



Full Length Article

Plasma anti-FXa level as a surrogate marker of the adequacy of thromboprophylaxis in critically ill patients: A systematic review



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ABSTRACT

Background: Critical care patients are prone to venous thromboembolism (VTE) and, thus, pharmacological thromboprophylaxis is generally advised. Low-molecular weight heparins (LMWHs) have become the drug of choice in ICU patients, since their predictable and reproducible dose response. Monitoring their pharmacological effect is not usually necessary except in special occasions (i.e. with obese or renal failure patients), where anti-FXa level measuring is recommended. However, there is neither recommendation of adequate anti-FXa levels in critically ill patients nor is it known whether peak or trough level should be measured. The aim of this systematic review was to evaluate the recommended LMWH doses, and the reasons to monitor anti-FXa levels. **Methods:** We searched MEDLINE, Scopus, Cochrane Central Register of Controlled Trials and ClinicalTrials.com to identify all potentially relevant studies. Prospective studies done in critically ill patients were included if at least one anti-FXa level (i.e. peak or trough) after any specified LMWH thromboprophylaxis dose was measured.

Results: Total 18 eligible studies including 1644 patients were included. There was a wide variation in the median peak anti-FXa levels (<0.1–0.35 IU/ml). Trough levels were generally low. Of note, none of the studies detected any correlation with bleeding events and anti-FXa levels. Low trough level increased incidence of DVT in one study only.

Conclusion: Based on the current literature, no definite conclusions can be drawn on targeted anti-FXa level in critically ill patients when using LMWH thromboprophylaxis.

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1. Introduction

Critically ill patients are at increased risk of venous thromboembolism (VTE) because of several additive risk factors [1,2], with the critical illness itself acting as a hypercoagulable state [3,4]. In addition, withholding anticoagulant prophylaxis because of an elevated bleeding risk may predispose to VTE [5]. Therefore, the incidence of deep vein thrombosis (DVT) varies widely, from 10% to almost 100% [2,6]. Hospital mortality rates in patients with VTE have been reported to be relatively high, up to 28% [7]. In addition, VTE has been associated with increased risks of longer durations of mechanical ventilation and hospitalization [1].

Current guidelines of the American College of Chest Physicians (ACCP) recommend the use of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) to prevent VTE in critically ill patients [8]. However, data supporting the thromboprophylactic effects of LMWH and UFH are mainly based on studies in medical and surgical ward patients, in which LMWHs were superior to UFH in preventing VTE [9]. LMWHs have also become the drug of choice for patients in the intensive care unit (ICU) owing to their more predictable

and reproducible dose responses without the need for monitoring [10]. Furthermore, LMWHs have a lower risk of heparin-induced thrombocytopenia than UFH [11]. However, despite the almost routine use of pharmacological prophylaxis, the incidence of VTE has remained relatively high, between 5% and 16% [11,12], raising questions about the adequacy of current recommendations in heterogeneous high-risk groups of ICU patients.

The antithrombotic effects of LMWHs are mainly owing to their enhancement of the inhibitory effects of the intrinsic anticoagulant anti-thrombin III (AT III) on activated factor X (FXa) and thrombin (FIIa). Each LMWH has its own pharmacological profile (i.e., molecular weight distribution and anti-FXa/anti-FIIa activities), which must be considered when interpreting laboratory results [13]. As all LMWHs are predominantly cleared by the kidneys, patients with renal insufficiency may be predisposed to bleeding. Therefore, monitoring the pharmacological effects of LMWHs by measuring anti-FXa levels has been recommended only in patients with renal insufficiency or with other special circumstances (e.g., morbid obesity) [10]. To date, recommendations for adequate anti-FXa levels in critically ill patients have not been proposed, nor is it known whether the peak or trough level should be measured. Peak levels are generally regarded as reflecting thromboprophylactic effect, whereas trough levels are regarded as reflecting accumulation. However, it is unclear whether high peak levels predispose to bleeding

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or low trough levels to thrombosis. This systematic review was designed to determine anti-FXa levels in blood of critically ill patients after prescribed LMWH thromboprophylaxis and to evaluate whether clinically relevant events (e.g., VTE or bleeding) correlate with anti-FXa levels.

2. Methods

This systematic review is based on the methodology recommended by the Cochrane Collaboration. PRISMA Statement and Moose reporting recommendations were used. The protocol was published on the PROSPERO register (www.crd.york.ac.uk/PROSPERO, number CRD42015025744) before final data extraction.

2.1. Data sources and search strategy

MEDLINE, SCOPUS, the Cochrane Library, and the ClinicalTrials.com databases were searched in collaboration with a librarian with the University of Helsinki, using the terms Venous Thrombosis/thromboprophylaxis/Venous Thromboembolism AND Critical Care/Intensive Care Unit/Critical Illness AND LMWH. There were no restrictions on language, date, or type of publication. The initial search was completed in May 2015. The reference lists of all retrieved articles were manually reviewed to identify any potentially relevant studies. Details of the search strategies are shown in Supplement 1.

