Bariatric surgery: studies on its consequences with emphasis on thrombotic and bleeding complications

Çelik, F.

Citation for published version (APA):
Çelik, F. (2014). Bariatric surgery: studies on its consequences with emphasis on thrombotic and bleeding complications
Fixed dose enoxaparin after bariatric surgery: the influence of body weight on peak anti-Xa levels

F. Celik, A.D.R. Huitema, J.H. Hooijberg, A.W.J.M. van de Laar, D.P.M. Brandjes, V.E.A. Gerdes

*Obesity Surgery* 2014 Sep 16.
ABSTRACT

Introduction:
There is lack of data on the pharmacodynamics of low molecular weight heparins in obese patients.

Purpose:
To investigate the correlation between anti-Xa levels and body weight with fixed dose enoxaparin after bariatric surgery and to investigate the percentage of patients that reach the desired prophylactic range for anti-Xa levels.

Materials and Methods:
Blood for anti-Xa peak levels measurement was drawn 3-5 hours after administration of enoxaparin at the planned visit 8-16 days after surgery. Patients were included in three categories: <110 kg (group 1), 110-150 kg (group 2), >150 kg (group 3).

Results:
51 patients were included (43.9 ± 9.9 yrs, 75% women). Mean anti-Xa level was 0.37 ± 0.14 IU/ml. This level was the highest in group 1 (0.47 ± 0.13 IU/ml) and lowest in group 3 (0.23 ± 0.07 IU/ml). No subprophylactic (<0.2 IU/ml) anti-Xa levels were detected in group 1, whereas this was observed in 38% in patients in group 3. Supraprophylactic levels (>0.5 IU/ml) were most often present in group 1 (36%). With multivariable regression analysis, body weight (β -.720 (95% confidence interval -.717; -.993), p <0.001) was an independent predictor of anti-Xa levels, whereas lean body weight was not independently associated. This was confirmed in a non-linear mixed effects analysis of the data.

Conclusion:
Patients with excessive body weight may not be adequately treated with fixed dose enoxaparin thromboprophylaxis while patients with lower body weight may have an increased bleeding risk. Body weight is a better predictor of anti-Xa levels compared to lean body weight.
INTRODUCTION

Venous thromboembolism (VTE) prophylaxis is a concern for obese patients as they are at higher risk of VTE than the non-obese [1-3]. Although the American College of Chest Physicians Guidelines (ACCP) recommend higher doses of low molecular weight heparins (LMWH) as thromboprophylaxis in bariatric surgery patients, consensus regarding dosing and monitoring is lacking [4,5]. In the Netherlands, higher fixed doses of enoxaparin are typically used after bariatric surgery. However, the potential for underdosing using standard prophylactic doses remains with increasing body weight [6-8]. There is minimal data for dosing enoxaparin in patients above a weight limit of 150 kg. Our hypothesis was that patients using fixed dose enoxaparin would have more often subprophylactic anti-Xa levels with higher body weight and that patients with lower weight would have more often anti Xa-levels above the advised prophylactic range. To test this hypothesis, we planned an observational study on the effects of body weight on anti-Xa peak levels in patients undergoing bariatric surgery receiving fixed dose enoxaparin.

METHODS

Study design and population
This prospective study was undertaken in patients who had their first scheduled visit at the outpatient clinic of the Slotervaart Hospital 8-16 days after bariatric surgery and still using enoxaparin according to the local thromboprophylaxis protocol: fixed dose subcutaneous enoxaparin 40 mg every 12 hours for 14 days, with the first dose administered in the evening on the day of surgery. If the date of the first appointment did not match the last day of enoxaparin use, we asked participants to continue the prophylaxis up to two days longer. Patients with at least one of the following criteria were excluded: enoxaparin dosage different from that specified in the protocol, antithrombin III deficiency, and renal insufficiency (eGFR<30 ml/min). Approval for the study was obtained from the local ethical committee of the Slotervaart Hospital (Amsterdam, the Netherlands) and was performed in accordance with the guidelines of the Declaration of Helsinki. All patients provided written informed consent.

