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Anti-factor Xa level monitoring of low-molecular-weight heparin for prevention of venous thromboembolism in critically ill patients (AXaLPE): protocol of a randomised, open-label controlled clinical trial

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ABSTRACT

Introduction Whether and when to monitor the amount of anti-factor Xa (aFXa) activity in critically ill patients with complex diseases to prevent venous thromboembolism (VTE) remain unclear. This study is a randomised controlled trial to investigate the effect of aFXa level monitoring on reducing VTE and to establish a new method for accurately preventing VTE in critically ill patients with low-molecular-weight heparin (LMWH).

Methods and analysis A randomised controlled trial is planned in two centres with a planned sample size of 858 participants. Participants will be randomly assigned to three groups receiving LMWH prophylaxis at a 1:1:1 ratio: in group A, peak aFXa levels will serve as the guide for the LMWH dose; in group B, the trough aFXa levels will serve as the guide for the LMWH dose; and in group C, participants serving as the control group will receive a fixed dose of LMWH. The peak and trough aFXa levels will be monitored after LMWH (enoxaparin, 40 mg, once daily) reaches a steady state for at least 3 days. The monitoring range for group A's aFXa peak value will be 0.3–0.5 IU/mL, between 0.1 and 0.2 IU/mL is the target range for group B's aFXa trough value. In order to reach the peak or trough aFXa levels, groups A and B will be modified in accordance with the monitoring peak and trough aFXa level. The incidence of VTE will serve as the study's primary outcome indicator. An analysis using the intention-to-treat and per-protocol criterion will serve as the main outcome measurement.

Ethics and dissemination The Xuanwu Hospital Ethics Committee of Capital Medical University and Peking University First Hospital Ethics Committee have approved this investigation. It will be released in all available worldwide, open-access, peer-reviewed publications.

Trial registration number NCT05382481

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To minimise bias and confounding variables, this project is a two-centre, randomised and open-label controlled clinical trial.
⇒ It will explore whether to monitor anti-factor Xa and its timing when low-molecular-weight heparin is used to prevent venous thromboembolism (VTE) in critically ill patients.
⇒ The follow-up period of this study is short, and long-term VTE is not evaluated.

BACKGROUND

Venous thromboembolism (VTE) includes deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE). The risk factors for PTE and DVT are the same, both are clinical manifestations of VTE in various parts and stages. DVT can be concurrent with PTE, which causes death. Additionally, it is the most prevalent and preventable reason for hospital deaths. The prevention of hospital-acquired VTE is a focus of health services and the first hospital strategy in the world to increase patient security.[1–6] Additionally, 20–50% of patients with VTE in the chronic phase can develop post-thrombotic syndrome,[3 6] and chronic thromboembolic pulmonary hypertension develops in up to 5% of patients with PTE.[6] Both conditions have major impacts on a patient's quality of life.[3]

In comparison with fixed dosages, modifying doses based on anti-factor Xa (aFXa) monitoring did not reduce the incidence of VTE in patients, according to a 1994 study by Alhenc-Gelas *et al*.[7] Fixed doses of low-molecular-weight heparin (LMWH) has been employed for many years in thromboprophylaxis.[8–11] However, in clinical application, this

dose was found to be inappropriate for pregnant women, children, obese patients and patients with renal insufficiency. Peak aFXa levels should be monitored to alter the dose of LMWH in these patients.[12–14] This fixed dose of enoxaparin may be metabolized at various rates in critically ill patients with different complex conditions. When 40 mg once daily enoxaparin was administered, the monitoring of aFXa levels revealed that more than 50% of patients undergoing thoracic, plastic and abdominal surgery had insufficient anticoagulation.[15–17] In a single-centre, non-randomised clinical trial (RCT), Pannucci *et al* examined the effectiveness of 40 mg enoxaparin per day in preventing VTE in patients undergoing colorectal surgery. Peak aFXa levels were examined in 106 individuals, of whom 72 (67.9%) had insufficient anticoagulation (peak aFXa <0.3 IU/mL) and 47 had undetectable aFXa trough levels; that is, in the majority of patients, anticoagulation was undetectable for at least 12 hours each day. Thus, fixed-dose enoxaparin anticoagulant prophylaxis is typically insufficient in patients undergoing colorectal surgery.[18] Despite following the recommended LMWH prophylactic regimen, 'breakthrough' VTE episodes are frequently observed in surgical patients. Patients undergoing abdominal and pelvic surgery and taking 40 mg of enoxaparin daily experienced an incidence of symptomatic plus asymptomatic VTE ranging from 4.8% to 12.6% in numerous multicentre RCTs.[19 20] After LMWH prophylaxis, VTE occurred in up to 37.2% of critically ill patients with sepsis.[21] After prophylaxis with LMWH in critically ill patients with severe COVID-2019, 31 (28%) patients had VTE.[22] Additional research revealed a strong correlation between asymptomatic and symptomatic VTE in patients with low postoperative aFXa levels.[15 18]