2.2. Study selection

Predefined inclusion criteria were used. Studies had to be prospective in design, performed in adult (age > 18 years) critical care patients, include more than 10 patients, use any LMWH thromboprophylaxis, and include at least one anti-FXa measurement at a known time point after specified LMWH administration. All abstracts and titles were screened independently by two reviewers (AV and AK). The full text of every identified article was read. Agreement between the two reviewers on article inclusion was high (kappa value 0.89), with any disagreements resolved through discussions.

2.3. Data extraction and quality assessment

The selected studies were independently reviewed by the same two investigators (AV and AK), and data were extracted using predefined criteria, including the study design, patient population, anti-FXa results, and clinical outcomes (i.e., DVT, symptomatic DVT, pulmonary embolism (PE), symptomatic PE, and major or minor bleeding based on the original trial definition). The quality of eligible studies was assessed using the Downs and Black checklist [14], and any disagreement was resolved by consensus. Quality assessment is presented as total Downs and Black score (maximum, total score 27), as well as by subgroup scores (reporting, external validity, internal validity-bias, internal validity-confounding). Because of the high heterogeneity of clinical outcomes in included studies, quantitative analyses could not be performed.

3. Results

The initial search identified 5206 citations, after duplicates were removed. Of these, 31 studies were retrieved for more detailed evaluation and 18 studies, including 1644 patients, were included in the final systematic review (Fig. 1). These studies were mainly observational, with only two randomized clinical trials (RCTs) identified. Trial characteristics are presented in Table 1. Most of these studies (10 observational studies and two RCTs) tested the effects of different dosages of enoxaparin [15–26], whereas four observational studies assessed dalteparin [27–30], and one each tested certoparin [31] and nadroparin [32]. No studies testing tinzaparin were identified. The median peak anti-FXa levels in ICU patients varied widely, from <0.1 IU/mL [31] to 0.35 IU/mL [27]. The median trough anti-FXa levels were reported in four studies, and they varied between undetectable and <0.1 IU/mL [27,31,18,20].

The quality of the studies according to the Down and Black score is shown in Table 2. The median total score (interquartile range, IQR) was 19 [15–20]/27. The median subscores (IQR) were 8.5 [7–10]/11 for reporting, 1 [1–2]/3 for external validity, 5 [4–5]/7 for internal validity-bias, and 3 [2–5]/7 for internal validity-confounding and power.

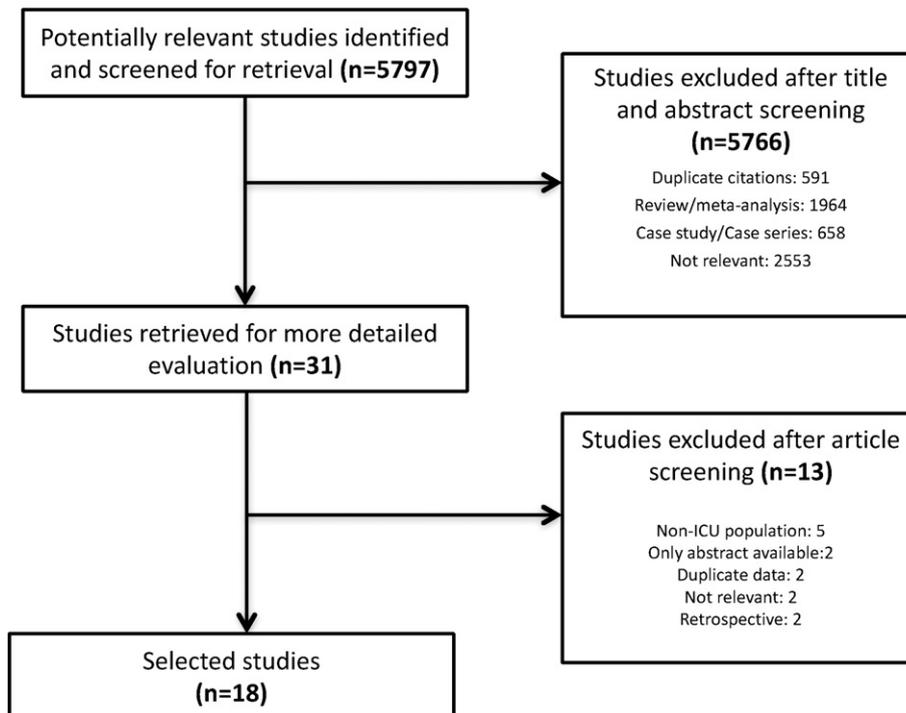


Fig. 1. Flow chart of the study selection.

3.1. Certoparin

The only observational study of certoparin included 62 critically ill patients. Treatment with 3000 IU OD certoparin resulted in a median peak anti-FXa level that was undetectable <0.1 (IQR <0.1 – 0.2) IU/mL. Only 28% of patients were within the antithrombotic range using the study definition of target value. When the dosage was doubled to 3000 IU bid, the median peak anti-FXa level did not change but 47% patients were within the recommended range. Median trough levels in patients administered 3000 IU OD and bid certoparin were undetectable <0.1 (IQR <0.1 – 0.17) and <0.1 (IQR <0.1 – 0.26) IU/mL, respectively. One patient in the lower dose group experienced severe PE, but the anti-FXa concentration of this patient was not reported. There was no correlation between bleeding and high anti-FXa levels (>0.3 IU/mL) [31].

