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REVIEW

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# Critical appraisal of evidence for anti-Xa monitoring and dosing of low-molecular-weight heparin in renal insufficiency

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**ABSTRACT**

**Introduction:** Several guidelines advise to monitor therapeutic LMWH therapy with peak anti-Xa concentrations in renal insufficiency with subsequent dose adjustments. A better understanding of the clinical association between peak anti-Xa concentrations and clinical outcomes is mandatory, because misunderstanding this association could lead to erroneous, and potentially even harmful, LMWH dose adjustments

**Areas covered:** We reviewed the evidence of the widely applied therapeutic window for anti-Xa peak concentrations and report on the evidence for pharmacokinetic dose reduction in renal insufficiency, limitations of peak and trough anti-Xa concentration monitoring.

**Expert opinion:** The added value of peak anti-Xa monitoring in patients with renal insufficiency, receiving a dose reduced for pharmacokinetic changes, is not supported by data. Enoxaparin and nadroparin should be adjusted to 50–65% and 75–85% of the original dose for patients with a creatinine clearance (CrCL) of <30 ml/min and 30–60 ml/min, respectively. Tinzaparin should be adjusted to around 50% of the original dose for patients with a CrCL of <30 ml/min. In case anti-Xa monitoring is applied, trough concentration anti-Xa monitoring is preferred over peak monitoring, aiming at a maximum concentration of 0.4 IU/mL for once-daily dosed tinzaparin and 0.5 IU/mL for twice-daily dosed enoxaparin and nadroparin.

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Low molecular weight heparin; LMWH; renal insufficiency; anti-Xa; therapeutic window; therapeutic drug monitoring; dosing; pharmacokinetics; trough concentration; peak concentration

## 1. Introduction

Therapeutic doses of low-molecular-weight heparins (LMWHs) are used for the treatment and prevention of venous thrombosis for several indications, such as venous thromboembolism (VTE) and atrial fibrillation (AF).

LMWHs are fragments of unfractionated heparin (UFH) and have several advantages over UFH. One of these is a longer half-life, which enables intermittent administration instead of continuous infusion, thereby making LMWHs suitable for (subcutaneous) administration by the patient at home instead of by a nurse in a hospital. Another advantage is that LMWHs have a more predictable antithrombotic effect, because LMWHs predominantly only affect the activity of factor Xa. In contrast, UFH also affects factor II. Because of this, UFH dosing should be monitored and adjusted using the activated partial thromboplastin time (aPTT) hemostatic parameter. However, since LMWH does not affect factor II, aPTT monitoring is deemed unnecessary in LMWH therapy.

Conversely, LMWHs also have some disadvantages compared to UFH. LMWHs, which consist of small fragments of UFH, have a different route of elimination. UFH is eliminated by the reticuloendothelial system and the liver, but LMWHs are eliminated by glomerular filtration in the kidneys. In consequence, LMWHs can accumulate in patients with renal insufficiency, resulting in an increased risk of bleeding in these patients. The anticoagulant effect of LMWHs can be monitored by determining anti-Xa concentrations in the patient's blood. The LMWH interacts with the endogenous anticoagulant protein antithrombin III (AT). In an indirect way, this AT-LMWH complex results in an increased plasma anti-Xa concentration, which can be determined with a chromogenic assay and is considered to be directly proportional to the LMWH plasma concentration. A meta-analysis confirmed an increased risk of bleeding in patients with severe renal insufficiency when treated with unadjusted therapeutic LMWH doses [1]. Accumulation of LMWHs in these patients is confirmed by increased anti-Xa concentrations.

As a consequence of the risk of LMWH accumulation in renal insufficiency, several guidelines recommend upfront LMWH dose reductions in these patients, with anti-Xa peak concentration therapeutic drug monitoring (TDM) 3 to 4 (or even up to 5) hours after administration [2–4]. For once-daily dosed LMWHs, such as tinzaparin, anti-Xa peak concentrations have been reported to be within the 1.0–2.0 IU/mL range [5]. For twice-daily dosed LMWHs, such as nadroparin, enoxaparin and dalteparin, different ranges of anti-Xa peak concentrations have been reported in guidelines, ranging from 0.5 or 0.6 IU/mL as the lower boundary to 1.0 IU/mL as the upper boundary [6,7]. These different therapeutic ranges illustrate the need for a better understanding of the clinical association between