The American Association for the Surgery of Trauma suggested modifying aFXa monitoring in surgical and trauma intensive care unit (ICU) patients in 2021 such that more patients have aFXa levels within the desired range. However, studies on whether VTE can be reduced are inconclusive.[23] Although little evidence exists, the 2020 Western Trauma Association advises patients with moderate to severe trauma, burns and surgical oncology requiring ICU hospitalisation consider monitoring enoxaparin aFXa levels.[24] LMWH anticoagulation is safe and effective for preventing VTE in trauma patients, according to a meta-analysis. A meta-analysis of five studies with a combined total of 1617 patients, 724 in the aFXa surveillance group and 893 in the control group without aFXa surveillance, revealed the safety and effectiveness of LMWH anticoagulation for the prevention of VTE in trauma patients. In comparison with the control group, the VTE events in the aFXa monitoring group were considerably fewer (OR 0.44, 95% CI 0.29 to 0.68, p=0.0002). The incidence of bleeding events did not appear to differ between the aFXa monitoring group and the control group as a result of the small number of bleeding incidents. Anti-Xa monitoring might be beneficial for trauma patients receiving LMWH anticoagulation to prevent VTE. Subgroup analysis, peak and trough aFXa monitoring were used in two trials and three studies, respectively, to determine the dosage of LMWH. The results showed no difference between the control group without aFXa monitoring (3 of 198) and the group with peak aFXa monitoring (3 of 158). Peak aFXa monitoring did not reduce VTE occurrence, but the incidence was low, and there was no VTE event in one of two investigations. The incidence of VTE was significantly lower in the aFXa trough level guided LMWH dosage group (27 of 502) than in the control group (78 of 637) without aFXa monitoring in trauma patients.[25]

Patients who are critically ill have complex medical situations, such as sedation, mechanical ventilation, central venous catheters, prolonged immobility and severe inflammation, as well as modifications in renal clearance, medication bioavailability and coagulation. Thus, these patients are at high risk of both VTE and bleeding.[24 26] However, few studies have examined whether and when to monitor these patients for VTE prevention. To solve the problem of 'breakthrough' VTE in critically ill patients, this work proposes a randomised controlled study method to explore the effect of aFXa monitoring-based LMWH prevention to reduce VTE incidence in critically ill patients. This study also plans to assess the timing of aFXa monitoring, whether peak or trough monitoring, and to summarise the precise method of LMWH dosing to prevent VTE in critically ill patients, to decrease mortality and to reduce serious complications.

METHODS AND ANALYSIS

Study purpose

1. We will determine whether the dosage of LMWH in critically ill patients should be based on monitoring aFXa levels and whether it can reduce VTE in comparison with the LMWH dose-fixed group without aFXa monitoring.
2. In critically ill patients, the effects of LMWH dose adjustment based on aFXa peak and trough level monitoring will be compared to determine the best timing for VTE prevention with aFXa monitoring.

Study design

This study will be a randomised, open-label controlled clinical trial. The study started on 16 May 2022 and will end on 31 December 2024. Patients in critical condition who are eligible for LMWH to prevent VTE after signing the informed consent form will be randomly divided into three groups. The LMWH dose will be guided by the peak aFXa levels in group A, the LMWH dose will be guided by the trough aFXa levels in group B and the no aFXa monitoring LMWH dose-fixed group will be the control group (group C). The incidence of VTE and bleeding will be compared among the three groups. ICU physicians from two hospitals will consecutively recruit participants. The primary outcome, VTE evaluation, will be evaluated by an impartial vascular sonographer who is blinded to the study assignment to avoid potential observer bias in the

assessment. Laboratory doctors blinded to trial assignment will monitor aFXa activity levels and haemoglobin for the secondary study result independent of the experiment, and data analysis of all primary and secondary outcomes will be performed by statisticians at the Peking University Clinical Research Institute.

Patient and public involvement

Patients and the public were not involved in the design of the study. However, we plan to involve our participants in communication and education during the research process to increase awareness and knowledge, to build confidence and control with self-management, and finally prevent VTE.

Patients or the patients' close relations (spouse/partner, close relative, caregiver) will be informed about the patients' enrolment and the nature of the study. They will meet the investigator for an informative interview, to obtain the information leaflet and to sign a confirmation that they were informed about the patient's participation in the trial. While this document is a study protocol, the dissemination and implications of the study results will involve patient and peer-support organisations and public policymakers. We would like to thank all participants.

Ethical approval

The study procedures and informed consent form were approved by the ethics committees of all participating hospitals, and the study was registered as NCT05382481 at www.clinicaltrials.gov on 15 May 2022.

