Anti-factor X Activity Levels with Continuous Intravenous Infusion and Subcutaneous Administration of Enoxaparin after Coronary Artery Bypass Grafting: a Randomized Clinical Trial

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Short title

Pharmacokinetics of enoxaparin after CABG

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Word count

2940 words.

Abstract

Background: Low-molecular-weight heparin enoxaparin is widely used in pharmacological thromboprophylaxis after coronary artery bypass grafting (CABG). The aim of this study was to compare anti-factor X activity (anti-Xa) levels when the thromboprophylactic dose of enoxaparin was provided after CABG, with two different administration routes: continuous intravenous infusion (CIV) and subcutaneous bolus (SCB) injection. We hypothesized that the current standard method of SCB administration might lead to lower anti-Xa levels than recommended in other patient groups, due to reduced bioavailability.

Methods: In this prospective, randomized, controlled clinical trial, 40 patients scheduled for elective CABG were randomized to receive 40 mg of enoxaparin per day either as CIV or SCB for 72 h. Enoxaparin was initiated 6–10 h after CABG. Anti-Xa levels were measured 12–14 times during the study period. The primary outcome i.e. the maximum anti-Xa concentration over 0–24 h ($C_{max0–24h}$), was calculated from these measured values. Secondary outcomes were $C_{max25–72h}$ and the trough concentration of anti-Xa after 72 h of enoxaparin initiation (C_{72h}).

Results: Twenty patients were randomized to the CIV-group and 19 to the SCB-group. The median anti-Xa $C_{max0–24h}$ was significantly lower in the CIV-group than in the SCB-group: 0.15 [interquartile range (IQR) 0.13–0.19] IU/mL versus 0.25 (IQR 0.18–0.32) IU/mL, $p < 0.005$. The median anti-Xa $C_{max25–72h}$ was 0.12 (IQR, 0.1–0.17) IU/mL versus 0.23 (IQR 0.19–0.31) IU/mL, respectively, $p < 0.005$. At 72 h, there was no difference between the groups in their anti-Xa levels.

Conclusions: In this low-risk CABG patient population, SCB administration of a thromboprophylactic dose of enoxaparin provided anti-Xa levels that are considered

sufficient for thromboprophylaxis in other patient groups. CIV administration resulted in lower anti-Xa levels compared to the SCB route.

INTRODUCTION

The administration of low-molecular-weight heparins (LMWHs) has become routine in postoperative thromboprophylaxis of patients undergoing on-pump coronary artery bypass grafting (CABG).[1–5] Unfortunately, neither the timing nor the dosage of LMWHs after CABG are clearly stated in the current literature, and clinical practice seems to vary between hospitals.

LMWHs such as enoxaparin have a predictable and reproducible dose-response, and laboratory monitoring is rarely needed.[3] When required, the effect of enoxaparin can be assessed by measuring anti-factor X activity (anti-Xa) levels.[6–8] According to the literature, anti-Xa levels of 0.1 IU/ml at any time and peak-levels 0.2 IU/ml are considered sufficient for thromboprophylaxis.[9] The theoretical bioavailability of enoxaparin after a subcutaneous bolus (SCB) injection is as high as 90%.[7,10] However, the bioavailability of LMWH following SCB administration might be diminished due to the presence of subcutaneous edema or the use of vasoconstrictors, resulting in subtherapeutic thromboprophylactic anti-Xa levels, particularly in critically ill patients.[11,12]

In CABG patients, the use of cardiopulmonary bypass (CPB) with crystalloid priming and transfusions evokes major changes in the intraoperative intravascular volume, leading to subcutaneous edema during the postoperative period.[13] CPB also triggers a multifactorial coagulopathy caused by hemodilution, inflammation, and the consumption of coagulation factors.[14,15] These changes might have a confounding effect on anti-Xa levels after CABG evident after both subcutaneous and intravenous administration of enoxaparin.

The aim of this study was to compare the anti-Xa levels after CABG with two different administration routes i.e. continuous intravenous infusion (CIV) and SCB, when a

thromboprophylactic dose of enoxaparin was administered with a non-weight-based dosage and an early initiation time (6 - 10 hours' postoperatively). The SCB administration of enoxaparin follows the current thromboprophylaxis practice after CABG in our hospital We hypothesized that a SCB of a putative thromboprophylactic dose of enoxaparin might lead to low anti-Xa levels after CABG due to CPB-triggered edema and the use of vasoconstrictors like norepinephrine.[11,13] We further hypothesized that as an alternative, the CIV administration of enoxaparin might lead to more consistent anti-Xa levels. As far as we are aware, the CIV administration of LMWHs after CABG has not been investigated earlier.