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**Article highlights**

- No therapeutic window for peak anti-Xa concentrations for venous diseases in patients with renal insufficiency has been identified. Adjusting the therapeutic LMWH dose in patients with renal insufficiency, taking into account the pharmacokinetic differences, without additional anti-Xa monitoring, will suffice.
- There is consistent data on how LMWH anti-Xa clearance is affected by different degrees of renal insufficiency. For enoxaparin and nadroparin doses should be adjusted to 50-65% and 75-85% of the original dose for patients with a creatinine clearance of <30 ml/min and 30-60 ml/min respectively. For tinzaparin the dose should be adjusted to around 50% of the original dose for patients with a creatinine clearances of <30 ml/min.
- There is increasing awareness that trough anti-Xa concentrationslevl might be a more suitable safety and efficacy parameter. In case anti-Xa monitoring is deemed necessary, maximum trough anti-Xa concentrations of 0.4 IU/mL for once-daily dosed tinzaparin and 0.5 IU/mL for twice-daily dosed enoxaparin and nadroparin seem to be suitable.
- Anti-Xa assay results should be interpreted cautiously since many factors affect the results, such as LMWH batch-to-batch differences in the same brand, patient characteristics (e.g. cirrhosis, hyperbilirubinemia) and assay characteristics.
- Patient or clinical intervention characteristics may play a more important role in causing a bleed rather than the anti-Xa concentration.

peak anti-Xa concentrations and clinical outcomes. This is mandatory, because misunderstanding this association could lead to erroneous, and potentially even harmful, LMWH dose adjustments.

In this review, we discuss the need for anti-Xa monitoring and LMWH dosing in patients with renal insufficiency with therapeutic doses of LMWHs. First, we review the evidence of the widely applied therapeutic window for anti-Xa peak concentrations. Second, we compare the safety of unmonitored LMWHs with aPTT-monitored UFH in patients with no renal insufficiency. Third, we discuss how LMWH pharmacokinetics is affected by renal insufficiency and how to correct for these changes. Last, data on trough anti-Xa concentration monitoring is introduced.

## 2. Review of evidence of the widely applied therapeutic window for anti-Xa peak concentrations

Current guidelines provide therapeutic windows for anti-Xa peak concentrations for patients on *therapeutic doses* of LMWHs for venous diseases. The use of a therapeutic window implies that anti-Xa concentrations below the lower range of this window would be associated with an increased risk of (recurrent) VTE, whereas concentrations above the upper range of the window would be associated with an increased risk of bleeding. Since peak anti-Xa concentrations monitoring are advised, this implies that *peak* anti-Xa concentrations are directly correlated to the anticoagulant effect of LMWHs. The corresponding studies are discussed in the following section and are summarized in Table 1.

In a TIMI 11A study, Antman and colleagues compared two dosing regimens of enoxaparin (1.0 mg/kg vs 1.25 mg/kg twice daily) in 630 patients with acute coronary syndrome (ACS) [8]. The article did not contain information on the renal function of these patients. The authors observed no significant difference in the incidence of thrombotic events but concluded that the incidences of major bleeding was significantly higher (6.5% versus 1.9%) for the higher dosing regimen with corresponding higher mean anti-Xa peak concentrations (1.5 IU/mL and 1.0 IU/mL, respectively). This study provides the main supporting evidence for the upper limit of 1.0 IU/mL for the anti-Xa therapeutic range.

Some critical observations can be made regarding the results of this study. First, the risk of bleeding was significantly higher in patients who underwent a catheterization procedure (7.9% and 2.7%) than in those who did not (1.5% and 0%). There was no statistically significant difference in the bleeding risk between the two groups of patients who did not undergo the procedure, which implies that it is more likely that the invasive procedure contributed to the risk of bleeding rather than the LMWH dosing regimen. In addition, major bleeding occurred shortly after the procedure, with a median onset time of approximately 35 hours, regardless of the dose regimen. Second, a significantly higher percentage of patients in the major bleeding group had received heparin concomitantly in support of diagnostic and/or interventional catheterization procedures. No correction was performed in the outcome analysis for the abovementioned variables. In addition to these critical observations, it is important to mention that, even in the lower dose group with the lower bleeding incidence, the mean anti-Xa peak concentration was 1.0 IU/mL, meaning that half of the patients had concentrations above 1.0 IU/mL, which is above the therapeutic window.