Study population

Participants will be recruited from 16 May 2022 at Xuanwu Hospital of Capital Medical University and Peking University First Hospital. The inclusion criteria are: (1) age ≥18 years old; (2) critically ill patients who need LMWH anticoagulation prophylaxis after VTE risk assessment; (3) voluntary participation in the study and signing of the informed consent form. The exclusion criteria are: (1) renal insufficiency with creatinine clearance <30 mL/min (creatinine clearance estimated by the Cockcroft-Gault equation); (2) patients with high bleeding risk or diseases that could cause severe bleeding, such as intracranial haemorrhage, traumatic brain injury, blood system diseases, etc; (3) a short estimated total hospitalisation time of 3 days; (4) patients allergic to LMWH; (5) pregnant women; (6) history of heparin-induced thrombocytopenia; (7) patients diagnosed with iliac vein compression syndrome, which is a syndrome caused by venous reflux disorders in the lower extremities caused by iliac vein compression[27]; (8) acceptance of non-enoxaparin drug prophylaxis according to the judgement of the attending physician. Participants can withdraw from the study at any time without affecting future treatment. For each participant withdrawing from the study, relevant information collected for early termination and reason for withdrawal will be recorded.

Randomisation and blinding

The random assignment algorithm was created by a statistician using SAS software, V.9.3, on a computer, and the patients will be randomised to nine blocks at a 1:1:1 ratio. Printed, opaque sealed envelopes will be used for the experimental and control groups. After determining the number of selected subjects, the corresponding opaque letter will be opened, and the researchers will select the method corresponding to the serial number to prevent VTE.

The sonographers, laboratory doctors and statisticians will be blinded to the grouping. All study outcomes will be assessed by an independent adjudication committee that is unaware of the type of treatment. For VTE assessment, videos or photos of ultrasonography will be available as well as clinical files for bleeding events.

Interventions

Drug prophylaxis and physical prophylaxis are necessary for critically ill patients with intermediate, high and very high VTE risk (Caprini Risk Assessment Model[28]). Patients who meet the criteria for LMWH prophylaxis will be randomly divided into three groups. In group A, the LMWH dose will be guided by the peak value. In group B, the LMWH dose will be guided by the trough value. In group C, the LMWH dose will be fixed and not guided by aFXa monitoring; this group will serve as the control group. A stable state should be obtained after the third dose of LMWH in all three groups after they receive standard prophylaxis (enoxaparin, 40 mg, once daily). To track the peak and trough levels of aFXa, peripheral venous blood will be collected from groups A, B and C at 4–6 hours and 12 hours after subcutaneous injection. The research method for the control group and the two intervention groups, groups A and B, is shown in figure 1.

The target of monitoring the aFXa peak value in group A will be between 0.3 and 0.5 IU/mL[17 19 20 26]; the target of monitoring the aFXa trough value in group B will be between 0.1 and 0.2 IU/mL[17 19 20]; and the doses in group A and group B can be changed in accordance with monitoring of the aFXa peak and trough targets (figures 2 and 3). Figure 4 depicts the flow chart for the group C fixed enoxaparin dose.

Before starting medication, deep vein ultrasound and blood coagulation tests will be performed on the three groups of patients. Every day, bleeding signs and VTE symptoms will be noted, every week, ultrasonography will be used to track the onset of DVT in both lower extremities. The patients will be monitored for adverse events, such as bruising, allergies, thrombocytopenia brought on by heparin and mortality.

The three patient groups will all undertake the same clinical standard physical precautions to avoid VTE.

All examinations will be completed according to the schedule for enrolment and follow-up.