3.2. Dalteparin

Four studies were identified. The first study, involving patients in the ICU with renal insufficiency (creatinine clearance “CrCl” <30 mL/min) administered 5000 IU OD dalteparin, reported median peak anti-FXa levels 4 h (hrs) after treatment to be 0.29 (IQR 0.20–0.42) IU/mL after 3 days and 0.34 (IQR 0.27–0.45) IU/mL after 17 days. Trough levels were undetectable. The incidence of major bleeding was 7.2% and two patients died of bleeding complications. However, there was no correlation between anti-FXa levels and deaths [27]. Similar results were observed in a small observational study of patients with renal insufficiency (CrCl <30 mL/min) [29].

The third study was a before and after study, in which dalteparin dosage was doubled if the anti-FXa level at 12 h was below <0.1 IU/mL. The protocol reduced the total incidence of VTE (12.8% vs. 7.0%, $p = 0.009$). Moreover, if the median anti-FXa level was below <0.1 IU/mL at 12 h, the rates of VTE (14.4% vs. 5.4%, $p = 0.05$) and DVT (14.4% vs. 3.2% $p = 0.01$) were significantly higher [28].

In the fourth study, the pharmacokinetics of dalteparin were assessed in edematous and non-edematous ICU patients. There were no between-group differences in mean \pm standard deviation (SD) peak (0.15 ± 0.05 vs. 0.14 ± 0.06 IU/mL) and trough (0.05 ± 0.06 vs. 0.02 ± 0.02 IU/mL) anti-FXa concentrations [30].

3.3. Enoxaparin

Median peak anti-FXa levels tended to be lower in ICU than in medical ward patients: 0.16 (IQR 0–0.22) vs 0.2 (IQR 0.15–0.27) IU/mL [16]. Similar results were observed when the area under curve (AUC)_{0–12 h} was measured (SD 2.63 ± 1 vs. 4.26 ± 1.7 IU/mL/h) [21]. Two RCTs also showed positive correlations between enoxaparin dosage and median peak and mean anti-FXa levels [22,23]. Five studies reported trough levels, which were generally low (0–0.10 IU/mL) and in one study the low trough level correlated with the incidence of DVT (37 vs. 11%, $p = 0.026$) [19]. Median trough levels were generally low or undetectable [18,20]. Nine studies reported adverse events, with none of these studies detecting any correlation between bleeding events and anti-FXa levels [15,18–20,22,23,24,33,26].

3.4. Nadroparin

Only one observational study was found, in which nadroparin 2850 IU OD was compared in three different patient groups: ICU patients on vasopressors ($n = 15$), ICU patients not on vasopressors ($n = 15$), and surgical ward patients ($n = 15$). The mean peak anti-FXa levels at 3 h were 0.09 (95% confidence interval (CI) 0.05–0.10), 0.23 (95% CI 0.18–0.27), and 0.28 (95% CI 0.23–0.31) IU/mL respectively. Trough levels were not measured, and clinical outcomes were not reported [32].

4. Discussion

This systematic review, which included 16 observational studies and two RCTs, found a lack of evidence regarding optimal targeted anti-FXa levels in critically ill patients. Median peak anti-FXa levels (<0.1 – 0.35 IU/mL) [31,27] and mean anti-FXa levels (0.09–0.40 IU/mL) [32,23] varied widely, depending on the type and dose of LMWH and on the study population. In addition, the trough levels were consistently low [27,31,18,20,29,30,24,33]. Data on peak and trough anti-FXa levels after LMWH thromboprophylaxis in ICU patients are sparse, and more research is certainly needed. Irrespective of LMWH drug and dose, peak and trough anti-FXa levels were generally low throughout the studies, but correlations between anti-FXa levels and clinically relevant outcomes, such as DVT, PE, and bleeding, remain uncertain. However, one study found that a low trough anti-FXa level significantly increased the incidence of DVT (37% vs. 11%, $p = 0.026$) [19].

These findings may have several explanations. First, AT III levels in critically ill patients were consistently low, correlating with low anti-FXa levels [31,21]. Low AT III levels may be due to elevated levels of other heparin-binding proteins (e.g., fibronectin and vitronectin), as observed in an animal endotoxin model [34]. Second, the absorption of subcutaneously administered LMWH may be reduced in patients treated with a vasopressor, reducing systemic bioavailability [32]. Third, critically ill patients often receive excessive amounts of intravenous fluids, resulting in peripheral edema, which may affect LMWH pharmacokinetics and reduce its bioavailability [17].

Administration of a standard prophylactic dosage of LMWH to obese ICU patients results in lower anti-FXa activity than in non-obese individuals [28,20]. However, enoxaparin dose may be positively correlated with anti-FXa levels, with adequate peak anti-FXa levels achieved using a weight-adjusted dose of enoxaparin (1 mg/kg once daily) [23].