A study by Montalescot et al. included 803 patients with ACS who received twice-daily enoxaparin, with death, myocardial infarction (MI), or major bleeding at 30 days as endpoints [9]. When indicated, catheterization was performed with ad hoc percutaneous coronary intervention (PCI), as needed. All patients were treated with enoxaparin and aspirin, and 75% of the population also received a P2Y12 inhibitor. Ten percent of the patients had a creatinine clearance of less than 30 mL/min. The authors observed an association between low anti-Xa concentrations and mortality. An anti-Xa peak concentration of < 0.5 IU/mL was a significant predictor for mortality or myocardial infarction at 30 days follow-up (OR 4.40) in a multivariate analysis. This study provides the main supporting evidence for the lower limit of 0.5 IU/mL for the anti-Xa therapeutic range.

Several critical observations can be made regarding these data. According to the baseline characteristics, there were several statistically significant differences between the groups. Patients in the < 0.5 IU/mL group were older (73 versus 64 years), had lower renal function (55.8 versus 78.3 mL/min), had a higher incidence of cardiac and coronary injury (53% versus 30% STEMI, 70% versus 42% NSTEMI), and had a higher TIMI risk score (3.2 versus 2.6). Even though several corrections were applied in the multivariate analysis (although the exact corrections applied are not reported), patients in the < 0.5IU/mL group received lower doses of LMWH than the other group (0.66 versus 0.91 IU/kg) since the protocol allows dose reductions at the discretion of the physician, based on a history of bleeding events or a high bleeding risk. As a result, in this study, the anti-Xa concentration seems to be a proxy for cardiovascular frailty since physicians prescribed lower LMWH

Table 1. Summary of the results and critical observations of the studies being part of the main body of evidence for a peak anti-Xa therapeutic window.

| Study group | Reference | Design | Endpoints | Findings | Critical observations |
|---|---|---|---|---|---|
| Antman et al. | [8] | Enoxaparin 1.0 versus 1.25 mg/kg BID in patients with unstable angina/NQMI patients (n = 630) | Major bleeding, death, recurrent myocardial infarction or recurrent ischemia requiring revascularization | No significant difference in the incidence of thrombotic events.<br>Incidence of major bleeding was significantly higher (6.5% versus 1.9%) in the higher dosing regimen with corresponding higher mean anti-Xa peak levels (1.5 IU/mL and 1.0 IU/mL respectively) | • ACS population also receiving additional antithrombotics like UFH and aspirin<br>• Patients undergoing catherization had a higher risk of bleeding<br>• No difference in risk of bleeding between the two doses in patients that did not undergo catherization<br>• Major bleedings occurred shortly after the invasive procedure (median onset-times of approximately 35 hours), regardless of the used dose regimen<br>• In the major bleedings group a higher number of patients also received heparin<br>• No correction in the outcome analysis for potential effect modifiers such as catheterization or concomitant heparin use |
| Montalescot et al. | [9] | Enoxaparin 1.0 mg/kg BID with dose reduction at discretion of physician in patients with unstable angina or NSTEMI (n = 803) | Death, death or myocardial infarction, and major bleeding | An anti-Xa peak level of <0.5 IU/mL was as a significant predictor for mortality or myocardial infarction at 30 days follow-up (OR 4.40) in a multivariate analysis. | • ACS population also receiving additional antithrombotics like aspirin and P2Y12 inhibitors<br>• More patients with cardiovascular frailty were present in the <0.5 IU/mL group. Since these patients were allowed to receive lower enoxaparin doses a correction should have been performed in the performed multivariate analysis. Therefore, an unbiased association between anti-Xa levels and outcome cannot be established.<br>• The outcome at 30 days is related to anti-Xa levels of 30 days earlier without providing information on antithrombotic treatment in the period in-between. |
| Nieuwenhuis et al. | [10] | Dalteparin BID (dose adjusted in order to attain anti-Xa levels within a window) versus UFH in patient with acute VTE (n = 194) | Major bleeding | In the dalteparin group, higher anti-Xa levels after the initial bolus were associated with increased risk of bleeding. The risk increased from 8% (n = 7) with peak anti-Xa <0.8 IU/mL to 18% (n = 2) with peak anti-Xa 0.8–1.0 IU/mL and to 50% (n = 1) with peak anti-Xa >1.0 IU/mL | • The observed association was statistically not significant due to the low number of patients with bleedings in the higher anti-Xa level groups (n = 3; 3% of patients).<br>• Studying the association between the observed maximum anti-Xa level and bleeding incidence, paradoxically the incidence of bleeding was 13% for patients with anti-Xa <0.8 IU/mL, 8% for patients with 0.8–1.0 IU/mL and 6% for patients with >1.0 IU/mL.<br>• Observed median anti-Xa concentration was equal in patients with and without a bleeding event (0.43 IU/mL)<br>• Authors demonstrated that the performance state, bleeding diathesis and recent trauma were prognostic factors for major bleedings suggesting that patient or intervention characteristics play a more important role in causing a bleeding. |