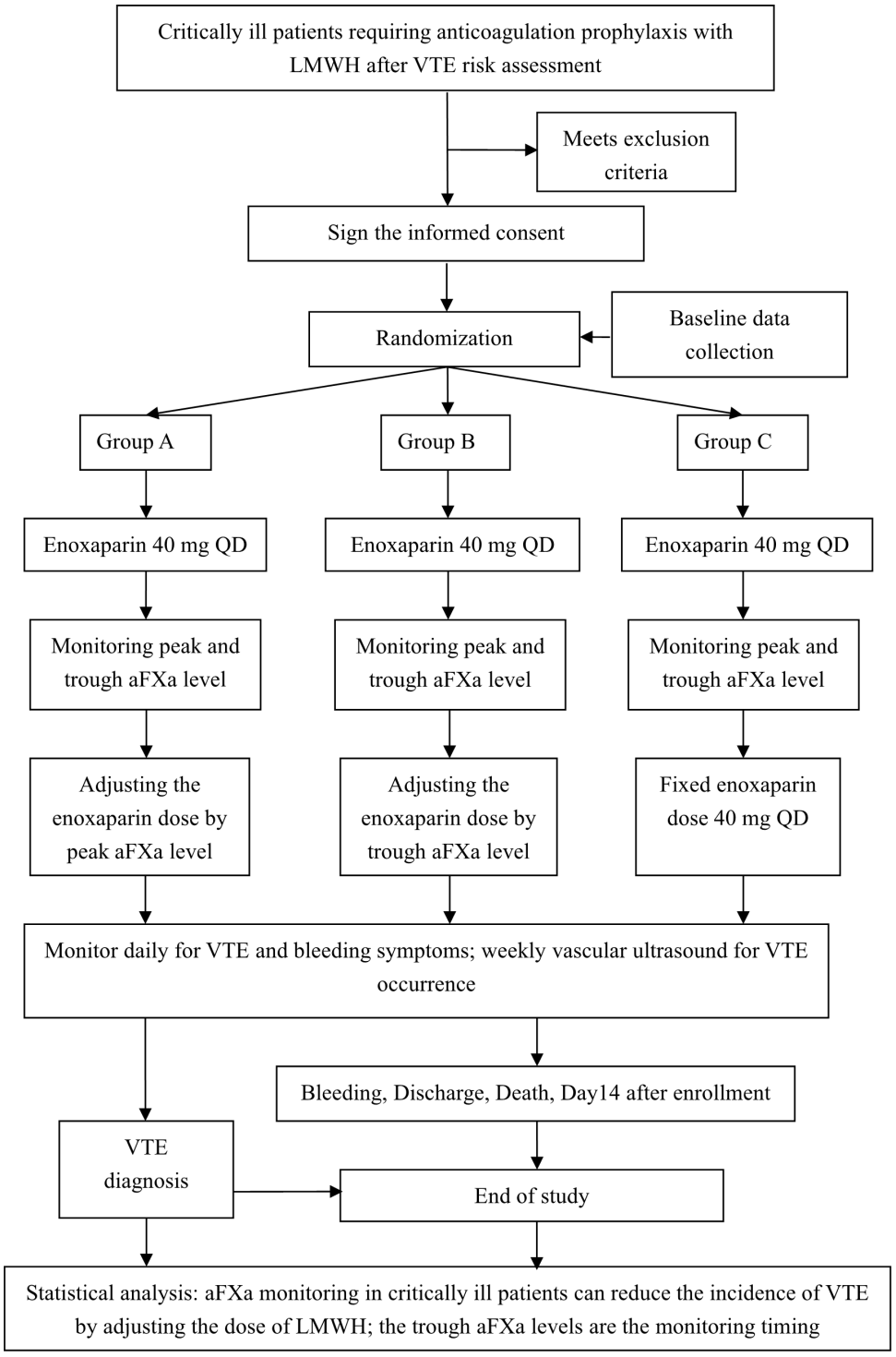

Figure 1 Anti-factor Xa (aFXa) level guiding flow chart for a randomised controlled trial of low-molecular-weight heparin (LMWH) in the prevention of venous thromboembolism (VTE) among critically ill patients. QD, once a day.

aFXa level measurement procedure

Venous blood samples will be collected in 3.2% buffered sodium citrate-containing vacuette tubes. The blood volume will be 3 mL to the 3 mL labelled tubes (a whole blood: sodium citrate ratio of 9:1). After collection, tubes will be capped and inverted 5–10 times to fully mix with the anticoagulant. Within 1 hour, after centrifugation for 15 min at 2500 g at room temperature, the samples will be put into the STA-R Evolution sample rack, and STA-Liquid anti-FXa reagent will be applied for automatic detection in the STAGO STA-R Evolution automatic coagulation analyser. Blood collection and testing will be completed within 2 hours and recorded.

Primary outcome

The primary outcome measure is the incidence of VTE. The incidence of VTE includes symptomatic VTE and asymptomatic VTE.[29]