METHODS

This was a prospective, single-center, randomized controlled trial. The study protocol was approved by the local university district's research ethics committee (ETLR15064M) and the Finnish Medicine Agency (EUDRACT 59/2015 2015-001127-24). Written consent was obtained from all study patients participating in the trial. The study protocol was registered before patient enrollment at clinicaltrials.gov (NCT02474212). This manuscript was prepared in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[16] The study population included patients designated for elective on-pump-CABG surgery in the tertiary referral level hospital in Finland.

Patients aged 18–90 years with a body mass index (BMI) of 18–33 kg/m^2 and an indication for postoperative pharmacological thromboprophylaxis were eligible to be included in this trial. The exclusion criteria were as follows: any long-term anticoagulant medication, except low-dose aspirin; any other indication for anticoagulation except postoperative thromboprophylaxis; known heparin-induced thrombocytopenia; hypersensitivity to any

LMWH or heparin; major bleeding within the week prior to the operation; platelet count less than 20×10^9/L; glomerular filtration rate (GFR) less than 30 mL/min/1.73m^2 via the Cockcroft-Gault equation; known to be positive for HIV, hepatitis B or C infection; or pregnancy. Study patients were randomized into two groups according to the route of enoxaparin administration (Klexane®, Sanofi-Aventis, Helsinki, Finland). A block randomization with blocks of four patients was used.

The CIV-group received 40 mg of enoxaparin daily as a continuous intravenous infusion at a fixed rate. No initiation IV-bolus was delivered as there were no preliminary safety data on intravenous administration of enoxaparin after CABG. The intravenous infusion was prepared by diluting 20 mg of enoxaparin in 50 mL of 0.9 % saline to obtain a final concentration of 0.4 mg/mL. Patients were administered the contents of two 50 mL syringes over 24 h using an automatic infusion pump. The constant infusion rate was 4.2 mL/h, resulting in an enoxaparin infusion rate of 1.68 mg/h. Cessation for less than 1 h was considered insignificant. The SCB-group received 40 mg of enoxaparin daily as a single subcutaneous bolus injection from prefilled syringes.

A study period of 72 h was chosen to reach steady-state anti-Xa levels after subcutaneous administration of enoxaparin. If any indication requiring anticoagulation other than thromboprophylaxis occurred during the study period, the study was discontinued. After 72 h, thromboprophylaxis was continued according to the institution's clinical practice (i.e., 40 mg of enoxaparin SCB once daily). The anti-Xa values were not used for clinical decision-making during the study period.

All randomized patients underwent on-pump CABG. Perioperative treatment was performed according to the standard institutional practice. After weaning from CPB and decannulation, a

fixed bolus dose of 200 mg protamine was administered to all patients to reverse heparinization.

According to the study protocol, enoxaparin was initiated 6–10 h after the end of CABG in both study groups, following our institution's current clinical practice. The exact initiation time depended on the extent of postoperative bleeding, measured by the chest tube drainage volume. A drainage volume less than 150 mL/h prior to initiation was considered acceptable. No mechanical thromboprophylaxis was used during the study period. Prior to the initiation of the study drug, the baseline laboratory values of hemoglobin (Hb), antithrombin (AT), and anti-Xa were determined.

The anti-Xa levels were measured every 3 h during the first 24 h. In the CIV-group, additional measurements were obtained at 1.5 and 4.5 h after the initiation of enoxaparin administration. In addition, anti-Xa levels were obtained 27, 48, 51, and 72 h after the beginning of the study. In the SCB-group, the anti-Xa levels at 3, 27, and 51 h represent the peak concentrations, and at 24, 48, and 72 h, the trough concentrations of enoxaparin. The primary and secondary outcomes of maximum anti-Xa concentration (anti-Xa $C_{max0\text{-}24h}$), anti-Xa $C_{max25–72h}$, and anti-Xa C_{72h}, respectively, were calculated from these anti-Xa measurements.

Anti-Xa levels were analyzed using the chromogenic assay method (reagent: STA liquid anti-Xa 4; analyzer: STA-R Max, Diagnostica Stago, France). The anti-Xa data of study patients were collected until the patient exited the study. All available data were used in the final statistical analysis.

The white blood cell count, Hb concentration, platelet count, creatinine, international normalized ratio, C-reactive protein, and bilirubin were measured from daily blood samples.

The patient's weight was measured daily during the study period to estimate the amount of edema.

