A fixed dose approach to thrombosis chemoprophylaxis may be inadequate in heavier critically ill patients

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In Australia and New Zealand, overweight and obese adults represent about two-thirds of the adult population, and the mean body mass index (BMI) of critically ill patients has almost reached the obese category.[1,2] Patients who are overweight or obese are at greater risk of complications, including venous thromboembolism (VTE).[3]

For unselected patients requiring intensive care unit (ICU) admission, the prophylactic administration of low molecular weight heparin (LMWH) mitigates VTE risk.[4,5] For patients in the normal weight range, the effect of LMWH is predictable; however, in otherwise healthy individuals, excessive weight is known to affect the pharmacokinetics of LMWH.[6,7] In ICUs, conditions such as shock, frequently administered therapies such as vasopressors and complications such as oedema also substantially affect the pharmacokinetics of subcutaneously administered drugs.[8,9]

Data evaluating the use of LMWH for VTE prophylaxis in heavier critically ill patients are limited. This has led to uncertainty regarding optimal dosing regimens for this group.[10] While inadequate dosing will increase the risk of thrombosis, excessive dosing will increase the risk of bleeding, and both conditions can have catastrophic consequences for a patient.[11,12] Accordingly, inadequate evidence and concerns about underdosing or overdosing may lead to considerable variation in practice between clinicians.

The effect of LMWH may be quantified using the biomarker of plasma anti-factor Xa concentration — the so-called anti-Xa level. In healthy individuals, anti-Xa levels peak 4–6 hours after subcutaneous administration of enoxaparin, with steady state concentrations achieved after three or more doses.[13] Despite uncertainty about target anti-Xa levels for effective prophylaxis in critically ill patients, it is generally agreed that peak levels in the range 0.2–0.5 IU/mL and trough levels ≥ 0.1 IU/mL are appropriate targets for minimising risk of thrombosis without increasing risk of bleeding.[10,14-17] Indeed, in a sequential period study of 205 patients after trauma, an intervention of increasing enoxaparin dose based on trough anti-Xa levels (ie, if a trough anti-Xa level was < 0.1 IU/mL after three doses, enoxaparin dose was increased) reduced rates of venous thrombosis by sevenfold.[18]

ABSTRACT

Objectives: Overweight patients are at greater risk of venous thromboembolism. We aimed to describe prescribing patterns of thrombosis chemoprophylaxis in critically ill patients weighing ≥ 100 kg and quantify the effectiveness of these regimens using the surrogate biomarker of plasma anti-Xa level.

Design, setting and patients: A prospective single-centre cohort study was conducted over a 6-month period. Patients weighing ≥ 100 kg who were prescribed enoxaparin for chemoprophylaxis and expected to remain in the intensive care unit for > 48 hours were eligible. Anti-Xa levels were measured once a patient had received at least three consecutive doses of enoxaparin. Peak levels were measured 4–6 hours after the third dose and trough levels were measured before the fourth dose. Anti-Xa levels were compared with established target ranges for peak and trough anti-Xa levels (0.2–0.5 IU/mL and > 0.1 IU/mL, respectively).

Results: Eighty-eight patients met the eligibility criteria, and anti-Xa levels for 42 patients were obtained. Fixed dose chemoprophylaxis approaches varied considerably, with 40 mg once daily (54/88 [61%]) and 40 mg twice daily (20/88 [23%]) being the most frequently prescribed regimens. No patient had a peak anti-Xa level > 0.5 IU/mL. When comparing 40 mg once daily versus twice daily, the once daily regimen had lower median trough levels (0.01 IU/mL [interquartile range (IQR), 0.00–0.04] *v* 0.09 IU/mL [IQR, 0.05–0.13]; $P < 0.001$) and greater proportions of patients with levels below the established range (< 0.1 IU/mL) (15/16 [95%] *v* 7/14 [50%]; $P = 0.002$) and levels that were undetectable (0.00 IU/mL) (8/16 [50%] *v* 1/14 [7%]; $P = 0.01$).

Conclusions: At a single centre, thrombosis chemoprophylaxis prescribing patterns for heavier critically ill patients varied considerably. Current fixed dose approaches may be inadequate in this cohort.