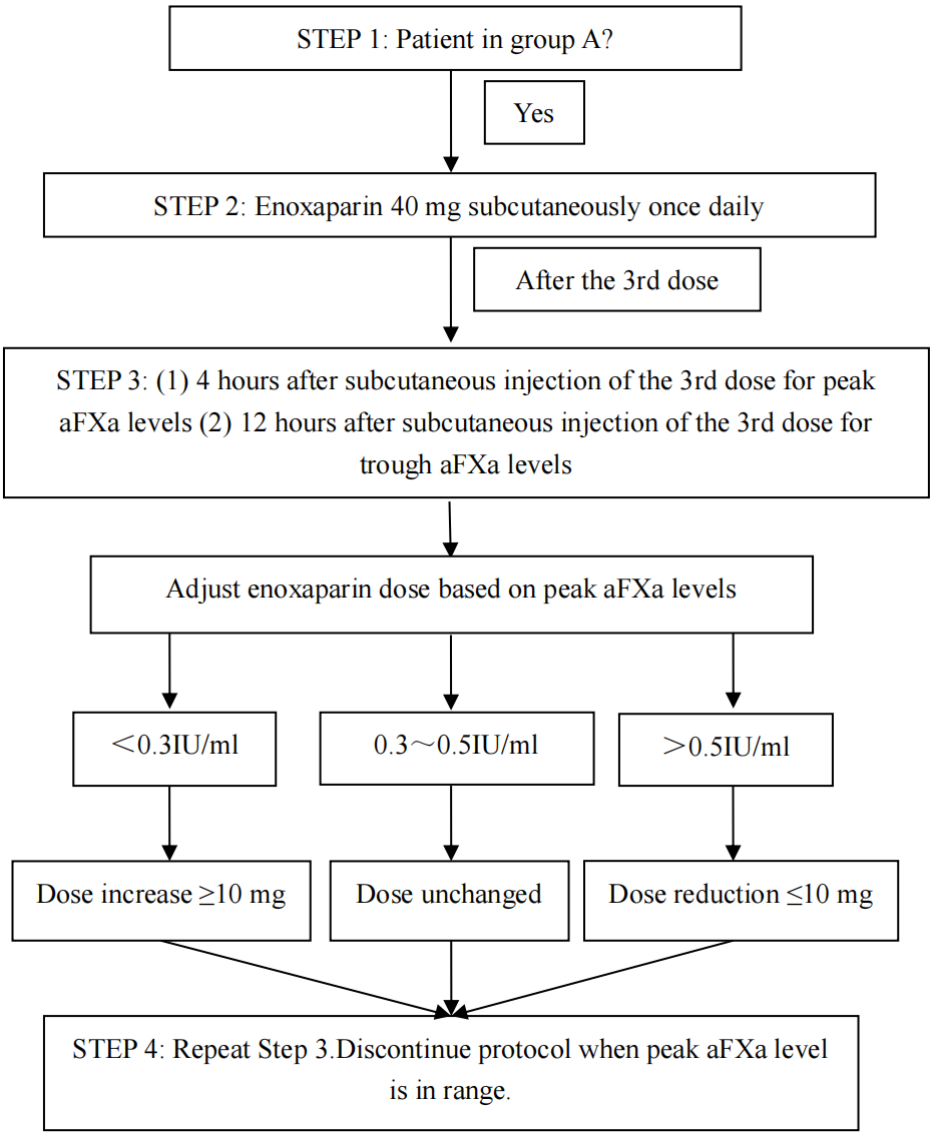

Figure 2 The flow chart for adjusting the dose of enoxaparin based on the peak anti-factor Xa (aFXa) level in group A.

Symptomatic VTE is any imaging-confirmed symptomatic VTE event including VTE, central vein thrombosis (eg, inferior vena cava or portal vein) and/or pulmonary embolism.

Asymptomatic VTE is a common disease in the ICU that is caused by the patient's primary disease. Level 1A recommends vigilance against the occurrence of asymptomatic VTE in ICU patients.[29] Patients will be screened for lower extremity DVT with weekly deep vein ultrasonography.

Pulmonary embolism will be diagnosed according to the 2018 'China Thrombotic Disease Prevention and Control Guidelines' diagnostic process.

Ultrasound diagnostic criteria for lower extremity DVT

Venous duplex ultrasound combines two components to assess DVT: B-mode or greyscale imaging with transducer compression manoeuvres; and Doppler evaluation consisting of colour-flow Doppler imaging and spectral Doppler waveform analysis. Thrombi are typically referred to as acute, subacute or chronic. Acuity of the DVT is assessed by the appearance of the thrombus on B-mode imaging (eg, hypoechoic, isoechoic or hyperechoic), vein lumen size, vein wall appearance, venous compressibility, function of the venous valves and presence of collateral circulation. In this study, venous duplex ultrasound distinguished and diagnosed acute, subacute and chronic DVT.[30 31]

CT pulmonary angiography diagnostic criteria for PTE

CT pulmonary angiography (CTPA) is regarded as the gold-standard imaging modality for the investigation of acute pulmonary embolism. It has become the preferred examination method for the diagnosis of PTE. The direct sign of CTPA is a filling defect in the pulmonary artery, which is partially or completely surrounded by opaque blood flow (orbital sign) or a complete filling defect, and the distal blood vessels are not visualised; the indirect signs include a wedge-shaped lung field and band-like density, increased shadow or discoid atelectasis, central pulmonary

