factor that

introduces variability in the anti-Xa activity measured is the addition versus omission of exogenous antithrombin to the anti-Xa assay, which has been previously shown in the estimation of UFH and rivaroxaban concentrations [13,14]. Some anti-Xa reagents contain antithrombin to correct for in vivo antithrombin deficiency, as LMWHs need to complex with antithrombin to be able to bind and deactivate factor Xa [15]. Especially in patients with long-term use of LMWH, acquired antithrombin deficiency can develop when antithrombin production does not equal antithrombin loss through clearance of the LMWH-antithrombin complex, as was also found for patients on long-term UFH therapy [16]. In our study, the Stago Liquid anti-Xa assay without supplementation of exogenous antithrombin was used for anti-Xa activity measurement, which could possibly lead to lower anti-Xa levels measured in antithrombin deficient patients. In comparison, in the study of Nigten et al., the antithrombin-supplemented Biophen Heparin reagent was used [11]. The previously mentioned anti-Xa target ranges do not specifically state whether anti-Xa activity should be determined with or without addition of exogenous antithrombin. This underscores the uncertainties of anti-Xa activity-based LMWH dosage in patients on in-center HD.

The SMPC of the LMWH Dalteparin advises a target range of 0.5-1.0 IU/mL anti-Xa activity during dialysis [12]. This target range likely originates from a clinical validation of Enoxaparin in the prevention of deep vein thrombosis after hip replacement [17]. Although the clinical efficacy of this anti-Xa target range has not been validated for the use of Dalteparin in the prevention of coagulation of the ECC during dialysis, we evaluated correspondence of this target range to the LMWH dosing schedule based on patient bodyweight. It was striking that only half of the patients who received the correct LMWH dose based on their bodyweight actually reached an anti-Xa activity level within the above mentioned target range. Elevated anti-Xa levels during dialysis were found to relate to higher anti-Xa activity levels post-dialysis, with almost a quarter of the total patient cohort leaving the dialysis clinic with an anti-Xa activity exceeding 1.0 IU/mL. However, from this study it was not apparent that a higher anti-Xa level also translated in an increased bleeding risk, as no bleeding complications were reported. The clinical consequences of increased anti-Xa levels during and after dialysis need to be assessed in future prospective studies.

During the study period, we also did not observe clinically significant coagulation of the ECC, independent of the anti-Xa activity measured. Even in the group of patients that received lower LMWH dosages than advised based on their weight and did not reach the anti-Xa activity target range of 0.5-1.0 IU/mL, adequate dialysis was still possible. That a lower anti-Xa activity could still be adequate for efficient dialysis has also been suggested in other studies, which advise a lower target range compared to the Dalteparin SMPC [5,10]. The following observation also argues for a possible

decrease in LMWH dosage in a selection of dialysis patients. In daily practice, an increase in LMWH dosage because of clotting complications of the ECC is often perpetuated in subsequent dialysis sessions. In the ideal situation, the LMWH dosage should be decreased again after several adequate dialysis sessions in which coagulation of the ECC does not occur. However, in the busy daily routine of the dialysis clinic, decreasing the LMWH dosage upon a series of uneventful dialysis sessions might not get priority of the attending clinician. We therefore believe that periodic assessment of anti-Xa activity during dialysis can actively identify patients in which the nephrologist should consider decreasing the LMWH dosage. Due to the design of this study, we can only hypothesize if aiming for a lower anti-Xa activity level during dialysis still enables optimal dialysis efficiency while reducing haemorrhagic risk.

In this study, we also assessed to what extent the APTT could give information on LMWH levels during dialysis, as the anti-Xa assay is not readily available in some hospital laboratories. The APTT is used for monitoring therapy with UFH, but is thought to be less appropriate for guiding LMWH dosage due to its relative insensitivity to LMWHs [15]. However, as the APTT depends on the factor Xa available in patient plasma, we hypothesized that significant LMWH levels during dialysis would also reflect in the APTT. It should be mentioned that the PT/INR is unfit for monitoring LMWHs as the PT reagent used in this study neutralizes LMWH levels up to 1.5 IU/mL anti-Xa activity. Upon comparison of APTT with anti-Xa activity during dialysis, we found a poor correlation, preventing direct translation of APTT in anti-Xa activity. However, from our data it became apparent that an APTT >175 seconds always corresponded to an anti-Xa activity of >1.0 IU/mL. The APTT might therefore be of value to identify a small selection of patients in whom decrease of LMWH dosage should be attempted, when anti-Xa activity measurement is not at hand. The above-mentioned APTT cut-off point obviously differs between different types of APTT reagents, and should therefore be validated by individual laboratories.