Data collection and measurements
Blood for anti-Xa peak levels measurement was drawn 3-5 hours after administration of enoxaparin, at the planned visit to the outpatient clinic 8-16 days after surgery. Medical
information was retrieved from the electronic patient files: demographics, obesity-associated comorbidities, smoking status, body length, BMI, type of bariatric surgery, VTE and bleeding complications after surgery. Body weight was measured on the same day the blood was drawn. Blood pressure was measured using a Dinamap (automated Vital Signs Monitor, 300 series device, Welch Allyn Protocol Inc., Beaverton, Oregon USA). Blood pressure cuff size was chosen based on the circumference of the arm.

**Outcome and data definitions**

Outcome of the study was the percentage of patients within the prophylactic range in different weight categories and the relation between body weight and anti-Xa levels. Age at the time of surgery was registered. Type 2 diabetes was defined as an HbA1c >6.5% and/or being on antidiabetic drugs. Hypertension was defined as a blood pressure of above 140/90 mmHg and/or being on antihypertensive drugs. Dyslipidemia was defined as use of statins and/or a raised total cholesterol level, LDL or triglycerides above the 95th percentile according to the definition proposed by the American Heart Association [9]. Obstructive sleep apnea (OSA) was defined as OSA proven with formal sleep study. Smoking was defined as current use of cigarettes. Major bleeding complications were defined according to the ISTH criteria [10]. All other bleeding cases were defined as minor. Lean body weight (LBW) was defined according to the formula of Janmahasatian [11]. Creatinine clearance was computed according to the formula of Salazar [12]. The target range for prophylactic anti-Xa was defined as 0.2 to 0.5 IU/ml [13,14]. Levels below 0.2 IU/ml were defined as subprophylactic and above 0.5 IU/ml as supraprophylactic.

**Laboratory assessments**

One blood sample was taken per patient to determine the peak anti-Xa level. Blood samples were collected in 3.2% sodium citrate containing tubes. All samples were centrifuged twice (15 min, 2500 xg at 15°C). Plasma was aliquoted and stored at -80°C until further use. Anti-Xa level was determined using a chromogenic assay (Berichrom Heparin Assay, Siemens Healthcare) on a Sysmex CA-1500 analyzer (Siemens Healthcare). Results were expressed as anti-Xa level (IU/ml).

**Statistical analysis and power considerations**

To investigate the relationship between body weight and peak anti-Xa levels, different weight categories were defined; patients weighing < 110 kg (group 1), between 110 and 150 kg (group 2) and above 150 kg (group 3). Based on the findings in the literature [13,15],
we assumed that the difference in anti-Xa levels would be at least 30% between the lowest and highest body weight categories. A sample size of 15 patients in each weight category was calculated to have 90% power to detect this difference. Baseline characteristics of the patients were summarized using descriptive statistics. The summary statistics included the mean ± standard deviation (SD) or median (range) for continuous variables and the frequency and percentage for categorical variables. To examine the differences between the study groups, the One-way Anova, Kruskal Wallis test or Chi² test was used, dependent on the distribution of the variable. Univariate and multivariable linear regression with backward method analysis was used for the computation of 95% confidence intervals (95% CI). A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software package (version 19). Finally, a population pharmacodynamic (PD) model was developed using non-linear mixed effects modelling (NONMEM, version 7.2, ICON, Leopardstown, Dublin, Ireland). As no data in the absorption phase was available, the absorption rate was fixed to 0.505 hour⁻¹, according to Patel et al. [16]. As only single time points per individual were available a naïve pooling approach was chosen. An open one-compartment model was used and clearance (CL) and volume of distribution (V) were estimated. Renal function as measured by estimated glomerular filtration rate (eGFR) calculated according to the Salazar formula was introduced on clearance [12]. To separate the effects of renal function and body size, first the eGFR was normalized for LBW by: eGFR normalized = eGFR measured*70/LBW according to Janmahasatian et al. [17]. Subsequently, the different body weight measures were introduced on CL and V using allometric scaling. The best descriptor was selected based on goodness-of-fit as judged as the minimal value of the objective function. Final parameter estimates were used to simulate anti-Xa time profiles at steady state for the different weight categories.