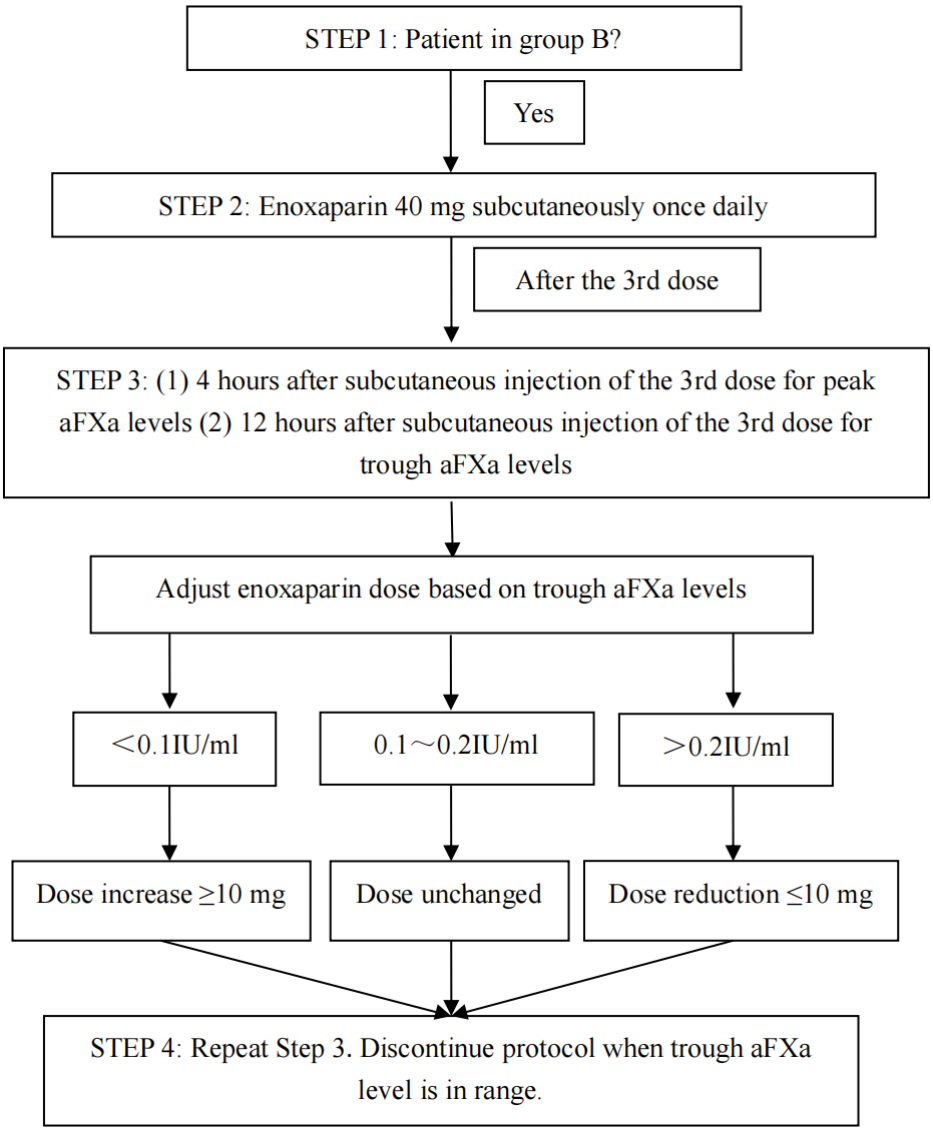

Figure 3 The flow chart for adjusting the dose of enoxaparin based on the trough anti-factor Xa (aFXa) level in group B.

artery expansion and distal vascular branch reduction or disappearance.[32]

Secondary outcomes

First, following fixed-dose LMWH prophylaxis as usual, the first aFXa peak and trough target-reaching rates will be observed following steady state. Second, bleeding rate. Severe bleeding consists of a haemoglobin drop of 2 g/L or transfusion requiring ≥2 units, occurring in any critical location (intracranial, intraspinal, intraocular, retroperitoneal, intrapericardium) or haemorrhage that could lead to death. If any of these conditions is met, it will be considered severe bleeding. Non-major bleeding consists of bleeding that does not meet the criteria for major bleeding but requires the discontinuation of prophylactic anticoagulants in the opinion of the lead clinician. Third, the number of hospitalised deaths.

Study data collection and follow-up plan

Baseline assessment and follow-up

This study will collect the following information: demographic characteristics, medical history and laboratory testing (routine blood, biochemistry, urine tests and blood coagulation). Laboratory assays for blood coagulation (D-dimer, activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen) within 24 hours before enoxaparin administration will serve as baseline data. The blood coagulation will be followed up at 3 days, 7 days, 14 days, VTE and bleeding events after enoxaparin. The STAGO STA-R Evolution coagulation analyser (STAGO STA-R Evolution, France) will be used for measuring D-dimer, PT, APTT, fibrinogen and aFXa levels. After randomisation, the participants will receive the corresponding planned treatment and will be followed up based on the same schedule and procedures for the three groups. LMWH prophylaxis, detection of aFXa, VTE and bleeding signs and symptoms,