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The major objectives of this study were to describe approaches to thrombosis chemoprophylaxis and quantify LMWH effectiveness, using anti-Xa levels as a biochemical surrogate, in critically ill patients weighing ≥ 100 kg. Rates of VTE and bleeding during hospitalisation and in-hospital mortality were also measured. The primary hypothesis was that there would be considerable variation in prescribing patterns for patients weighing ≥ 100 kg. Secondary hypotheses were that peak and trough anti-Xa levels would be lower than recommended for all dosing regimens, and that levels would be lower in patients receiving once daily dosing than those receiving twice daily dosing.

Methods

Design

A prospective single-centre cohort study was conducted over a 6-month period (23 April 2019 to 31 October 2019). The study was approved by the Melbourne Health Human Research Ethics Committee with a waiver of consent for all data collected.

Setting

The Royal Melbourne Hospital ICU is a closed mixed ICU that admits about 3000 medical, surgical and trauma patients each year. Of these patients, more than 1700 receive invasive mechanical ventilation. The ICU is staffed by ten full time equivalent (FTE) intensivists, 40 FTE registrars, 13 FTE residents and three FTE clinical pharmacists. Intensivists conduct ward rounds twice daily, and are accompanied by a clinical pharmacist during weekday morning ward rounds. Intensivists complete a checklist for each patient every day, which includes confirmation that VTE chemoprophylaxis has been prescribed or is contraindicated. The local guideline recommendation is that patients weighing ≥ 100 kg with preserved renal function (defined as an estimated creatinine clearance [eCrCl] > 30 mL/min) should receive enoxaparin subcutaneously at a dose of 40 mg twice daily. In the absence of high quality evidence, this is a guideline rather than an enforced policy.

Patients

During the study period, all admitted patients were weighed by nursing staff daily using digital scales that are integrated into ICU beds (Hillrom, Batesville, Indiana, USA). Daily screening rounds were conducted to identify suitable patients during the 6-month study period. Patients were eligible if they weighed ≥ 100 kg, had enoxaparin prescribed and administered on the medication chart, and were likely to remain in the ICU for more than 48 hours. Patients were excluded if they were pregnant, aged < 18 years, had abnormal coagulation values on ICU admission (international normalised ratio > 1.5, activated partial thromboplastin time > 60 s or platelet count < 50 × 10^9/L), or were receiving therapeutic doses of enoxaparin or another anticoagulant such as heparin infusion or warfarin.

Data collection

For each eligible patient, we recorded demographic details, calculated BMI, calculated ideal body weight using the Devine formula,[19] and recorded ICU length of stay, hospital length of stay and ICU admission diagnosis. We also collected data on dosing regimens for each eligible patient, including dose and frequency of enoxaparin prescriptions. For all included patients, factors known to influence VTE prophylaxis effectiveness and risk of bleeding or thrombosis were extracted.[20] These variables included whether the patient received mechanical ventilation, vasopressor use within 24 hours of anti-Xa sampling, risk of bleeding using the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly score)[21] and presence of active malignancy. Renal function was assessed using automated estimated glomerular filtration rate and serum creatinine level.[22] We also calculated eCrCl during data analysis, using the Cockcroft–Gault formula.[23] The use of renal replacement therapy at the time of anti-Xa level sampling was also noted.

Main outcome measures

The main outcome measures were dosing regimens, peak and trough anti-Xa levels, and associations between anti-Xa levels and dosing regimens. To obtain steady state levels, blood used to measure peak and trough anti-Xa levels was obtained once three doses of enoxaparin at a consistent dosing regimen had been administered.[13] Peak levels were measured 4–6 hours after the third dose and trough levels were measured within 90 minutes before the fourth dose. Arterial or venous blood samples were collected in 2.7 mL sodium citrate serum tubes, which were centrifuged for 15 minutes at 3000 rpm. Plasma was analysed within 1 hour of arrival at the laboratory, or stored at –70°C for subsequent batch sampling.