Some limitations to our study design need to be acknowledged. Firstly, the degree of clotting of the ECC was assessed subjectively, without the use of a pre-defined scoring system. In this way, subtle differences in ECC clotting status between patients might not have been recognized in an optimal manner. Secondly, as previously stated, the anti-Xa target range to which we correlated the weight-based LMWH dosing protocol was not validated for clinical efficacy in prevention of ECC clotting. Even though no hard evidence exists for this target range, the data we find in this study suggest that anti-Xa measurements can be used to identify patients in whom titration to a lower LMWH dosage should be considered. It seems legitimate in the prevention of haemorrhagic complications to reduce LMWH dosage to the lowest level still effective for anticoagulation. Future studies are needed to

delineate a clinically effective anti-Xa target range, and should also incorporate recommendations on optimal time of anti-Xa sampling during dialysis and preferred anti-Xa reagent. **Finally, one could argue that inclusion of patients on VKA is a limitation of our study. However, in daily practice in the dialysis clinic also these kind of patient are dosed with LMWH during dialysis, and no distinction is made in dosing protocol between VKA users and non-users. Therefore, we feel it is important to include VKA users in our analyses to reflect the real-time situation. As no bleeding or thrombotic complications occurred in our study, we cannot determine the effect of VKA use on either of these events. To further evaluate how use of VKA reflects in laboratory parameters, we performed a sub-group analysis for VKA users versus non-users for anti-Xa activity level and APTT during dialysis (Supplemental figure 1). From this analysis, it became apparent that peak APTT clotting times were significantly longer for VKA users, while no significant effect of VKA use on anti-Xa activity levels was observed. This finding touches on the debate on which parameter offers the best reflection of overall patient coagulation status. Factor deficiencies will come to light in a prolonged APTT, but also factors that are not associated with in vivo coagulation, such as lupus inhibitors, will influence the APTT [15]. On the other hand, the anti-Xa activity is a more direct measure of LMWH but does not take overall patient coagulation status into account. Our data support the notion that the APTT reflects factor deficiencies due to use of VKA, which remain undetected in the anti-Xa activity assay. From a clinical perspective, this might implicate an increased bleeding risk in dialysis patients with concomitant use of VKA. The guidelines for LMWH dosing we assessed in this study do not advise a different strategy for VKA users, however, it seems advisable to tightly monitor these patients for bleeding complications and reduce LMWH dosage if necessary. As stated previously, no clinically relevant bleeding events were recorded in our study. The clinical validity of this putative VKA effect on bleeding risk warrants further study, in which also patients starting with dialysis should be included, as complications might be more evident in the initial phase of titration to appropriate LMWH dosage.**

Conclusion

In conclusion, this current study provides evidence that periodic measurement of the anti-Xa activity can aid in the identification of dialysis patients amenable for further lowering of LMWH dosage. If such an intervention reduces patient risk of post-dialysis haemorrhagic complications should be assessed in future prospective studies.

Acknowledgements

We are indebted to the patients of the dialysis clinic of the Catharina Hospital Eindhoven for their willingness to participate in this study.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

- 1 Gunal AI, Duman S, Ozkahya M, Toz H, Asci G, Akcicek F, et al.: Strict volume control normalizes hypertension in peritoneal dialysis patients. *Am J Kidney Dis* 2001;37:588–593.
- 2 Guideline V, V CG: Section V. Chronic intermittent haemodialysis and prevention of clotting in the extracorporeal system. *Nephrol Dial Transplant* 2002 [cited 2017 Jan 3];17 Suppl 7:63–71.
- 3 Lim W, Cook DJ, Crowther MA: Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: a meta-analysis of randomized trials. *J Am Soc Nephrol* 2004;15:3192–206.
- 4 Grau E, Siguenza F, Maduell F, Linares M, Olaso MA, Martinez R, et al.: Low molecular weight heparin (CY-216) versus unfractionated heparin in chronic hemodialysis. *Nephron* 1992 [cited 2017 Jan 3];62:13–17.
- 5 Polkinghorne KR, McMahon LP, Becker GJ: Pharmacokinetic studies of dalteparin (Fragmin), enoxaparin (clexane), and danaparoid sodium (orgaran) in stable chronic hemodialysis patients. *Am J Kidney Dis* 2002 Nov;40:990–995.
- 6 Ouseph R, Ward RA: Anticoagulation for intermittent hemodialysis. *Semin Dial* 2000 [cited 2017 Jan 3];13:181–187.
- 7 Sridharan S, Berdeprado J, Sivalingam M, Farrington K: Dalteparin dosing in high-flux haemodialysis and haemodiafiltration. *Nephron - Clin Pract* 2013;122:53–57.
- 8 Verhave G, Weijmer MC, Jaarsveld BC Van: Anticoagulation with dalteparin and nadroparin in nocturnal haemodialysis. *Neth J Med* 2015;73:270–275.
- 9 Antistolling bij hemodialyse, 2012 | Nederlandse Federatie voor Nefrologie [cited 2017 Jan 3]; Available from: <https://www.nfro.nl/richtlijnen/antistolling-bij-hemodialyse-2012>
- 10 Pauwels R, Devreese K, Van Biesen W, Eloit S, Glorieux G, Vanholder R, et al.: Bedside monitoring of anticoagulation in chronic haemodialysis patients treated with tinzaparin. *Nephrol Dial Transplant* 2014;29:1092–1096.
- 11 Nigten J, De Groot KA, Grootendorst DC, Koolen SLW, Herruer MH, Schut NH: Pharmacokinetics of dalteparin during haemodialysis. *Nephron - Clin Pract* 2013;124:179–183.
- 12 Dalteparine | Farmacotherapeutisch Kompas [cited 2017 Jan 3]; Available from: <https://www.farmacotherapeutischkompas.nl/bladeren-volgens-boek/preparaatteksten/d/dalteparine>
- 13 Kitchen S, Theaker J, Preston FE: Monitoring unfractionated heparin therapy: relationship