RESULTS

Patient characteristics
A total of 51 patients were included. Mean age was 43.9 ± 9.9 years and 38 (75%) were women. Diabetes was present in 14%, hypertension in 45%, dyslipidemia in 22%, and sleep apnea in 16%. Eight patients (16%) were current smokers. Mean weight was 127.5 ± 25.9 kg (range of 81-179) and BMI 42.2 ± 7.1 kg/m² (range 27-65). Mean days of enoxaparin use before blood samples were drawn was 12.4 ± 2.7 days (range 8 to 16 days). Time between last enoxaparin administration and obtaining of blood sample was 218 ± 24 minutes. The majority of patients (n=47, 92%) underwent a Roux-en-Y gastric bypass (RYGB), while...
4 patients (8%) had a revisional gastric bypass procedure after previous gastric banding. All surgeries were performed laparoscopically. There was a lower proportion of women in the highest body weight group (table 1). The patients in this highest weight group were younger and had a higher median eGFR, while there were no differences in duration of enoxaparin use in days (table 1).

**Peak anti-Xa levels in the different weight groups**
Mean anti-Xa level of the total study group was 0.37 ± 0.14 IU/ml. This level was the highest in group 1 (0.47 ± 0.13 IU/ml) and lowest in group 3 (0.23 ± 0.07 IU/ml) (table 2). In group 2, 94.4% of the patients were within the prophylactic range, while this was 64.7% for group 1 and 62.5% for group 3. Supraphylactic levels (>0.5 IU/ml) were most often present in group 1 (35.3%) (table 2). No subphylactic (<0.2 IU/ml) levels were detected in group 1 and 2, whereas this was observed in six patients in group 3 (37.5%).

**Table 1. Baseline patient characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Total n=51</th>
<th>&lt;110 kg n=17</th>
<th>110-150 kg n=18</th>
<th>&gt;150 kg n=16</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>43.9 ± 9.9</td>
<td>49.2 ± 8.4</td>
<td>41.6 ± 10.4</td>
<td>40.8 ± 9.4</td>
<td>0.022</td>
</tr>
<tr>
<td>gender (women)</td>
<td>38 (75)</td>
<td>14 (82.4)</td>
<td>16 (88.9)</td>
<td>8 (50)</td>
<td>0.023</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>127.5 ± 25.9</td>
<td>100.2 ± 7.6</td>
<td>123.6 ± 7.7</td>
<td>160.9 ± 7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LBW</td>
<td>65.3 ± 13.8</td>
<td>54.6 ± 8.2</td>
<td>62.7 ± 6.8</td>
<td>79.7 ± 12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>42.2 ± 7.1</td>
<td>36.8 ± 4.3</td>
<td>40.8 ± 3.6</td>
<td>49.3 ± 6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR</td>
<td>84.0 (44.8–247.0)</td>
<td>65.8 (44.8–85.3)</td>
<td>85.5 (52.8–128.1)</td>
<td>113.6 (73.4–247.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>enoxaparin,days</td>
<td>12.4 ± 2.7</td>
<td>12.5 ± 2.8</td>
<td>12.4 ± 2.4</td>
<td>12.3 ± 2.9</td>
<td>0.974</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, median (range) or number of patients (%). Abbreviations: LBW= lean body weight, BMI=body mass index, eGFR= estimated glomerular filtration rate. Lean body weight (LBW) was defined according to the formula of Janmahasatian [11]. eGFR is computed according to the Salazar formula [12]. P value is based on the one-way Anova, Kruskal Wallis test or Chi2 test, dependent on the distribution of the variable.
Fixed dose enoxaparin after bariatric surgery: the influence of body weight on peak anti-Xa levels

Factors associated with anti-Xa levels

A strong association between peak anti-Xa level and actual body weight ($\beta$ -0.720 (95% confidence interval (CI) -0.717; -0.993), $p < 0.001$) was observed in the univariate analysis. With multivariable regression analysis, body weight remained an independent predictor of anti-Xa level when the variables age, gender and creatinine clearance were included. The correlation between LBW and anti-Xa level ($\beta$ -0.622, (95% CI -0.624; -0.924), $p < 0.001$) and BMI and anti-Xa level ($\beta$ -0.485, 95% CI -0.554; -0.969), $p < 0.001$) were weaker. The inverse correlation between body weight and peak anti-Xa level is graphically shown in Figure 1.