Because of the lack of good quality RCTs [35], evidence of the effectiveness of LMWH thromboprophylaxis in ICU patients is mainly based on measurements of plasma levels of anti-FXa, as anti-FXa is a surrogate marker for anticoagulant effects. Correct anti-FXa levels have been determined only in patients undergoing orthopedic surgery [36,9]. It has not yet been determined whether peak or trough level should be measured. The generally recommended peak anti-FXa level for thromboprophylaxis is 0.1–0.3 IU/mL in medical and surgical patients [37]. The rates of VTE in patients undergoing hip surgery with trough (12 h after administration of enoxaparin) anti-FXa activity of >0.1 IU/mL, <0.1 IU/mL, and <0.05 IU/mL were reported to be 6.3%, 14.6%, and 18.8%, respectively. Anti-FXa levels >0.2 IU/mL were associated with hematomas [36]. These values are also generally used as references for anticoagulant effects in ICU patients in the observational studies included in this review.

Two of the observational studies were conducted in critically ill patients with renal insufficiency. Administration of a prophylactic dose of dalteparin to patients with impaired renal function (CrCl <30 mL/min) did not alter median peak anti-FXa levels [29,27] nor was there evidence of an increased risk of bleeding, despite a mean \pm SD CrCl of 18.9 ± 6.5 mL/min [27]. Lower serum creatinine and urea levels (not specified) were associated with a greater clearance of LMWH (certoparin), as measured by lower plasma anti-FXa levels [31].

Renal insufficiency is one of the most frequent reasons for omission of pharmacological thromboprophylaxis or for preferring UFH over LMWH [5]. Current research evidence does not support this practice, but these data are observational and limited. Moreover, urinary CrCl is an imprecise estimate of glomerular filtration rate in critically ill patients [38]. A meta-analysis that included patients with severe renal insufficiency (CrCl <30 mL/min) found that only when therapeutic doses of enoxaparin were administered were anti-FXa levels elevated and the risk of major bleeding increased [39]. Prophylactic administration of enoxaparin but not of tinzaparin showed similar accumulation findings in elderly medical patients with impaired renal function (CrCl 34 ± 11.4 mL/min) [40].

Table 1
The characteristics of the selected studies.

Study	Population	Study design	Thromboprophylaxis	Anti-FXa timing	Peak anti-FXa levels IU/ml	Trough anti-FXa levels IU/ml	Adverse events	Anti-FXa assay
<i>Certoparin</i>								
[31]	Mixed ICU	Single-center, prospective, open label study (n = 30 + 32)	Certoparin 3000 IU s.c. OD and 3000 IU s.c. bid	At 0, 4, 12 and 24 h	Median (IQR) at 4 h < 0.1 (<0.1–0.2) vs. <0.1 (<0.1–0.28)	Median (IQR) <0.1 (<0.1–0.17) vs. <0.1 (<0.1–0.26)	One PE in certoparin 3000 IU OD group	Coamatic Heparin©/Coamatic Heparin©
<i>Dalteparin</i>								
[27]	ICU patients with renal insufficiency (CrCl <30 ml/min)	Multi-center, single-arm, open label study (n = 138/156)	Dalteparin 5000 IU s.c. OD	At 0, 1, 2, 4, 8, 12, 20 and 24 h and on days 3, 10 and 17	Median (IQR) at 4 h: after 3 days 0.29 (0.20–0.42), 10 days 0.35 (0.24–0.43), 17 days 0.34 (0.27–0.45)	Median (IQR) <0.10 (<0.10– <0.10) (n = 120)	5.1% DVT, 7.2% major bleeding, 1.4% HIT. Two patients died with bleeding.	Stachrom–Heparin/Spectrolyze Heparin Xa/Electrochrome Beckman Coulter©
[28]	TICU	Single-center, before and after, prospective study (n = 190/785)	Before: dalteparin 5000 IU s.c. OD, after: dalteparin 5000 IU s.c. OD if anti-Xa <0.1 IU/ml 5000 IU s.c. bid	At 12 h	Not measured	Not measured	Pre vs. post protocol: overall VTE 12.8% vs. 7.0% (p = 0.009)	Not reported
[29]	Mixed ICU patients with renal insufficiency (CrCl <30 ml/min)	Single-center, prospective, cohort study (n = 19)	Dalteparin 5000 IU s.c. OD	At 4 h and 22–23 h	Mean (95% CI) at 4 h 0.30 (0.27–0.33)	Only 3/19 patients had levels above detection threshold (>0.1)	One catheter-related thrombus, two macroscopic bleeding	Rotochrom Heparin Kit©
[30]	Mixed ICU	Two-center open label study, edematous (n = 7) vs. nonoedematous (n = 7)	Dalteparin 2500 IU s.c. OD	At 0, 3, 4, 6, 8, 12 and 24 h	Mean (SD) at 3 h: 0.15 (0.05) vs. 0.14 (0.06)	Mean (SD) 0.05 (0.06) vs. 0.02 (0.02)	Not reported	Spectrolyze Heparin Xa©
<i>Enoxaparin</i>								
[15]	SICU (trauma ISS 24 ± 10.9)	Single-center, prospective, open label study (n = 61). LMWH dosing was increased if peak anti-FXa was <0.2 IU/ml	Enoxaparin 30 mg s.c. bid (initial dose) up to 60 mg s.c. bid	At 4 h on the 3rd dose and before the 4th dose	At 4 h sub-therapeutic (<0.2) in 70.5% (n = 43)	Not reported	4.9% VTE, did not correlate to anti-FXa levels. No bleeding events.	Hemosill©