The chest tube drainage volume was recorded on the operation day and on the first postoperative day to evaluate postoperative bleeding. The E-bleeding Score was used to grade the severity of bleeding.[17] A radiologist performed a compression ultrasound of the lower extremities on the third study day to rule out asymptomatic deep vein thrombosis (DVT).

Statistical analysis

The primary outcome was the maximum level of anti-Xa within 0–24 h ($C_{max0–24h}$). The C_{max} represents the highest anti-Xa levels in the CIV group and thus offers the closest surrogate to the peak anti-Xa levels following SCB administration and makes it possible to conduct comparisons between two administration routes. The secondary outcomes were anti-Xa C_{max} within 25–72 h ($C_{max25–72h}$) and anti-Xa level after 72 h of initiation of enoxaparin (C_{72h}). $C_{max25–72h}$ represents the steady-state level of anti-Xa, and C_{72h} is the final trough level of anti-Xa. In case of patient drop out during study period, all pre-discontinuing anti-Xa values received were used in the data analysis.

Based on the standard study size calculation, 20 patients per group were required to achieve 80% power to detect a clinically significant reduction of 33% (from 0.3 to 0.20, standard deviation, SD 0.11) of anti-Xa C_{max} with a p-value of 0.05. Any missing data was handled as missing completely at random data. No input methods were used. The normality of data was evaluated using the Shapiro-Wilkins test. The anti-Xa data were non-normally distributed. Non-parametric statistical methods were used in the analysis of anti-Xa $C_{max,}$ values i.e. non-parametric data are represented as medians and interquartile ranges (IQR). The study groups

were compared via Mann-Whiney U-test, Pearson chi-square test, and Fisher's exact test. The SPSS software program was used for statistical analyses (version 23.0, IBM, Armonk, NY).

RESULTS

Three hundred and five elective CABG patients were screened between April 2016 and June 2018. Two hundred and sixty two were excluded either for logistic reasons or not meeting the inclusion criteria. Written informed consent was obtained from 43 eligible patients who were subsequently enrolled in the study prior to the procedure. A perioperative cardiac echo led to the exclusion of three patients after enrolment. Forty patients were randomized; one patient was excluded from the allocated intervention in the SCB-group, as the surgical procedure changed after randomization to combined CABG and aortic valve replacement. Thus, the final study population included 39 patients. Twenty patients were randomized to the CIV-group and nineteen to the SCB-group. A detailed subject flow with the reasons for exclusion is shown in the CONSORT diagram (Figure 1). The initiation of anticoagulation in case of postoperative atrial fibrillation (POAF) and wrong timing of enoxaparin were most common reasons for drop out. There were no significant differences in baseline characteristics, preoperative laboratory values, and perioperative data between groups (Table 1). During the 72-h study period, three (15%) patients in the CIV-group and 10 (52.6%) patients in the SCB-group were excluded. Seventeen patients in the CIV-group and nine in the SCB-group completed the study per protocol. The measured anti-Xa levels of both study groups are presented in Figure 2. The median anti-Xa levels prior to initiation of enoxaparin were as follows: CIV-group < 0.1 (IQR 0.0–0.05) IU/mL, and SCB-group < 0.1 (IQR 0.0–0.05) IU/mL.

Primary and Secondary Outcomes

The median anti-Xa $C_{max0–24h}$ was significantly lower in the CIV-group than in the SCB-group: 0.15 (IQR 0.13–0.19) IU/mL versus 0.25 (IQR 0.18–0.32) IU/mL, $p < 0.005$ (Table 2). The median anti-Xa $C_{max25–72h}$ was significantly lower in the CIV-group compared to SCB-group. Within the CIV-group, anti-Xa $C_{max0–24h}$ and $C_{max25–72h}$ levels significantly decreased towards the end of the study period (Table 2). This comparison could not be made within the SCB-group due to the high drop-out rate.

Clinical Outcomes

The median volume of chest tube drainage on the day of the operation was 270 (IQR 240–370) mL in the CIV-group and 350 (IQR 285–510) mL in the SCB-group ($p = 0.071$). On the first postoperative day, the volumes of chest tube drainage were 365 (IQR 235–505) mL and 305 (IQR 208–533) mL, respectively ($p = 0.851$). Three of the thirty-nine (7%) patients experienced clinically significant bleeding according to the E-Bleeding Score during the study period.[17] The postoperative laboratory values are shown in Table 3. There were no significant differences between the groups in any of these values. A compression ultrasound of the lower extremities was performed on 19 patients in the CIV-group and 14 patients in the SCB-group on the third study day. There were logistical reasons to explain why ultrasound was not performed on all study patients. No DVTs were detected.