1
2
3 between eight anti-Xa assays and a protamine titration assay. Blood Coagul Fibrinolysis 2000
4 Mar [cited 2017 Jan 6];11:137–144.
5
6 14 Gosselin RC, Funk DM, Taylor JM, Francart SJ, Hawes EM, Friedman KD, et al.: Comparison of
7 anti-Xa and dilute Russell viper venom time assays in quantifying drug levels in patients on
8 therapeutic doses of rivaroxaban. Arch Pathol Lab Med 2014 Dec;138:1680–1684.
9
10 15 Vandiver JW, Vondracek TG: Antifactor xa levels versus activated partial thromboplastin time
11 for monitoring unfractionated heparin. Pharmacotherapy 2012 Jun;32:546–558.
12
13 16 Coene KLM, van der Graaf F, van de Kerkhof D: Protocolled Redefinition of the Therapeutic
14 Range for Unfractionated Heparin: Lost in Translation? Clin Appl Thromb 2016 Nov 16; DOI:
15 10.1177/1076029616679508
16
17 17 Levine MN, Planes A, Hirsh J, Goodyear M, Vochelle N, Gent M: The relationship between
18 anti-factor Xa level and clinical outcome in patients receiving enoxaparine low molecular
19 weight heparin to prevent deep vein thrombosis after hip replacement. Thromb Haemost
20 1989 Nov 24 [cited 2017 Jan 25];62:940–944.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tables

Table 1: Patient characteristics

	Study cohort		Excluded patients		Eligible patients		P
N	83		23		106		
Parameter	mean	SD	mean	SD	mean	SD	
Age (years)	71.28	11.08	70.4	12.24	67.22	15.62	0.20
Dialysis vintage (months (median and 25th-75th percentile))	27	11-56			32	14-68	0.60
Target weight (kg)	74.45	12.87	73.04	14.73	72.68	15.23	0.60
Dalteparin dosage (IU)	4512	1467	4345	2151	4478	1618	0.02
	%						
Male	54.2		53.8		52.2		0.80
High Flux Haemodialysis	55.4		58.5		69.6		0.51
Haemodiafiltration post dilution	44.6		41.5		30.4		0.22
Diabetes Mellitus present	28.9		34.0		54.5		0.02
Catheter access	25.3		25.5		27.3		0.50
Vitamin K antagonist usage	26.5		56.5		33.0		0.01

Legend Table 1: P-value represents chi-square analysis, unpaired student T test or Mann-Whitney U analysis, depending on distribution of the data, between the study cohort and the cohort of excluded patients.

Table 2: Anti-Xa activity (IU/mL) pre-, during- and post-dialysis for the two study months separately.

Samples drawn	Pre-dialysis anti-Xa activity (IU/mL)		During dialysis anti-Xa activity (IU/mL)		Post-dialysis anti-Xa activity (IU/mL)	
	median	25 th -75 th percentile	median	25 th -75 th percentile	median	25 th -75 th percentile
Month 1	0	0-0	0.82	0.60-1.11	0.32	0.24-0.48
Month 2	0	0-0	0.77	0.60-1.05	0.33	0.26-0.46
p*	0.09		0.20		0.1	

Legend Table 2: *P = results of a Wilcoxon Signed Rank test

Table 3: Anti-Xa activity (IU/mL) for patients stratified based on LMWH dosage according to bodyweight (kg).

	Dalteparin dosage based on bodyweight (kg)					
	below		correct		above	
Anti Xa during dialysis (IU/mL)	N	%	N	%	N	%
< 0.5	16	15.2	4	3.8	0	-
0.5-1.0	26	24.8	50	47.6	6	5.7
>1.0	6	5.7	46	43.8	11	10.5

Legend Table 3: Pooled data of the 83 included patients.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Supplemental table 1. Overview of Dalteparin dosage in the study cohort.

Dalteparin dosage IU/L	October (% of total)	November (% of total)
1250	1.2	2.4
1875	1.2	1.2
2500	25.3	22.9
3750	2.4	1.2
5000	57.8	56.6
7500	4.8	6.0
2x2500	3.6	4.8
1x2500+1x1250	1.2	1.2
1x5000+1x1250	2.4	2.4

Legend Supplemental Table 1: Administered Dalteparin dosages of the study cohort in the months October and November.

Figure 1: Study flow chart.

Figure 2: Correlation between peak anti-Xa activity and APTT 15 minutes after start of dialysis (R^2 0.269).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43

Supplemental Figure 1. Comparison of peak anti-Xa activity (left) and peak APTT (right) levels during dialysis between vitamin K antagonist (VKA) users and non-users. Box represents first to third quartile, horizontal line within box represents median. Whiskers represent minimal and maximal value, circles represent extreme values. Asterisk indicates significant difference ($P < 0.01$, Mann-Whitney U-test).