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Table 1 (continued)

Study	Population	Study design	Thromboprophylaxis	Anti-FXa timing	Peak anti-FXa levels IU/ml	Trough anti-FXa levels IU/ml	Adverse events	Anti-FXa assay
[16]	MICU vs. general medical ward	Single-center, prospective, controlled open label study (n = 15 + 16)	Enoxaparin 40 mg s.c. OD	at 0, 1, 3, 6 and 12 h	Median (IQR) 3 h 0.16 (0–0.22) vs. 0.2 (0.15–0.27)	Not measured	Not reported	Rotachrom HBPm/LMWH©
[17]	TICU (ISS >10)	Single-center, prospective cohort study, nonoedematous (n = 11/14) vs. edematous (n = 10/11).	Enoxaparin 30 mg s.c. bid	At 0, 5, 1, 2, 3, 4, 6, 8 and 12 h	Median 0.27 vs. 0.12. IQR not reported	Not reported	Not reported	Chorm Z Heparin Kit©
[18]	MICU	Single-center, prospective, observational study (n = 55)	Enoxaparin 40 mg s.c. OD	At 0, 4, 12 and 24 h	Median (IQR) at 4 h 0.22 (0.17–0.26)	Median (IQR) 0 (0–0.03)	12.7% DVT, 1.8% PE. No bleeding complications	STA-STACLOT Heparin©
[19]	SICU	Single-center, prospective, observational study (n = 54)	Enoxaparin 30 mg s.c. bid	At 4 h and 1 h before the 4th dose	Mean (SD) at 4 h low trough group 0.17 (0.1) vs. normal trough group 0.27 (0.1)	Low trough (≤ 0.1) n = 27 vs. normal trough (> 0.1) n = 27	Low through anti-FXa level correlated to incidence of DVT (37 vs. 11%, p = 0.026)	Not reported
[20]	Mixed ICU	Single-center, prospective, observational study (n = 89)	Enoxaparin 40 mg s.c. OD	At 0, 4, 12 and 24 h	Median (IQR) at 4 h 0.18 (<0.1–0.52)	Median (IQR) <0.1 (<0.1–0.43)	No thromboembolic complications	Coamatic Heparin©
[21]	Mixed ICU vs. medical ward patients	Single-center, prospective, controlled open label study (n = 16 + 13)	Enoxaparin 40 mg s.c. OD	At 0, 1, 3, 6, 12 h on day 1 and at 3 h on days 2–5	Mean AUC (SD) at 0–12 h 2.63 (1) vs. 4.26 (1.7)	Not measured	Not reported	Rotachrom HBPm/LMWH©
[22]	Mixed ICU	Single-center, prospective, randomized double blind study (n = 18 + 16 + 20 + 18)	Enoxaparin 40, 50, 60 or 70 mg s.c. OD	At 0, 4, 12 and 24 h	Median at 4 h 0.13, 0.14, 0.27 vs. 0.29. IQR not reported	Not reported	One minor nosebleed	Coamatic Heparin©
[23]	Mixed ICU	Single-center, prospective, randomized double blind study (n = 20 + 20 + 19 + 19)	Enoxaparin 40 mg s.c. OD, 30 mg s.c. bid, 40 mg s.c. bid or 1 mg/kg s.c. OD	At 0, 4, 12, 16, 24 h daily for 3 days	Mean at 4 h on the 1st day: 0.20, 0.08, 0.17, 0.34 on the 3rd day: 0.13, 0.14, 0.33, 0.40. SD not reported	Not reported	No adverse events	Coamatic Heparin©
[24]	TICU (ISS >10)	Single-center, prospective, open label, cohort study (n = 17)	Enoxaparin 40 mg s.c. OD	At 4 and 24 h (on day 3)	Mean (SD) at 4 h 0.19 (0.09)	Mean (SD) 0.04 (0.04)	One DVT, no bleeding	Not reported
[33]	Mixed ICU	Single-center, prospective, open label study (n = 36)	Enoxaparin 30 mg s.c. bid	At 0, 3, 6, 9 and 12 h	Median (IQR) 3 h 0.24 (0.19)	Median (IQR) 0.10 (0.09)	One DVT, one bleeding, one thrombocytopenia	Stago Rotachrom Heparin kit©
[26]	MICU sepsis patients	Single-center, prospective, open label study (n = 16)	Enoxaparin 40 mg s.c. OD	At 4 h on days 1, 2, 3, 6, 9, 12 and 15	Mean (SD) at 4 h 0.17 (0.17)	Not measured	One DVT, two bleeding events	Coamatic Heparin©
<i>Nadroparin</i>								
[32]	ICU vs. general surgery ward	Single-center, ICU patients on vasopressors (n = 15) vs. ICU patients not on vasopressors (n = 15) vs. surgical ward patients (n = 15)	Nadroparin 2850 IU s.c. OD	At 0, 3, 4, 6, 8 and 12 h, LMWH given at least 3 days	Mean (95%CI) at 3 h: 0.09 (0.18–0.37) vs. 0.23 (0.18–0.27) vs. 0.28 (0.23–0.31)	Not measured	Not reported	Coamatic Heparin©