Abbreviations: ACS = acute coronary syndrome, BID = twice daily, IU = international units, NSTEMI = non-ST-elevation myocardial infarction, NQMI = Non-Q-wave myocardial infarction, OR = odds ratio, UFH = unfractionated heparin, VTE = venous thromboembolism

doses to more frail cardiovascular patients, which naturally resulted in lower anti-Xa concentrations in this group. It is noted that this group had the highest incidence of death or myocardial infarction. Unfortunately, the authors do not describe in their article that they accounted for this higher risk in their analysis. A final critical remark is fact that the authors studied the association between the anti-Xa peak concentration before catheterization and the outcome 30 days later without providing information on the period in-between, such as on antithrombotic therapy dosing, duration of treatment, withdrawal, and so on. For example, a patient has an anti-Xa concentration of 0.6 IU/mL before catheterization, was switched to a vitamin K antagonist one week after the intervention, and has an incidence of bleeding another week later. If this would be the case, this bleeding is probably not related to the anti-Xa concentration of 0.6 IU/mL.

A study by Nieuwenhuis and colleagues is also often referred for supporting evidence for the upper limit of the therapeutic window of 1.0 IU/mL [10]. They evaluated the incidence of bleeding in 194 patients with acute DVT, randomized to twice-daily dalteparin or unfractionated heparin. Three patients (1.5%) had renal insufficiency, which was defined as a creatinine concentration of > 45 mg/L (400 umol/L). In the dalteparin group, higher anti-Xa concentrations after the initial bolus were associated with increased bleeding risk. The bleeding risk increased from 8% (n = 7) with peak anti-Xa < 0.8 IU/mL to 18% (n = 2) with peak anti-Xa 0.8–1.0 IU/mL and even to 50% (n = 1) with peak anti-Xa > 1.0 IU/mL. However, only two patients had a concentration of > 1.0 IU/mL, of which one had a bleed. This association was statistically not significant due to the low number of patients with bleeding in the higher anti-Xa groups (n = 3, corresponding to 3% of all patients). Paradoxically, with the association between the observed maximum anti-Xa concentration and bleeding incidences, the incidence of bleeding was 13% for patients with anti-Xa < 0.8 IU/mL, 8% for patients with 0.8–1.0 IU/mL, and 6% for patients with > 1.0 IU/mL. A final critical observation is that the median anti-Xa concentration was equal in patients with and without a bleeding event (0.43 IU/mL), and was even below the supposed therapeutic window. The authors demonstrated that the performance state, bleeding diathesis, and recent trauma were prognostic factors for major bleeding, suggesting that patient or intervention characteristics played a more important role in causing a bleed.

In conclusion, based on the review of these studies, the studies that support a therapeutic window for anti-Xa concentrations for venous diseases were performed in populations with arterial diseases who already were 'at risk' for the outcome because of the nature of their diseases. Moreover, in the ACS studies, patients also received other antithrombotic agents concomitantly, which even further increased their bleeding risk. Moreover, all the studies also have several statistical and methodological shortcomings, which means that it is unlikely to be able to correctly assume an unbiased clear association between anti-Xa concentrations and clinical outcome. This conclusion can be supported by the fact that other studies that were conducted with patients with venous diseases did not report any relationship between anti-Xa concentrations and clinical outcome [11–15].

## 3. Safety of unmonitored LMWHs versus aPTT-monitored UFH

Interindividual variability in LMWH pharmacokinetics and pharmacodynamics is known to be significant [16,17]. Multiple studies have reported that only approximately 50% of patients with neither renal insufficiency nor obesity achieve peak concentrations within the supposed therapeutic range. Results below and above the range had been seen [1,8,9,11,12,15,18,19].