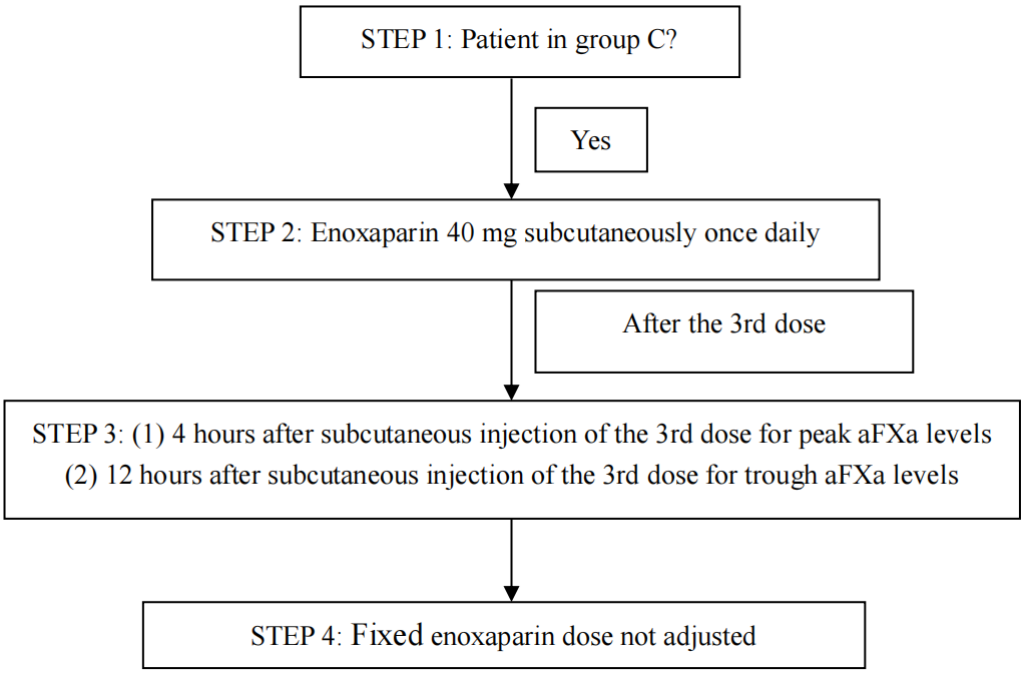

Figure 4 The flow chart for the group C fixed enoxaparin dose. aFXa, anti-factor Xa.

other concomitant medications and adverse events will be recorded in detail (table 1). The endpoint of this study will be VTE occurrence, haemorrhage, discharge, death and the 14th day after enrolment.

Sample size

The sample size was calculated using the NCSS-PASS software, V.11. Data in a previous meta-analysis study showed that the incidence of VTE in the aFXa trough level monitoring guidance group and the fixed-dose LMWH control group without aFXa monitoring was 5.4% (27 of 502) and 12.2% (78 of 637) among trauma patients, respectively.[25] Therefore, we expect that the incidence of VTE will be 5.4% in the trough aFXa level monitoring group, 5.4% in the peak aFXa level monitoring group and 12.2% in the control group without aFXa monitoring at a fixed dose of LMWH. With these assumptions,

Table 1 Follow-up schedule

Follow-up content	0 day	1 day	2 days	3 days	4 days	7 days	14 days*
Informed consent	√						
Baseline data	√						
Demographic information	√						
VTE symptoms and signs	√	√	√	√	√	√	√
VTE ultrasound	√					√	√
VTE risk assessment	√	√	√	√	√	√	√
Bleeding symptoms and signs	√	√	√	√	√	√	√
Bleeding risk assessment	√	√	√	√	√	√	√
Liver and kidney function†	√			√		√	√
Blood coagulation‡	√			√		√	√
Anti-factor Xa level monitoring§				√			
Haematuria and stool routine testing	√			√		√	√
Adverse events¶		√	√	√	√	√	√

*The 14th day after enrolment.
†Liver and kidney function tests include serum creatinine, ALT and AST.
‡Blood coagulation includes D-dimer, APTT, PT and fibrinogen.
§Anti-factor Xa monitoring: except for the third day, anti-factor Xa level monitoring is based on whether the peak or trough target is reached.
¶Adverse events: bleeding, allergy, heparin-induced thrombocytopenia and death.
ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; PT, prothrombin time; VTE, venous thromboembolism.

assuming a 5% loss to follow-up rate, enrolment of 858 participants in three arms (at 1:1:1 ratio, 286 participants in each group) is required to provide 80% power, with a two-sided significance level of 0.05.

Statistical consideration

Professional statistical software (SAS, V.9.3) will be used. A two-sided test will be used and p values less than 0.05 will be considered statistically significant. Quantitative indicators will be described as the mean and SD for normally distributed data, or the median and IQRs for non-normally distributed data, whereas categorical indicators will be described as the number of cases and percentages. Comparisons of the two groups will be analysed using appropriate methods according to the types of indicators. For comparisons between groups of quantitative data, the t-test or Wilcoxon rank-sum test will be used according to data distribution; for categorical data, the X^2 test or Fisher's exact probability method (if the X^2 test is not applicable) will be used.

The dataset will adopt the full analysis set (FAS) population: according to the basic principle of intention-to-treat analysis, the FAS and the per-protocol set (PPS) will be analysed according to the protocol of the main study regarding the incidence of VTE. However, we mainly refer to the FAS. The safety dataset is defined as actual data on at least one treatment with recorded safety indicators.

Analysis of main research indicators

The primary outcome, the incidence of VTE, will be analysed by PPS and FAS at the same time. The X^2 test will be used to compare the incidence of VTE in groups A, B and C; the risk of VTE in the peak aFXa level monitoring group and trough aFXa level monitoring group will be compared (considering confounding factors). Logistic regression will be used to analyse the factors that influence VTE, and the OR value will be obtained.

Analysis of secondary research indicators

First, after routine fixed-dose prophylaxis with LMWH results in a steady-state concentration, the first peak and trough aFXa level target-reaching rates will be measured. The X^2 test will be used to compare the target-reaching rates of the two groups. Second, regarding bleeding rate, the X^2 test will be used to compare the incidence of bleeding among the three groups; the risk of VTE in the peak aFXa level monitoring group and the trough aFXa level monitoring group will be compared (considering confounding factors). Logistic regression will be used to analyse the factors that influence bleeding, and the OR value will be obtained. Third, regarding in-hospital mortality, the X^2 test will be used to compare the mortality of the three groups.