Abbreviations

ICU, indicates intensive care unit; CrCl, creatinine clearance; TICU, trauma intensive care unit; SICU, surgical intensive care unit; MICU, medical intensive care unit; ISS, injury severity score; LMWH, low-molecular weight heparin; s.c., subcutaneous; OD, once daily; bid, twice daily; hrs, hours; h, hour; IQR, interquartile range; CI, confidence interval; SD, standard deviation; AUC, area under curve; PE, pulmonary embolism; DVT, deep venous thrombosis; HIT, heparin induced thrombocytopenia; VTE, venous thromboembolism.

Table 2
Down and Black checklist.

Study	Total score (27)	Reporting (10)	External validity (3)	Internal validity-bias (7)	Internal validity-confounding and power (7)
[15]	8	6	1	0	1
[32]	15	8	1	4	2
[27]	20	10	1	6	3
[28]	13	7	2	4	0
[16]	19	9	1	5	4
[17]	15	6	1	5	3
[31]	19	8	1	5	5
[18]	22	10	3	5	4
[19]	17	7	3	4	3
[20]	20	9	1	5	5
[21]	16	7	1	5	3
[29]	14	8	0	4	2
[23]	26	10	2	7	7
[22]	23	9	1	7	6
[30]	21	10	1	5	5
[24]	14	8	0	4	2
[33]	20	11	1	5	3
[26]	20	10	1	5	4
Median (IQR)	19 (15–20)	8.5 (7–10)	1 (1–2)	5 (4–5)	3 [2–5]

IQR indicates interquartile range.

Reporting

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in Sections 1 and 2?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of patients lost to follow-up been described?
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

External validity

1. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
2. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
3. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

Internal validity – bias

1. Was an attempt made to blind study subjects to the intervention they have received?
2. Was an attempt made to blind those measuring the main outcomes of the intervention?
3. If any of the results of the study were based on “data dredging”, was this made clear?
4. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case–control studies, is the time period between the intervention and outcome the same for cases and controls?
5. Were the statistical tests used to assess the main outcomes appropriate?
6. Was compliance with the intervention/s reliable?
7. Were the main outcome measures used accurate (valid and reliable)?

Internal validity – confounding (selection bias) and power.

1. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case–control studies) recruited from the same population?
2. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case–control studies) recruited over the same period of time?
3. Were study subjects randomized to intervention groups?
4. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
5. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
6. Were losses of patients to follow-up taken into account?
7. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

The critical illness itself often acts as a hypercoagulable state (e.g., sepsis or trauma) [3]. In addition, the severity of critical illness (e.g., multiple organ dysfunction score or severity of burn injury) was reported to correlate with lower anti-FXa [41,20]. Whether the latter

reflects an insufficient anticoagulant effect or the nature of anti-FXa as a surrogate marker requires further investigations.

These findings of low levels of anti-FX activity and several conditions that can alter LMWH bioavailability in intensive care patients have raised the question of the adequacy of thromboprophylaxis with dosing schemas applied to medical and surgical patients. Although VTE events have decreased with LMWH prophylaxis, thromboembolism has occurred, despite recommended dosing of LMWHs and even within recommended anti-FXa levels [19]. In addition to the reasons described above, uneventful thrombosis may result from a fear of bleeding, resulting in pauses and delays in thromboprophylaxis [5].

4.1. Strengths and limitations

To our knowledge, this is the first systematic review of the role of anti-FXa monitoring during LMWH thromboprophylaxis in critically ill patients. However, this study had several limitations. First, all included studies were relatively small, with most being observational and underpowered for clinical endpoints, and of low quality. Second, as the type of ICUs varied among studies (i.e., mixed, medical, trauma, and surgical) and patients had various degrees of renal failure, the study population was quite heterogeneous. The benefits and adverse effects of LMWH may vary in different subgroups of ICU patients. Third, the type and dose of LMWH varied among studies; because LMWHs have different pharmacological properties, it is unclear whether anti-FXa levels can be generalized. Fourth, there were methodological limitations concerning anti-FXa measurements, as the protocols of the included studies were not identical (e.g., times samples were obtained after LMWH administration, blood sample collecting procedures, and delay from sampling to analysis) and the analytic methods and reference levels differ among laboratories. Moreover, the reporting of measured anti-Xa activity concentrations in the studies varied (e.g., median, mean or AUC), making data interpretation difficult. Fifth, the secondary outcomes should also be considered a study limitation because the definitions of these adverse events (e.g., DVT, symptomatic DVT, PE, symptomatic PE, and minor or major bleeding) varied across studies. Sixth, the literature search was updated in May 2015; thus, more recent data may be missing.