Despite this relatively large interindividual variability, several meta-analyses have shown that LMWHs are at least as effective and safe as UFH. For example, Dolovich et al. performed a meta-analysis, comparing LMWHs with UFH in the treatment of venous thromboembolism. They concluded that, in this setting, LMWHs are as effective as UFH without statistically significant differences in risks for major bleeding, minor bleeding, thrombocytopenia, or the recurrence of VTE or pulmonary embolism [20]. It is important to mention that, in all the included studies, the UFH dose was adjusted according to the aPTT, and in only one out of the 13 studies in the meta-analysis the LMWH doses were adjusted to the achieve an anti-Xa peak concentration within a predefined window. Thus, based on these data, it can be concluded that LMWHs without anti-Xa monitoring are as safe and as effective as UFH with aPTT monitoring and subsequent dose adjustments. This is in line with recommendations to not monitor anti-Xa concentrations in patients without renal insufficiency. This evidence suggests that decreasing interpatient variability in drug exposure with TDM would not increase drug safety or efficacy. Thus, although interindividual variability is large, from a pharmacological perspective, LMWHs probably have a broad therapeutic window. This is supported by observations from an animal model, in which mice were given a dose of 100.000 IU/kg dalteparin and survived. In another model, rats were given tinzaparin 62.500 IU/kg daily for a minimum of 6 months but no lethal dose could be determined [21]. Moreover, case reports of unintentional LMWH overdoses with anti-Xa concentrations of up to 6 IU/mL did not report bleeding [22,23]. Finally, in the ACS study by Montalescot, patients with and without major bleeding had comparable anti-Xa concentrations of 0.91 and 0.83 IU/mL, respectively, which are both within the 'therapeutic window' [9]. Thus, from a clinical perspective, the risk of bleeding does not appear to be predicted by the anti-Xa concentrations and is perhaps better predicted by the clinical risk factors for bleeding [21].

Considering patients with renal insufficiency, in only two out of 13 studies in the meta-analysis performed by Dolovich et al. were patients with severe renal insufficiency excluded [24,25]. The remaining eleven studies did not exclude patients with renal insufficiency or describe upfront dose reductions in these patients.

In conclusion, despite relative large interindividual variability in LMWH pharmacokinetics and pharmacodynamics, even in patients without renal insufficiency, with anti-Xa concentrations above and below the therapeutic range, unmonitored LMWH is a safe as monitored UFH.

## 4. Correcting for pharmacokinetic changes of LMWHs in renal insufficiency

Given the reported increased anti-Xa concentrations and higher bleeding incidence in patients with severe renal insufficiency who are treated with LMWHs without dose adjustments [1], it can be anticipated that, when the dose of LMWH is adjusted for patients with renal insufficiency proportional to the changes in the (anti-Xa) pharmacokinetics, no anti-Xa monitoring would be required.

In a review article, Nagge and colleagues concluded that the clearance of each different LMWH is affected in a different way by renal insufficiency. The clearance of enoxaparin and nadroparin was reduced below a creatinine clearance (CrCL) of 50 ml/min, whereas, for tinzaparin, there was no accumulation in patients with a CrCl less than 20–30 ml/min [26].

A population pharmacokinetic analysis by Hulot and colleagues has shown that the anti-Xa clearance of enoxaparin was reduced by 31% in patients with moderate renal insufficiency (CrCl of 30–49 mL/min) and by 44% in patients with severe renal insufficiency (CrCl less than 30 mL/min) [27]. This aligns with findings of Cadroy et al., who observed that enoxaparin clearance in patients with chronic renal failure (CrCl 5–21 mL/min (mean, 11.4 mL/min)) was 1.9 times lower compared to healthy individuals (CrCl 88 to 140 mL/min (mean, 105 mL/min)) [28].

Data on comparative anti-Xa concentrations in patients with and without (different degrees of) renal insufficiency are sparse. Kruse et al. observed that enoxaparin anti-Xa concentrations in patients with severe renal insufficiency with a 50% dose were lower than in patients with moderate renal insufficiency with a 75% dose after the third dose [29]. However, anti-Xa in patients with CrCl > 60 ml/min were not studied and it is unclear whether monitoring after the third dose is not too early from a steady-state perspective in patients with severe renal insufficiency (CrCl < 30 ml/min). Collet et al. reported that patients with severe renal insufficiency should receive 64% of the recommended dose to attain comparable anti-Xa concentrations as in patients with CrCl > 60 ml/min. Patients with moderate renal insufficiency (CrCl 30 to 60 ml/min) should receive 84% of the recommended dose [30]. The bleeding risk in patients with severe renal insufficiency (CrCl < 30 ml/min) decreased with the use of adjusted enoxaparin doses [1].

Anti-Xa clearance of nadroparin in elderly healthy patients (mean CrCl 62 ml/min) was observed to be 1.4 times lower than in young healthy patients (mean CrCl 114 ml/min) [31]. In a study by Ojik et al., anti-Xa concentrations of 97 patients with eGFR < 60 mL/min and 100 patients with eGFR > 60 mL/min were monitored. Patients with an eGFR 30–60 ml/min received a therapeutic nadroparin maintenance dose of 75%, and patients with eGFR < 30 ml/min received a maintenance dose of 50%. The distribution of the peak anti-Xa concentrations was comparable between the patients with and without renal insufficiency, which proves that the recommended dose adjustments adequately correct for pharmacokinetic alterations in this population [32].