Population pharmacodynamic analysis

Also in the population pharmacodynamic model actual body weight proved to be the best weight descriptor to account for the effects of body size on PD. CL and V were estimated at 0.856 L/h (±22%) and 3.13 L (±31%). Introduction of actual body weight using allometric scaling resulted in a drop in objective function of 27 points. This indicates a considerable increase in goodness-of-fit. However, since these models are not hierarchical, this cannot be formally tested. Figure 2 shows the simulated anti-Xa time profiles for the different weight categories according to the final parameter estimates.

Table 2. Peak anti-Xa level measured 3-5 h after enoxaparin administration on day 8-16 after bariatric surgery in different weight groups.

<table>
<thead>
<tr>
<th></th>
<th>Total n=51</th>
<th>&lt;110 kg n=17</th>
<th>110-150 kg n=18</th>
<th>&gt;150 kg n=16</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-Xa level</td>
<td>0.37 ± 0.14</td>
<td>0.47 ± 0.13</td>
<td>0.39 ± 0.08</td>
<td>0.23 ± 0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>subtherapeutic</td>
<td>6 (11.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (37.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>therapeutic</td>
<td>38 (74.5)</td>
<td>11 (64.7)</td>
<td>17 (94.4)</td>
<td>10 (62.5)</td>
<td>0.054</td>
</tr>
<tr>
<td>supratherapeutic</td>
<td>7 (13.7)</td>
<td>6 (35.3)</td>
<td>1 (5.6)</td>
<td>0 (0)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or number of patients (%). 
P value is based on the one-way Anova or Chi2 test, dependent on the distribution of the variable.
VTE and bleeding complications
No thromboembolic events were reported during the first visit and also no major bleeding complications. Eight patients (16%) had a minor bleeding. Five patients were in group 1, two patients in group 2 and one patient in group 3 (p=0.157). All patients with minor bleeding complications had anti-Xa levels within the advised prophylactic range of 0.2-0.5 IU/ml.

Figure 1. Correlation between peak anti-Xa levels (drawn 3-5 hours after enoxaparin administration on day 8-16 after bariatric surgery) with body weight (kg). In the figure 95% confidence intervals are given for the regression line ($r_p$ of -0.720, p<0.001).
Figure 2. Simulated anti-Xa time profiles with 90% prediction intervals for the different actual body weight categories (dark gray: >150 kg, gray: 110-150 kg, light gray: <110 kg) according to the final parameter estimates of the population pharmacodynamic model.
DISCUSSION

This study shows that there is a strong negative correlation between body weight and peak anti-Xa levels. 38% of patients with excessive body weight (>150 kg) had subprophylactic anti-Xa levels with fixed dose enoxaparin while 35% of patients with lower body weight (<110 kg) were above the advised prophylactic range. Body weight was a better predictor of peak anti-Xa levels compared to LBW.

The current ACPP guidelines suggest that obese patients undergoing bariatric surgery should be treated with higher doses of LMWH than usual for non-obese, but do not specify by how much [5]. Several studies have reported various thrombosis prophylaxis regimens for obese patients based on the relation between fixed dose LMWH, body size measures and anti-Xa levels [7,8,18-21]. Information assessing the prophylactic dosing of LMWH in the obese population is largely derived from studies conducted in patients undergoing bariatric surgery, primarily assessing enoxaparin (table 3). However, because of the heterogeneity of the studies no firm conclusions can be drawn about the best prophylactic regimen.