The anti-Xa assays were run on site using existing laboratory infrastructure. The hospital haematology laboratory is accredited by the National Association of Testing Authorities, Australia, according to standards set out by the National Pathology Accreditation Advisory Council, and uses the STA-Liquid Anti-Xa testing kit (Stago, Melbourne, Australia). Each kit was calibrated according to manufacturer specifications. The hospital laboratory is also enrolled in a quality assurance program run by the Royal

College of Pathologists of Australasia, and regularly uses calibration samples for quality assurance.

Secondary outcomes

ICU and hospital discharge summaries were hand-searched and cross-referenced against International Classification of Diseases, tenth revision, Australian modification (ICD-10-AM) hospital codes. The codes of interest were major bleeding events and venous thrombosis (specifically, lower limb deep vein thrombosis and pulmonary embolus) during admission (Online Appendix). Major bleeding events were defined as bleeding events associated with significant risk of death (eg, significant intracerebral bleeding or catastrophic gastrointestinal bleeding) or major morbidity (eg, intraocular bleeding), or bleeding events which required immediate transfusion of two or more units of red blood cells.[24] Major bleeding events were manually identified from ICD-10-AM codes. An investigator (GY) reviewed each case with haemorrhage to determine whether there was a probable causal link with prophylactic enoxaparin use.

Statistical analysis

Continuous data were assessed for normality graphically (using histograms and quantile–quantile plots). Normally distributed data are presented as mean (SD), with comparisons between groups made using the student *t* test. Data that are not normally distributed are presented as median (interquartile range [IQR]), with comparisons between groups made using the Wilcoxon rank-sum test. Categorical data are summarised as number (percentage) and were compared using the -χ^2 test or Fisher exact test. Comparison of peak and trough anti-Xa levels between enoxaparin regimens was performed using one-way ANOVA (analysis of variance).

We assessed the extent to which peak and trough anti-Xa levels were associated with weight, BMI, eCrCl, and once daily enoxaparin regimens (20 mg, 40 mg and 60 mg once daily) versus twice daily enoxaparin regimens (20 mg and 40 mg twice daily) by fitting a simple linear regression model. We then developed a multivariate linear regression model for peak and trough levels using a forward stepwise method, retaining any variables that had a univariate association ($P < 0.10$) with the outcome. We performed data analyses using R software, version 4.0.2 (The R Foundation, Vienna, Austria).

Results

Between 23 April 2019 and 31 October 2019, 263 of 1555 admitted patients (17%) weighed ≥ 100 kg. Of them, 88 were eligible patients who comprised the study cohort, and 42 patients with anti-Xa levels comprised the nested cohort (Figure 1). Characteristics of patients in the nested cohort and those of all admitted patients weighing ≥ 100 kg for whom anti-Xa levels were not obtained are shown in Table 1. A comparison of processes of care and outcomes between these two groups is shown in Table 2. For the nested cohort, a comparison of physiological variables on admission across the different enoxaparin regimens is shown in Table 3.

Dosing regimens

Total daily dosing of enoxaparin ranged from 20 mg to 80 mg. The various regimens were 40 mg once daily (54/88, 61%), 40 mg twice daily (20/88, 23%), 20 mg once daily (7/88, 8%), 60 mg once daily (6/88, 7%) and 20 mg twice daily (1/88, 1%). Twenty-two patients (52%) in the nested cohort received a vasopressor (noradrenaline) on the study day. Three patients who had anti-Xa levels measured had an eCrCl lower than 30 mL/min, and all three were prescribed a 20 mg once daily regimen.