Tinzaparin is the LMWH with the highest molecular weight of the LMWHs and can be expected to be less dependent on renal clearance. Several studies have been published on the effect of renal insufficiency on tinzaparin peak anti-Xa concentrations. In two studies, no correlation was found between CrCl and anti-Xa peak concentrations in patients with CrCl > 50 ml/min, compared to patients with renal insufficiency as low as CrCl 20–29 ml/min [33,34]. A third study that examined trough anti-Xa concentrations confirmed this finding and found, in addition, a doubling in trough anti-Xa concentrations in patients with eGFR < 30 ml/min, when measured 5–7 days after treatment initiation in steady-state [35].

In conclusion, there is consistent data on how LMWH anti-Xa clearance is affected by different degrees of renal insufficiency. Adjusting the LMWH dose in patients with renal insufficiency, taking into account the pharmacokinetic differences,, is enough, and no additional anti-Xa monitoring is required.

## 5. Peak versus trough concentration monitoring in patients with renal insufficiency

From a pharmacokinetic point of view, monitoring peak concentrations as a proxy for drug accumulation of a solely renally excreted drug in patients with renal insufficiency seems to be less sensitive than monitoring trough concentrations [36]. Moreover, there is increasing awareness that trough anti-Xa concentrations might be a more suitable safety and efficacy parameter [14,37]. Lim et al. observed in patients with CrCl > 60 ml/min on once-daily dosed tinzaparin mean steady-state trough concentrations of 0.15 (standard deviation (SD) 0.12) IU/mL, which implies that 95% (+2 SD) of the patients had trough anti-Xa concentrations below 0.4 IU/mL [35]. For twice-daily dosed enoxaparin, Al-Sallami found a doubling of the bleeding risk of patients with trough anti-Xa concentrations above 0.5 IU/mL [37]. These trough anti-Xa concentrations could potentially be used as an upper limit to monitor LMWH accumulation and, subsequently, to adjust LMWH doses. Finally, given the increased LMWH half-life in patients with severe renal insufficiency, steady-state trough concentrations can be expected 5–7 days after initiation of treatment. However, to prevent accumulation in these patients, trough concentrations could already be monitored 3–4 days after initiation of treatment to avoid prolonged overtreatment, but one should be aware that steady-state has not yet been achieved at this time.

## 6. Conclusions

From this overview, it can be concluded that no therapeutic window for peak anti-Xa concentrations for venous diseases in patients with renal insufficiency has been identified. Interindividual variability of LMWH pharmacokinetics and pharmacodynamics is known to be large, with multiple studies reporting that only approximately 50% of patients with neither renal insufficiency nor obesity achieve peak concentrations in the supposed therapeutic range, albeit with predictive efficacy and safety profile. This lack of relevance of anti-Xa peak concentration is also supported by the fact that unmonitored LMWH is as safe and effective as monitored UFH. Adjusting the LMWH dose in patients with renal insufficiency, with consideration of pharmacokinetic differences, is enough,

and no anti-Xa monitoring is required. If anti-Xa concentration monitoring is considered, trough concentration monitoring is preferred over peak concentration monitoring as a safety and efficacy parameter, and, from a pharmacokinetic point of view, this is a more logical approach to check for drug accumulation in patients with renal insufficiency.

## 7. Expert opinion

Despite the invention of novel antithrombotic agents, such as the direct-acting oral anticoagulants (DOACs), LMWHs still remain the preferred treatment for peri-operative anticoagulation for patients with VTE or atrial fibrillation. LMWHs have relative short half-lives and are, therefore, more suitable in the pre-operative setting, are administered parenterally, and can be (partly) antagonized with protamine. LMWHs were developed as an easier alternative to UFH, so that no continuous infusion and routine monitoring of hemostatic parameters would be required. However, at the end of the previous decade, more studies on anti-Xa monitoring in special patient populations, such as patients with renal insufficiency and obesity, or during pregnancy, became available. In this review, the (un)need for anti-Xa monitoring in patients with renal insufficiency and subsequent dose adjustment is discussed.