5. Conclusion

No definite conclusions can be drawn regarding target anti-FXa levels in critically ill patients administered LMWHs for thromboprophylaxis. No recommendations can be made on the timing of anti-FXa monitoring or for dose adjustments for individual patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.thromres.2015.12.016>.

References

- [1] D. Cook, M. Crowther, M. Meade, et al., Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors, *Crit. Care Med.* 33 (2005) 1565–1571.
- [2] W.H. Geerts, D. Bergqvist, G.F. Pineo, et al., Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition), *Chest* 133 (2008) 381S–453S.

- [3] M. Sivula, V. Pettila, T.T. Niemi, M. Varpula, A.H. Kuitunen, Thromboelastometry in patients with severe sepsis and disseminated intravascular coagulation, *Blood Coagul. Fibrinolysis* 20 (2009) 419–426.
- [4] R.M. Van H, T. CM, V. EJ, et al., Hypercoagulability after burn injury, *J. Trauma Acute Care Surg.* 75 (2013) 37–43.
- [5] F. Lauzier, J. Muscedere, E. Deland, et al., Thromboprophylaxis patterns and determinants in critically ill patients: a multicenter audit, *Crit. Care* 18 (2014) R82.
- [6] J. Attia, J.G. Ray, D.J. Cook, J. Douketis, J.S. Ginsberg, W.H. Geerts, Deep vein thrombosis and its prevention in critically ill adults, *Arch. Intern. Med.* 161 (2001) 1268–1279.
- [7] G.P. Patel, J. Liberman, D. Gurka, E. Elpern, R.A. Balk, Complications of critical illness: rationale for prophylactic strategies, *Clin. Pulm. Med.* 12 (2005) 258–268.
- [8] S.R. Kahn, W. Lim, A.S. Dunn, et al., Prevention of VTE in nonsurgical patients. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines, *Chest* 141 (2012) e195S–e226S.
- [9] P.F. Leyvraz, F. Bachmann, J. Hoek, et al., Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin, *BMJ* 303 (1991) 543–548.
- [10] D.A. Garcia, T.P. Baglin, J.I. Weitz, M.M. Samama, Parenteral anticoagulants: anti-thrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines, *Chest* 141 (2012) e24S–e43S.
- [11] D. Cook, M. Meade, G. Guyatt, et al., Dalteparin versus unfractionated heparin in critically ill patients, *N. Engl. J. Med.* 364 (2011) 1305–1314.
- [12] F. Fraisse, L. Holzappel, J.M. Couland, et al., Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD, *Am. J. Respir. Crit. Care Med.* 161 (2000) 1109–1114.
- [13] L. Bara, A. Planes, M.M. Samama, Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis after hip surgery, *Br. J. Haematol.* 104 (1999) 230–240.
- [14] S.H. Downs, N. Black, The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions, *J. Epidemiol. Community Health* 52 (1998) 377–384.
- [15] T.W. Costantini, E. Min, K. Box, et al., Dose adjusting enoxaparin is necessary to achieve adequate venous thromboembolism prophylaxis in trauma patients, *J. Trauma Acute Care Surg.* 74 (2013) 128–133 discussion 134.
- [16] G. Gouya, S. Palkovits, S. Kapiotis, et al., Bioactivity of enoxaparin in critically ill patients with normal renal function, *Br. J. Clin. Pharmacol.* 74 (2012) 806–814.
- [17] C.E. Haas, J.L. Nelsen, K. Raghavendran, et al., Pharmacokinetics and pharmacodynamics of enoxaparin in multiple trauma patients, *J. Trauma* 59 (2005) 1336–1344.
- [18] S.Y. Lim, K. Jeon, H.-J. Kim, et al., Antifactor Xa levels in critically ill Korean patients receiving enoxaparin for thromboprophylaxis: a prospective observational study, *J. Korean Med. Sci.* 28 (2013) 466–471.
- [19] D. Malinoski, F. Jafari, T. Ewing, et al., Standard prophylactic enoxaparin dosing leads to inadequate anti-Xa levels and increased deep venous thrombosis rates in critically ill trauma and surgical patients, *J. Trauma* 68 (2010) 874–879.
- [20] A.J. Mayr, M. Dünser, S. Jochberger, et al., Antifactor Xa activity in intensive care patients receiving thromboembolic prophylaxis with standard doses of enoxaparin, *Thromb. Res.* 105 (2002) 201–204.
- [21] U. Priglinger, D. KG, G. A. et al., Prophylactic anticoagulation with enoxaparin: is the subcutaneous route appropriate in the critically ill? *Crit. Care Med.* 31 (2003) 1405–1409.
- [22] S. Robinson, A. Zincuk, T. Strom, T.B. Larsen, B. Rasmussen, P. Toft, Enoxaparin, effective dosage for intensive care patients: double-blinded, randomised clinical trial, *Crit. Care* 14 (2010) R41.