DISCUSSION

In our study, the maximum anti-Xa levels within 0–24 h and 25–72 h were significantly lower in CIV-group as compared with the SCB-group following a thromboprophylactic dose of enoxaparin in CABG patients. Both administration routes of enoxaparin provided anti-Xa levels (Cmax) that were over 0.1 IU/mL. At the end of the study period, the final trough levels of anti-Xa were low in both study groups.

We observed that the anti-Xa $C_{max0–24h}$ was 0.15 IU/mL in the CIV-group and 0.25 IU/mL in the SCB-group. In the current literature, there is no generally recommended level of anti-Xa for thromboprophylaxis after CABG, complicating the interpretation of our results. In other surgical patients, however, a peak anti-Xa level of 0.2–0.5 IU/mL is considered sufficient for thromboprophylaxis after subcutaneous administration of enoxaparin.[9] In the SCB-group, anti-Xa $C_{max0-24}$ was above this level and remained over 0.2 IU/mL during the part of the study period from 25 to 72 h. Unfortunately, numerous study patients in the SCB-group dropped out during the study period, leaving this anti-Xa $C_{max25-72h}$ as an observational remark without statistical significance.

In the CIV-group, both anti-Xa $C_{max0-72h}$ and $C_{max25-72h}$ were above 0.1 IU/mL. According to the literature, an anti-Xa level above 0.1 IU/mL is considered sufficient for thromboprophylaxis regardless of the timing of the measurement.[9] The continuous intravenous dosing of thromboprophylactic LMWH has been rarely studied, i.e. we could find no publications giving recommendations for anti-Xa levels associated with CIV administration of enoxaparin after CABG. We have previously described a trial conducted in 23 non-cardiac ICU patients with 40 mg per day CIV administration of enoxaparin leading to anti-Xa ($C_{max0-24h}$) levels less than 0.05 IU/mL.[18] In this CABG patient population, the anti-Xa ($C_{max0-24h}$) levels were higher (0.15 IU/mL) already during the first 24 hours. Furthermore, there was a significant reduction in anti-Xa $C_{max25–72h}$ levels compared to $C_{max0–24h}$ levels. It is possible that CPB had triggered an inflammatory response and furthermore, the administration of diuretics could increase plasma levels of coagulation factors and thus alter the pharmacokinetics of enoxaparin in this later postoperative period.[14] At 72 h, when the final trough level was obtained, anti-Xa levels were less than 0.1 IU/mL in both groups. A low trough level indicates that there had been no clinically significant accumulation of enoxaparin via either administration route.

In patients with normal renal function and body weight, the pharmacokinetics of enoxaparin is predictable, and anti-Xa monitoring is not recommended.[19] Nonetheless, 40 mg enoxaparin delivered subcutaneously has led to low anti-Xa levels, especially in obese, critically ill, trauma, and non-cardiac surgical patients.[20–23] Several factors are known to be associated with a critical illness that predispose the patient to unpredictable responses after the standard dosing of enoxaparin, e.g., subcutaneous edema and use of vasoconstrictors[11,24] and these are factors commonly present after elective, low-risk CABG operation. Dörffler-Melly et al. examined ICU patients and stated that the use of norepinephrine led to lower anti-Xa levels compared to patients not administered this vasoconstrictive agent.[11] In our study, rather few patients required norepinephrine, the dosage was low, and the infusion duration was brief. Thus, we are unable to clarify the effect of vasopressors on enoxaparin's bioavailability. Haas et al. found that peripheral edema and weight gain were associated with suboptimal anti-Xa levels in ICU trauma patients[24] but again due to the small sample size, we could not assess whether this occurred in our CABG patients.

In our trial, there was considerable variability in anti-Xa levels between individuals in both administration groups. The CPB-induced coagulopathy could explain this variation as it is known that multiple components are involved in this side effect. The use of crystalloid priming causes hemodilution intraoperatively and leads to weight gain and peripheral edema during the postoperative period.[13,14,25,26] Activation of the coagulation cascade and bleeding are responsible for the consumption of coagulation factors. [25,27–29] These CPB-mediated changes are most evident during the first 24 h postoperatively.[25,26,28,29] We believe that the CPB-mediated changes, especially hemodilution, have a prominent effect on the plasma levels of anti-Xa during the first 24 hours after the initiation of enoxaparin therapy.