The main body of evidence on (target) anti-Xa concentrations was sourced from several studies conducted in different populations, for example, ACS patients undergoing catheterization compared to the population that anti-Xa monitoring is currently used for, such as patients with atrial fibrillation or venous thrombo-embolism. In addition to several methodological and statistical limitations, these patients were more at risk for thrombo-embolisms or bleeding because of the nature of their diseases, the performed interventions (e.g. PCI), and use of additional antithrombotics. Patients who underwent catheterization had a higher bleeding risk compared to patients who did not, while, in the latter group, anti-Xa was not associated with bleeding risk. These studies provide insufficient evidence for a therapeutic window for anti-Xa concentrations in patients for the treatment of VTE or for prevention in AF. Supported by the evidence in animal studies, where rodents were given high doses of LMWH for a prolonged period but no lethal dose was achieved, and by evidence in accidental overdoses where no bleeding occurred despite high anti-Xa concentrations, the risk of bleeding appears to be not predicted by the anti-Xa concentration, but is perhaps better predicted by the clinical risk factors for bleeding.

Another argument for this reasoning is the fact that the supposed therapeutic range for peak concentration differs between once-daily (1.0–2.0 IU/mL) and twice-daily dosed LMWHs (0.6–1.0 IU/mL), without, according to a recent meta-analysis, a statistically significant different bleeding risk [38]. Paradoxically, another meta-analysis concluded that twice-daily dosed enoxaparin was associated with an increased bleeding risk compared to once-daily dosed enoxaparin in patients with acute venous thromboembolism. Although the twice-daily dosed patients received a higher mean daily dose (200 versus 151.5 IU/kg), they are expected to have lower anti-Xa peak concentrations [39]. In addition, for the twice-daily dosed LMWHs, the supposed therapeutic range of 0.6–1.0 IU/ml is equal for all LMWHs. Pharmacologically, an anti-Xa concentration of, for example, 1.0 IU/mL of enoxaparin has a lower anticoagulant effect than of nadroparin due to different factor Xa to factor IIa ratios (i.e. 2.7:1 for enoxaparin and 2.0:1 for nadroparin, which is a 35% difference in factor IIa potency).

Anti-Xa variability is high, and, even in patients without renal insufficiency, there is a considerable likelihood that anti-Xa concentrations below the target range can be expected, as shown in a recent pharmacokinetic study with 27 patients, which combined data obtained from these patients with a previously published population pharmacokinetic model [40]. Previous studies also show that a significant number, up to 50%, of peak anti-Xa concentrations can be outside the therapeutic window [1,8,9,11,12,15,18,19]. As a result, a substantial number of patients without renal insufficiency will have anti-Xa concentrations *below* the therapeutic range. Therefore, we would relatively overtreat (a significant number of) patients with renal insufficiency in case we would adjust LMWH doses in order to attain anti-Xa concentrations *within* the therapeutic range. Even higher dosages than those for normal patients could be indicated.

In addition to the absence of evidence to sufficiently substantiate a therapeutic window for anti-Xa peak concentrations in patients with venous diseases, there are several concerns regarding monitoring, interpreting, and extrapolating anti-Xa peak concentrations, as highlighted by Egan and Ensom [21]. For example, a comparison of five commercially available chromogenic assays for measurement of anti-Xa concentrations showed that interassay variability was relatively high (43% for enoxaparin and 27% for dalteparin). Moreover, batch-to-batch differences in the same brand enoxaparin resulted in anti-Xa concentration deviations of more than 0.2 IU/mL between patients [41]. Another concern is the extrapolation of anti-Xa concentrations measured in studies conducted before 1995 to currently obtained data. Since anti-Xa assays available before 1995 did not account for the inactivation of factor Xa by the presence of in vivo plasma calcium, they relatively overestimated anti-Xa concentrations compared to modern assays [21]. This concern should not be ignored since LMWHs originated during the second half of the previous decade and considerable data on anti-Xa normal concentrations are derived from the original studies. Patient characteristics can also affect the anti-Xa assay results. Anti-Xa activity can be underestimated in patients with reduced antithrombin activity (e.g. liver cirrhosis) and also in patients with hyperbilirubinemia [42].

Another concern, from a practical perspective, is that measuring anti-Xa peak concentrations is a complex challenge since sampling should be performed three to five hours after subcutaneous injection and after steady-state concentrations have been reached. Van Bergen and colleagues and Kufel and colleagues studied compliance to the TDM protocol, and, in both studies, 75% of the anti-Xa samples were not indicated or were taken at the wrong time. This illustrates that monitoring anti-Xa concentrations is a complex clinical challenge, which can introduce an additional risk since 25% and 42% of the incorrectly sampled anti-Xa concentrations in their studies were followed by an unjustified dose adjustments [43,44].

Table 2. Summary of arguments against routinely peak anti-Xa concentration monitoring in renal insufficiency.