The study management

The clinical trial and data will be managed by the committees (including audit, etc). The investigators will be given access to the cleaned datasets. The committees will be responsible for the data sharing process. All personnel will abide by the principle of confidentiality and will have no competing interests.

DISCUSSION

Patients in critical condition have a higher risk of bleeding and VTE. Schizodimos *et al* concluded that the same fixed dose of LMWH is not appropriate for all patients, especially in critically ill patient populations, and all ICU patients require VTE prophylaxis but are frequently at high risk of bleeding. The balance between thrombosis and bleeding requires an individualised approach to thromboprophylaxis. Current fixed-dose prevention measures for VTE are imperfect, and further research is needed.[33]

LMWH is the preferred choice for VTE prevention in critically ill patients, and novel oral anticoagulants and antiplatelet medications are not advised.[2 4–6] A network meta-analysis and systematic review of RCTs examining the effectiveness of thromboprophylaxis in critically ill patients was recently carried out. A total of 9619 patients from 13 RCTs were included. According to this study's findings, LMWH reduced the incidence of DVT in critically ill patients compared with control medication, and it might be more effective than unfractionated heparin, making it the primary strategy for thromboprophylaxis.[34]

Are the levels of aFXa activity measured? Should we monitor aFXa activity peaks or troughs? The answers to these questions are unknown in critically ill patients. In addition to the previously mentioned aFXa monitoring, LMWH anticoagulation in trauma patients lowers the incidence of VTE. In the subgroup analysis, three studies underwent aFXa trough monitoring to guide LMWH dosages, whereas two studies employed aFXa peak monitoring.[25] Moreover, standard-dose and intermediate-dose thromboprophylaxis have been examined in severely ill patients with COVID-19. In comparison with the increased-dose group in the intervention group, in which the median initial aFXa peak level was 0.26 (0.21–0.33), the standard-dose group's median initial aFXa peak level was 0.13 (IQR: 0.06–0.18). The doses of enoxaparin were 0.44 mg/kg and 0.93 mg/kg. The intervention group consisted of COVID-19-positive critically ill patients, and thromboprophylaxis doses were increased until aFXa levels were deemed acceptable for thromboprophylaxis.[35] Recent studies have shown that once daily enoxaparin prophylaxis is delivered, the peak range is best if at 0.3–0.5 IU/mL.[15 17 18 24] The 0.1–0.2 IU/mL range represents the 12-hour blood trough value.[15 17 18] As a result, in this trial, group A's peak target was set to 0.3–0.5 IU/mL, and group B's trough target was set to 0.1–0.2 IU/mL. Additionally, the trough value will be determined 12 hours rather than 24 hours prior to LMWH. This study is the first randomised controlled trial to use LMWH to monitor aFXa activity levels while preventing VTE in critically ill patients.

The primary outcome of this study is the occurrence of VTE in critically ill patients. Deep vein ultrasonography

will be used to screen for VTE once per week. The clinical manifestations of VTE are frequently more challenging to recognise because of the broad variations in the main diseases of patients and the influence of different circumstances, such as different types of catheterisation, mechanical ventilation, sedation and analgesia. Vascular ultrasonography is necessary to detect VTE. Arabi *et al* examined the association between surveillance for DVT among critically ill medical-surgical patients by ultrasonography and 90-day all-cause mortality. The surveillance group and the non-surveillance group consisted of 1682 patients and 383 patients, respectively. Surveillance ultrasonography was associated with an increase in DVT detection, earlier diagnosis of DVT and pulmonary embolism, and lower 90-day mortality.[36] Raskob *et al*'s study of the association between asymptomatic proximal DVT and mortality in acutely ill medical treatment patients also showed that asymptomatic proximal DVT was associated with higher all-cause mortality than no VTE and remained a relevant endpoint to evaluate the efficacy of anticoagulant thromboprophylaxis.[37]

This study has several limitations. First, the follow-up period of this study is short, and long-term VTE is not evaluated. Second, medical staff will be not blinded, but sonographers, examiners and statisticians will be blinded to reduce the bias of research results. Third, DVT diagnosis uses ultrasound diagnosis, not the 'gold-standard' angiography diagnosis, because critically ill patients are limited by their critical condition; thus, angiography is difficult to complete. Fourth, the dual-centre research, the laboratory testing will be carried out in their respective centres, rather than concentrated in one centre. However, both centres are teaching hospitals, the departments of their clinical laboratory have accredited by ISO 15189, and the operators will be professionally trained to ensure the quality of aFXa activity levels and other tests.

If the results of this study are confirmed, critically ill patients who are taking LMWH to prevent VTE must monitor the level of aFXa activity and alter their LMWH dosage in accordance with the aFXa peak or trough value. Lowering the incidence of DVT in critically ill patients and its impact on LMWH prophylaxis will be useful. It will be advantageous to lower the rate of LMWH preventive haemorrhage and the incidence of DVT in critically ill patients. This study aims to develop a new procedure for the precise prevention of VTE in critically ill patients using LMWH.

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Competing interests None declared.

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Patient consent for publication Not required.

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