Because of the inverse relation between anti-Xa levels and body weight [15,22-24] concerns have been expressed about possible underdosing in very obese patients with fixed dose LMWH [6-8]. Studies that used LMWH as thromboprophylaxis showed that with weight based dosing acceptable anti-Xa levels were reached [6, 25-29]. Since intravascular volume does not have a linear relationship with total body weight (TBW), there have been some concerns that LMWHs could be overdosed if administered based upon TBW [29,30]. Therefore, the use of LBW has been proposed [13]. In this study, the correlation between LBW and peak anti-Xa levels was weaker. An explanation might be the heterogeneity of the studies and the mathematical inconsistencies of the formula itself [31,32]. We think that the use of LBW is disputable as long as there is no gold standard. Wrong use of the formula may have consequences in clinical practice. An explanation for the stronger correlation between body weight and anti-Xa could be the higher glomerular filtration and renal plasma flow with increasing weight [33]. The elimination of LMWH is primarily through a non-saturable renal route. However, these hypotheses need clarification in future studies.
Table 3. Summary of studies that used fixed dose or weight based enoxaparin as thromboprophylaxis in obese patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Included patients, n</th>
<th>Female n (%)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Dosing enoxaparin</th>
<th>Blood sampling</th>
<th>Anti-Xa levels (IU/ml)</th>
<th>Patients within prophylactic range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khoursheed et al. [18]</td>
<td>Lap RYGB</td>
<td>39</td>
<td>31 (79)</td>
<td>32.4±10.7</td>
<td>122.3±24.5</td>
<td>44.5±6.1</td>
<td>40 mg once daily</td>
<td>4h after injection on post-op day 2 and 5</td>
<td>day 2: 0.19 (0.00-0.50), day 5: 0.13 (0.00-0.67)</td>
<td>Therapeutic range: 46.1% on day 2, 41% on day 5</td>
</tr>
<tr>
<td>Simone et al. [7]</td>
<td>Lap GBP, LAGB</td>
<td>Group A=24 Group B=16</td>
<td>A: 31 (87.5) B: 16 (93.7)</td>
<td>A: 40.0±9.8 B: 41.0±10.2</td>
<td>A: 135±25.4 B: 127±20.8</td>
<td>A: 48.8±6.6 B: 47.3±6.6</td>
<td>40 mg (A) or 60 mg (B), every 12h</td>
<td>4h after first and third dose</td>
<td>First dose: A: 0.17±0.08, B: 0.26±0.09 Third dose: A: 0.21±0.08, B: 0.43±0.11</td>
<td>First dose, subtherapeutic: A: 55%, B: 20% Third dose, supratherapeutic: A: 44%, B: 0% Third dose, supratherapeutic: A: 0%, B: 57%</td>
</tr>
<tr>
<td>Rowan et al. [8]</td>
<td>Lap GBP, LAGB</td>
<td>Group A=19 Group B=33</td>
<td>A: 31 (74) B: 24 (82)</td>
<td>A: 41.7±10.7 B: 40.8±9.1</td>
<td>A: 141.6±25.4 B: 135.6±27.9</td>
<td>A: 48.4±7.1 B: 48.5±8.5</td>
<td>30 mg (A) or 40 mg (B), every 12h.</td>
<td>4h after first and third dose</td>
<td>First dose: A: 0.06, B: 0.14 Third dose: A: 0.08, B: 0.15</td>
<td>Prophylactic range: First dose, A: 0%, B: 30.8%. Third dose, A: 9.1%, B: 41.7%.</td>
</tr>
<tr>
<td>Borkgren et al. [20]</td>
<td>Lap RYGB</td>
<td>Group A=124 Group B=99</td>
<td>A: 96 (77) B: 72 (73)</td>
<td>A: 44.7±10.1 B: 44.3±10.6</td>
<td>A: 125.5±18.2 B: 161.4±27.3</td>
<td>A: 44.9±3.7 B: 57.4±6.4</td>
<td>40 mg if BMI ≤50 (A) or 60 mg if BMI &gt;50 (B), every 12h during hospital stay, then once daily (10 days)</td>
<td>4h after third dose</td>
<td>A: 0.26±0.10, B: 0.32±0.13</td>
<td>Therapeutic: A: 78.9%, B: 69.1% Subtherapeutic: A: 21.1%, B: 14.4% Supratherapeutic: A: 0%, B: 16.5%</td>
</tr>
</tbody>
</table>
### Table 3. Continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Included patients, n (%)</th>
<th>Female n (%)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Dosing enoxaparin</th>
<th>Blood sampling</th>
<th>Anti-Xa levels (IU/ml)</th>
<th>Patients within prophylactic range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bickford et al. [26]</td>
<td>Obese trauma patients</td>
<td>86 (30)</td>
<td>52±1.8</td>
<td>113.3 IQR 30</td>
<td>35.3 IQR 9.8</td>
<td>0.5 mg/kg, every 12h</td>
<td>4h after third or fourth dose</td>
<td>0.42±0.01</td>
<td>Therapeutic:86% Supratherapeutic:9% Subtherapeutic:5%</td>
<td></td>
</tr>
<tr>
<td>Ludwig et al. [27]</td>
<td>Obese surgical IC patients</td>
<td>23 (57)</td>
<td>45.6±15.7</td>
<td>136.7±37.1</td>
<td>46.4±11.7</td>
<td>0.5 mg/kg, every 12h</td>
<td>4-6 h after third or fourth dose</td>
<td>0.34 (0.20-0.59)</td>
<td>Therapeutic:91%</td>
<td></td>
</tr>
<tr>
<td>Rondina et al. [28]</td>
<td>Obese medically ill</td>
<td>28 (46)</td>
<td>54.7±11.2</td>
<td>135.6±25.3</td>
<td>48.1±11.1</td>
<td>0.5 mg/kg once daily</td>
<td>4-6 h after first or second dose</td>
<td>0.25±0.11 (0.08-0.59)</td>
<td>Therapeutic:75% Supratherapeutic:0% Subtherapeutic:25%</td>
<td></td>
</tr>
<tr>
<td>Freeman et al [6]</td>
<td>Obese medically ill</td>
<td>Group A=11 (82) B=3 (33) Group C=11 (73)</td>
<td>A:9 B:3 C:8</td>
<td>A:45.5±7.2 B:43.8±15.7 C:42.7±12.3</td>
<td>A:175.0±39.9 B:171.2±42.8 C:179.6±30.3</td>
<td>A:63.4±11.6 B:60.7±12.4 C:61.3±12.2</td>
<td>A:40 mg once daily B:0.4 mg/kg once daily C:0.5 mg/kg once daily</td>
<td>4-6h after injection for up to three days</td>
<td>From Figure: A:0.15 B:0.22 C:0.30</td>
<td>Subtherapeutic. A:82%, B:36%, C:13% Supratherapeutic. A:0%, B:11%, C:0%</td>
</tr>
</tbody>
</table>