- No therapeutic window for peak anti-Xa concentrations for venous diseases in patients with renal insufficiency has been identified.
- Unmonitored LMWHs are as safe as aPTT-monitored unfractionated heparin in patients without renal insufficiency.
- There is large interindividual variability in anti-Xa levels, also in patients without renal insufficiency. Even in these patients up to 50% of anti-Xa peak levels outside the therapeutic window are observed with normal dosages. Of note, in clinical practice anti-Xa levels are neither monitored nor adjusted in these patients.
- There is consistent data on how LMWH anti-Xa clearance is affected by different degrees of renal insufficiency. For enoxaparin and nadroparin doses should be adjusted to 50–65% and 75–85% of the original dose for patients with a creatinine clearance of < 30 ml/min and 30–60 ml/min respectively. For tinzaparin the dose should be adjusted to around 50% of the original dose for patients with a creatinine clearances of < 30 ml/min.
- There is increasing awareness that anti-Xa trough levels might be a more suitable safety and efficacy parameter. In case anti-Xa monitoring is deemed necessary, maximum anti-Xa trough concentrations of 0.4 IU/mL for once-daily dosed tinzaparin and 0.5 IU/mL for twice-daily dosed enoxaparin and nadroparin seem suitable.
- Due to the small sampling window, correct peak monitoring is a complex clinical challenge with high risk of unjustified dose adjustments.

Abbreviations: aPTT = activated partial thromboplastin time, IU = international units, LMWH = low molecular weight heparin

Despite significant interindividual variability in patients without renal insufficiency, (unmonitored) LMWHs are as safe and effective as monitored UFH, which suggests a broad therapeutic window. In patients without renal insufficiency, anti-Xa monitoring is redundant, and dose reduction for pharmacokinetic alterations in patients with renal insufficiency no longer requires routine anti-Xa monitoring.

Table 2 summarizes the arguments against routinely anti-Xa peak monitoring in renal insufficiency.

Data on clearance values of LMWHs in patients with different degrees of renal insufficiency are the most suitable pharmacokinetic parameters to use to adjust doses for these patients. For enoxaparin and nadroparin, anti-Xa clearance is affected by impaired renal function and CrCl of < 30 ml/min and 30–60 ml/min are used as thresholds below which the LMWH dose should be adjusted to 50–65% and 75–85% of the dose, respectively. For tinzaparin, anti-Xa clearance is less affected by severely impaired renal function and a CrCl of < 30 ml/min could be used as a threshold below which the LMWH dose should be adjusted to approximately 50% of the original dose.

If anti-Xa monitoring is deemed necessary (e.g. in patients in whom renal function cannot be estimated accurately), trough instead of peak concentration monitoring seems more appropriate. As mentioned before, monitoring peak concentrations assumes a direct relationship between the peak concentration and efficacy or safety outcome. However, this relationship has not been confirmed for venous diseases. Alternatively, based on pharmacokinetic principles, trough concentrations are a sensitive approach to monitor impaired clearance and check for drug accumulation. Maximum trough anti-Xa concentrations of 0.4 IU/mL for once-daily dosed tinzaparin and 0.5 IU/mL for twice-daily dosed enoxaparin and nadroparin seem to be suitable, based on the currently available evidence. In addition, from a pharmacokinetic point of view, a lower trough concentration should be pursued in a once-daily dosing regimen rather than a twice-daily dosing regimen.

Unfortunately, there are no TDM studies on the association between trough anti-Xa concentrations and clinical outcome in patients with renal insufficiency and atrial fibrillation or venous thromboembolism. Future studies on monitoring LMWH safety (and efficacy) in patients with renal insufficiency should focus on trough concentration monitoring. Anti-Xa peak concentrations have always been used as the hemostatic parameter of choice, but one should be aware that this parameter is subject to several concerns and challenges, as mentioned above. Despite several analytical challenges, direct measurement of the LMWH concentration in the patient's blood for TDM would be the preferable way to monitor for LMWH accumulation in patients with renal insufficiency. Until those assays and data on LMWH concentrations in patients without renal insufficiency have become available, trough anti-Xa concentrations seem to be the second-best option.

In conclusion, to date, there is insufficient data to support peak anti-Xa monitoring in patients with renal insufficiency. Only correcting doses for pharmacokinetic changes in these patients without further monitoring seems reasonable. Trough anti-Xa concentration monitoring seems to be a more sensitive approach predictor to drug accumulation. A better understanding of the clinical association between peak anti-Xa concentrations and clinical outcomes is mandatory because misunderstandings of this association could lead to erroneous, and even potentially harmful LMWH, dose adjustments.

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