- [23] S. Robinson, A. Zincuk, U.L. Larsen, et al., A comparative study of varying doses of enoxaparin for thromboprophylaxis in critically ill patients: a double-blinded, randomised controlled trial, *Crit. Care* 17 (2013).
- [24] E.J. Rutherford, W.G. Schooler, E. Sredzienski, J.E. Abrams, D.A. Skeete, Optimal dose of enoxaparin in critically ill trauma and surgical patients, *J. Trauma* 58 (2005) 1167–1170.
- [25] J.L. Vincent, R. Moreno, J. Takala, et al., The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine, *Intensive Care Med.* 22 (1996) 707–710.
- [26] Z. Zenáhlíková, J. Kvasnicka, Z. Kudrnová, M. Sudrová, R. Brzezková, J. Mazoch, I.V.J. Malíková, D. Erhart, L. Pecen, FXa inhibition and coagulation changes during DVT prophylaxis by enoxaparin over the course of a 15-day follow-up in septic patients, *Clin. Appl. Thromb. Hemost.* 16 (2010) 584–590.
- [27] J. Douketis, D. Cook, M. Meade, et al., Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: an assessment of safety and pharmacodynamics: the DIRECT study, *Arch. Intern. Med.* 168 (2008) 1805–1812.
- [28] M.E. Droege, E.W. Mueller, K.M. Besl, et al., Effect of a dalteparin prophylaxis protocol using anti-factor Xa concentrations on venous thromboembolism in high-risk trauma patients, *J. Trauma Acute Care Surg.* 76 (2014) 450–456.
- [29] C.G. Rabbat, D.J. Cook, M.A. Crowther, et al., Dalteparin thromboprophylaxis for critically ill medical-surgical patients with renal insufficiency, *J. Crit. Care* 20 (2005) 357–363.
- [30] M.K. Rommers, N. Van DL, E. TCG, P.M.L.A. van DB, Anti-Xa activity after subcutaneous administration of dalteparin in ICU patients with and without subcutaneous oedema: A pilot study, *Crit. Care* 10 (2006).
- [31] S. Jochberger, V. Mayr, G. Luckner, et al., Antifactor Xa activity in critically ill patients receiving antithrombotic prophylaxis with standard dosages of certoparin: a prospective, clinical study. *Critical care (London, England)*, *Crit. Care* 9 (2005) R541–R548.
- [32] J.D.J.E. Dörrfler-Melly, A.C. Pont, J. Meijers, M.B. Vroom, H.R. Büller, M. Levi, Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors, *Lancet* 359 (2002) 849–850.
- [33] P.D. Vincent, M. Albert, M.-C. Champagne, et al., Factors influencing enoxaparin anti-Xa activity in surgical critically ill patients, *J. Crit. Care* 26 (2011) 347–351.
- [34] E. Young, T.J. Podor, T. Venner, J. Hirsh, Induction of the acute-phase reaction increases heparin-binding proteins in plasma, *Arterioscler. Thromb. Vasc. Biol.* 17 (1997) 1568–1574.
- [35] W. Alhazzani, W. Lim, R.Z. Jaeschke, M.H. Murad, J. Cade, D.J. Cook, Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials, *Crit. Care Med.* 41 (2013) 2088–2098.
- [36] M.N. Levine, A. Planes, J. Hirsh, M. Goodyear, N. Vochelle, M. Gent, The relationship between anti-factor Xa level and clinical outcome in patients receiving enoxaparin low molecular weight heparin to prevent deep vein thrombosis after hip replacement, *Thromb. Haemost.* 62 (1989) 940–944.
- [37] M. Laposata, D. Green, E.M. Van Cott, T.W. Barrowcliffe, S.H. Goodnight, R.C. Sosolik, College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: the clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban, *Arch. Pathol. Lab. Med.* 122 (1998) 799–807.
- [38] G. Bragadottir, B. Redfors, S.E. Ricksten, Assessing glomerular filtration rate (GFR) in critically ill patients with acute kidney injury—true GFR versus urinary creatinine clearance and estimating equations, *Crit. Care* 17 (2013) R108.
- [39] W. Lim, F. Dentali, J.W. Eikelboom, M.A. Crowther, Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency, *Ann. Intern. Med.* 144 (2006) 673–684.
- [40] I. Mahe, M. Aghassarian, L. Drouet, et al., Tinzaparin and enoxaparin given at prophylactic dose for eight days in medical elderly patients with impaired renal function: a comparative pharmacokinetic study, *Thromb. Haemost.* 97 (2007) 581–586.
- [41] H. Lin, I. Faraklas, J. Saffle, A. Cochran, Enoxaparin dose adjustment is associated with low incidence of venous thromboembolic events in acute burn patients, *J. Trauma* 71 (2011) 1557–1561.