Five patients also had anti-Xa concentrations > 0.1 IU/ml prior the initiation of enoxaparin. We considered this to be caused by incomplete UFH reversal, as relatively low protamine-

heparin ratio used. Also the rebound heparinization may have been present, as the median initiation time of enoxaparin was only six hours after the end of operation.[30] However, in our study, AT levels were only mildly decreased, thus their impact on enoxaparin effect was considered to be insignificant.

We did not observe any severe clinical adverse events; the volumes of chest tube drainage were low in both groups. Three patients required blood transfusions, but the anti-Xa levels did not differ in non-bleeding patients. In our study, the incidence of bleeding remained low in comparison with previous reports.[17,31] Thus, the early initiation of enoxaparin i.e. 6–10 h postoperatively, did not increase the bleeding risk in this low-risk CABG patient population.

Limitations

This study has numerous limitations. The study sample size was small and was calculated only for the laboratory endpoints, so it is not possible to draw any conclusion regarding the clinical outcomes. The inclusion criteria for this study were specific; therefore the enrolled patients represented only a low-risk CABG surgery population.[32] The body weight of the included patients was restricted, thus we are unable to draw inferences about very obese patients. This low-risk population was not optimal for evaluating the study hypothesis, as the presence of either subcutaneous edema or the need for vasoconstrictors was low. Based on the preliminary nature of the study, no initiation IV bolus was used in the CIV-group, which explains why there were lower anti-Xa levels in patients receiving this delivery form. The drop-out rate was high in the SCB-group, which meant that the sample size was too small to reveal potential differences between the groups in the secondary endpoints.

Conclusions

In conclusion, the working hypothesis of our study regarding diminished bioavailability of the SCB-administered non-weight based thromboprophylactic enoxaparin was not proven in CABG patients. However, a sufficient anti-Xa C_{max} level was reached e.g. one which is considered adequate for thromboprophylaxis for other surgical patients. Administration of enoxaparin via CIV also produced anti-Xa levels above 0.1 IU/ml. Further studies will be needed to confirm the clinical relevance of these findings.

Funding information

This study received research funding from Instrufoundation and Tampere University Heart Hospital. In addition, it was partly financially supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital.

Conflict of interest

None of the authors have any conflicts of interest.

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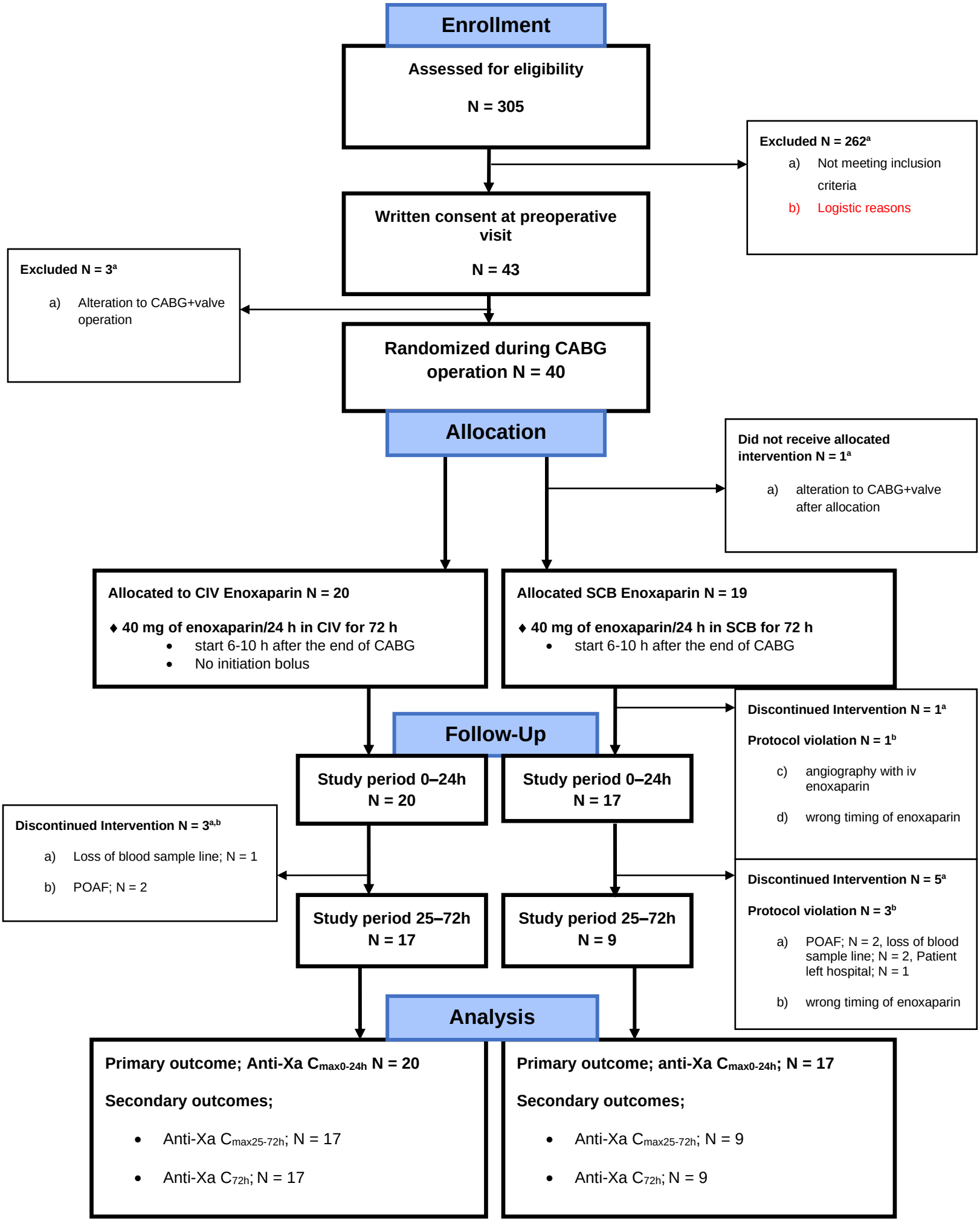
Figure 1. Patient flow chart.