**Abbreviations:** RYGB=Roux-en-Y gastric bypass, lap=laparoscopic, GBP=gastric bypass, LAGB=laparoscopic adjustable gastric banding, post-op=postoperative, mg=milligram, kg=kilograms, h=hours, IQR=interquartile range, IC=intensive care.
Based on the results of this study and the literature, it remains difficult to make definitive suggestions about dose adjustments for different weight categories. 94% of the patients in study group 2 (110-150 kg) achieved the prophylactic range. This corresponds with a dosing of 0.65 mg/kg. However, anti-Xa levels vary in study populations with the same mean weight and fixed dose regimens. Freeman et al. [6] showed that patients >150 kg reached adequate anti-Xa levels with a weight based dosing regimen of 0.5 mg/kg, while others showed that a twice daily weight based regimen was needed to reach adequate anti-Xa levels (table 3). Weight adjustment is probably justified, however, it remains uncertain which cut-off levels should be used to prevent sub- or supratherapeutic anti-Xa levels. This study was not designed to investigate outcomes like VTE and bleeding complications. We have shown that the risk of VTE is especially increased in patients who develop a complication after bariatric surgery, even while receiving some thromboprophylaxis [34]. If we consider to use higher doses of LMWH to prevent VTE in these patients with complications, monitoring of the anti-Xa levels seems warranted. On the other hand, 5 of the 8 minor bleeding complications in this study were in group 1 despite the normal prophylactic range. The results still indicate that we might be extra cautious in this weight category. An option is to lower the dose to 30 mg twice daily. This needs to be examined in further studies.

There are some limits in this study to address. The study population was too small to have power for the outcomes VTE and bleeding. The definition of the weight categories was arbitrary, but the middle group represented the general bariatric population and comparison with other studies was feasible. Our study extends published data on prophylactic enoxaparin dosing in obese patients in several ways. First, our data builds on prior reports by enrolling more patients weighing above 150 kg. Furthermore, the three groups were well comparable because of the weight distribution, duration of enoxaparin use and timing of blood sampling in the steady state.
CONCLUSION

With fixed dose LMWH as thromboprophylaxis, patients with excessive body weight may not be adequately treated while patients with lower body weight may have an increased bleeding risk. Because bariatric surgery patients are at risk for both VTE and bleeding, it is important to determine the optimal prophylactic doses of LMWH. Therefore, larger prospective trials are needed to investigate the relation between anti-Xa levels and outcomes with weight based dosing of LMWHs.

CONFLICT OF INTEREST DISCLOSURE STATEMENT

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.
REFERENCE LIST