Abbreviations: Anti-Xa; anti-factor X activity, C_{72h}; concentration at 72 h after initiation of enoxaparin, CABG; coronary artery bypass grafting, CIV; continuous intravenous infusion, $C_{max0\text{-}24h,}$ $C_{max25\text{-}72h}$; concentration maximums at time periods 0–24 and 25–7 2h, POAF; postoperative atrial fibrillation, SCB; subcutaneous bolus injection


Enrollment
Assessed for eligibility
N = 305
Excluded N = 262[a]
a) Not meeting inclusion criteria
b) Logistic reasons
Written consent at preoperative visit
N = 43
Excluded N = 3[a]
a) Alteration to CABG+valve operation
Randomized during CABG operation N = 40
Allocation
Did not receive allocated intervention N = 1[a]
a) alteration to CABG+valve after allocation
Allocated to CIV Enoxaparin N = 20
♦ 40 mg of enoxaparin/24 h in CIV for 72 h
start 6-10 h after the end of CABG
No initiation bolus
Allocated SCB Enoxaparin N = 19
♦ 40 mg of enoxaparin/24 h in SCB for 72 h
start 6-10 h after the end of CABG
Follow-Up
Discontinued Intervention N = 1[a]
Protocol violation N = 1[b]
c) angiography with iv enoxaparin
d) wrong timing of enoxaparin
Study period 0–24h N = 20
Study period 0–24h N = 17
Discontinued Intervention N = 3[a,b]
a) Loss of blood sample line; N = 1
b) POAF; N = 2
Discontinued Intervention N = 5[a]
Protocol violation N = 3[b]
a) POAF; N = 2, loss of blood sample line; N = 2, Patient left hospital; N = 1
b) wrong timing of enoxaparin
Study period 25–72h N = 17
Study period 25–72h N = 9
Analysis
Primary outcome; Anti-Xa Cmax0-24h N = 20
Secondary outcomes;
Anti-Xa Cmax25-72h; N = 17
Anti-Xa C72h; N = 17
Primary outcome; anti-Xa Cmax0-24h; N = 17
Secondary outcomes;
Anti-Xa Cmax25-72h; N = 9
Anti-Xa C72h; N = 9

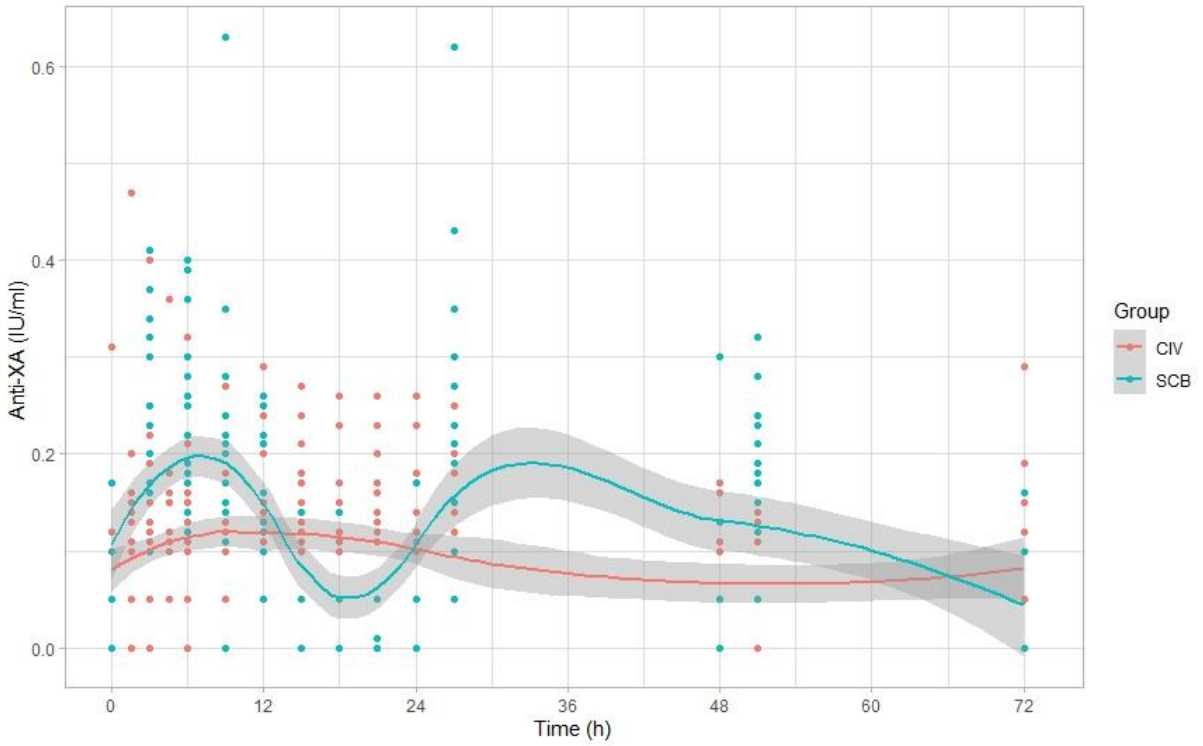


Figure 2. Y-axis: Measured anti-factor X activity levels during study. X-axis: time points when blood samples were drawn, hours after the initiation of enoxaparin. º; measured values over 1.5–3 interquartile range from the median, *; measured values over three interquartile ranges from the median.

Abbreviations: anti-Xa; anti-factor X activity, CIV; continuous intravenous infusion, IU; internatiol units, h; hours, SCB; subcutaneous bolus injection

Table 1.

Basic and Perioperative Characteristics of the Patients Prior Enoxaparin by Administration Group

	CIV N = 20	**SCB N = 19**
Male gender, N (%)	18 (90)	18 (94.7)
Age, years	67 (63–70)	69 (61–74)
Preoperative weight, kg	83.1 (74.9–91.9)	87.0 (69.0–96.0)
BMI, kg/m^2	27.6 (25.5–29.6)	27.8 (24.1–30.6)
EUROSCORE2, %	1.0 (0.7–1.5)	0.94 (0.7–1.5)
Diabetes, any type, N (%)	6 (30)	8 (42)
Hypertension, N (%)	17 (85)	16 (84.2)
Active smoker, N (%)	5 (25)	0 (0)
COPD, N (%)	4 (20)	3 (15.8)
Previous VTE, N (%)	0 (0)	0 (0)
Low dose aspirin, N (%)	20 (100)	18 (94.6)
Hemoglobin, g/l	143 (132–151)	148 (137–157)
WBC count, $x10^9/l$	6.75 (5.65–8.15)	6.7 (6.1–8.4)
Platelet count, $x10^9/l$	226 (180–272)	227 (191–267)
CRP, mg/l	1 (0.9–2.5)	1.1 (0.9–2.4)

Serum creatinine, µmol/l	79 (73–85)	73 (70–91)
GFR[a], ml/min/1,73m^2	87 (78–92)	90 (80–99)
ACT prior CPB, seconds	100 (96–114)	115 (98–126)
Heparin during CPB, mg/kg	6.1 (5.4–6.6)	5.9 (5.1–6.5)
CPB time, minutes	125 (94–141)	117 (103–138)
Aortic cross-clamp time, minutes	106 (80–118)	95 (82–112)
Blood loss in OR, ml	1800 (1600–2440)	2000 (1575–2240)
Crystalloids, OR, ml	5874 (5029–7224)	6338 (5000–6772)
Autologic RBCs returned, ml	820 (702–945)	900 (685–1100)
ACT in ICU, seconds	120 (118–126)	122 (112–148)
Norepinephrine-infusion ICU[b], N (%)	5 (25)	6 (31.6)
Dobutamine-infusion ICU[b], N (%)	0 (0)	1 (5.3)

Values are presented as median (25th to 75th quartile) or frequency (%).
Abbreviations: ACT; activated clotting time, BMI; body mass index, CIV; continuous intravenous infusion, COPD; chronic obstructive pulmonary disease, CPB; cardiopulmonary bypass, CRP; C-reactive protein, EUROSCORE2; European System for Cardiac Operative Risk Evaluation, FFP; fresh frozen plasma, GFR; glomerulus filtration rate, ICU; intensive care unit, OR; operating room, RBC; red blood cell count, SCB; subcutaneous bolus, VTE; venous thromboembolism, WBC; white blood cell [a)] Cockcroft Gault formula, [b)] at the time of initiation of enoxaparin

Table 2. Anti-Xa C_{max} by Administration Group

	CIV	SCB
$C_{max0–24h}$ IU/ml	0.15 (0.13–0.19)*º (N=20)	0.25 (0.18–0.32)* (N=19)
$C_{max25–72h}$ IU/ml	0.12 (0.05–0.17)º (N=17)	0.23 (0.19–0.31) (N= 9)
C_{max72h} IU/ml	0.05 (0.05–0.11)¶ (N=17)	0.05 (0.00–0.05)¶ (N=9)

Values are presented as median (25^{th} to 75^{th} quartile). Abbreviations: Anti-Xa; antifactor-X, C_{max}; concentration maximum, CIV; continuous intravenous infusion, SCB; subcutaneous bolus. * P-value < 0.05 between administration groups (CIV vs. SCB) in time interval 0–24 h, º P-value < 0.05 inside the administration group (CIV) in time intervals 0–24 h and 25–72 h, ¶ P-value > 0.05 between administration groups in time point of 72 h

Table 3.

Laboratory Values by Administration Group prior Enoxaparin and Study Dates 1, 2, 3[a]

	CIV	**SCB**
AT prior enoxaparin, %	75 (68–83)	74 (66–80)
Hb prior enoxaparin, g/l	130 (116–136)	125 (117–133)
Hb d1, g/l	116 (107–125)	121 (101–125)
Hb d2 g/l	108 (95–121)	110 (94–117)
Hb d3 g/l	100 (94–112)	105 (95–112)
WBC d1, x 10^9/l	10,4 (8.7–12.0)	9.6 (8.3–12.0)
WBC d2, x10^9/l	11.5 (9.7–13.6)	10.1 (9.15–11.2)
WBC d3, x10^9/l	10.1 (7.3–11.9)	8.6 (7.15–9.35)
Platelet count d1, x10^9/l	145 (109–176)	147 (123–165)
Platelet count d2, x10^9/l	151 (106–175)	139 (127–175)
Platelet count d3, x10^9/l	151 (122–181)	146 (130–181)
INR d1	1.3 (1.2–1.4)	1.3 (1.3–1.4)
INR d2	1.3 (1.2–1.4)	1.3 (1.2–1.4)
INR d3	1.2 (1.0–1.2)	1.2 (1.1–1.2)
Creatinine d1, µmol/l	62 (56–74)	66 (57–75)
Creatinine d2, µmol/l	70 (62–75)	69 (57–74)
Creatinine d3, µmol/l	70 (59–77)	68 (65–76)

Bilirubin, d1, µmol/l	10 (9–12)	12 (10–19)
Bilirubin, d2, µmol/l	11 (10–14)	15 (10–23)
Bilirubin, d3, µmol/l	9 (7–12)	11 (7–14)
CRP d1, mg/ml	66.8 (51.4–75.5)	67.9 (55.6–81)
CRP d2, mg/ml	149 (122.8–263.5)	175.8 (161.5–198.5)
CRP d3, mg/ml	161.9 (130.0–222.7)	162.0 (152.8–191.9)

Values are presented as median (25^{th} to 75^{th} quartile).
Abbreviations: AT; antithrombin, CABG; coronary artery bypass grafting, CIV; continuous intravenous infusion, CRP; C-reactive protein, d1; first postoperative day after CABG, d2; second postoperative day, d3; third postoperative day Hb; hemoglobin, INR; international normalized ratio, SCB; subcutaneous bolus, WBC; white blood cell. [a)] Laboratory measurements were taken 7 am in d1, d2, d3.