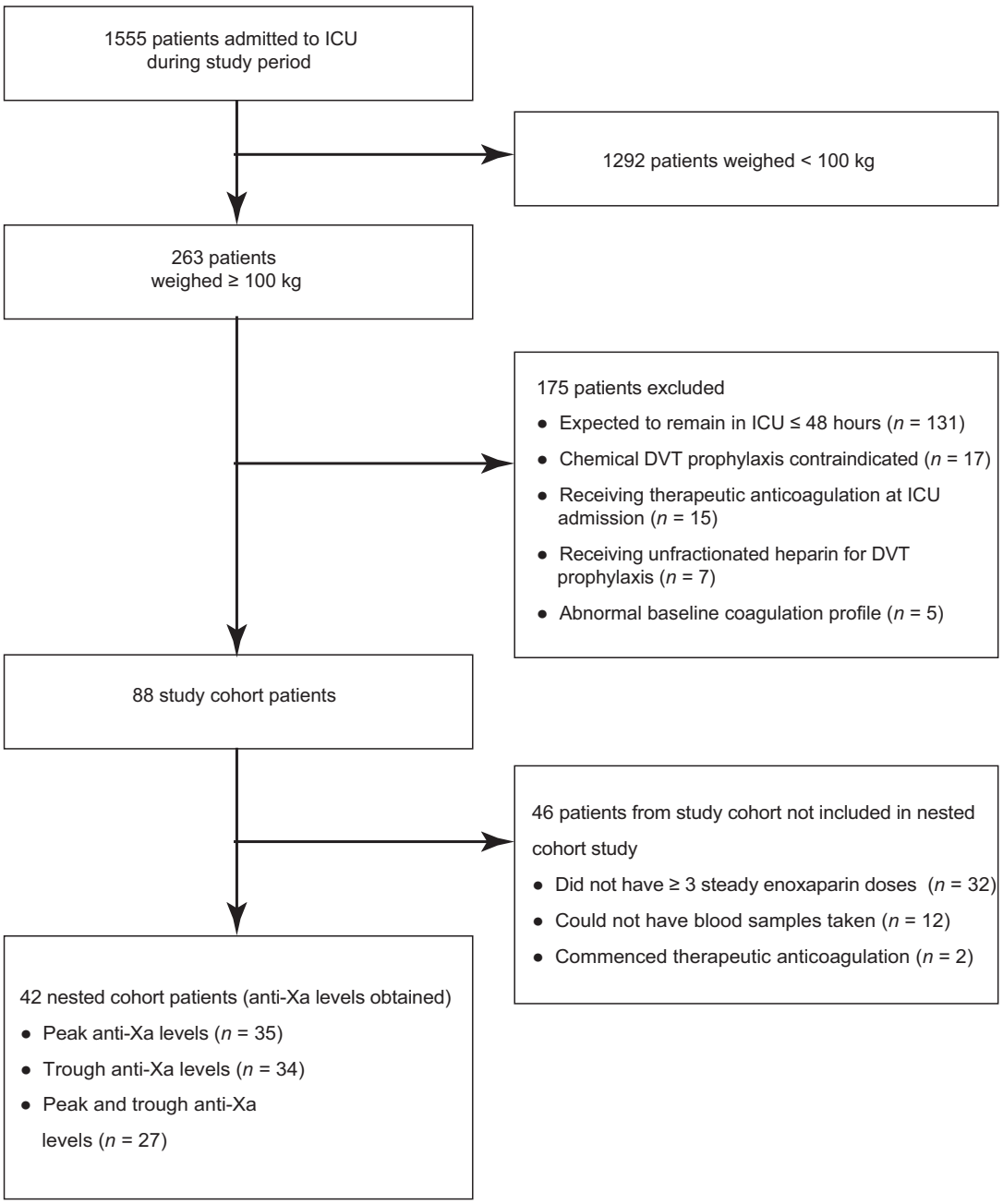
Anti-Xa levels

Plasma anti-Xa levels were obtained for 42 of the eligible patients (48%). This included a total of 35 peak levels and a total of 34 trough levels, and both peak and trough levels were obtained for 27 patients. The median time from dose to obtaining blood for peak anti-Xa level was 5.3 h (IQR, 5.0–5.7 h), and the median time between sample being obtained and next dose for the trough level was 30.0 min (IQR, 17.5–61.2 min). Median peak and trough anti-Xa levels are shown in Figure 2.

No statistically significant difference in peak anti-Xa levels was detected between the groups of patients receiving 40 mg twice daily and 40 mg once daily (0.16 IU/mL [0.12–0.22] *v* 0.15 IU/mL [0.12–0.18], respectively; $P = 0.65$). The highest peak level recorded was 0.34 IU/mL (patient receiving 40 mg twice daily), which did not exceed the threshold for increased bleeding risk (0.5 IU/mL). Five of 12 patients receiving 40 mg twice daily (42%) and six of 23 receiving any once daily dose regimen (26%) reached suggested target peak anti-Xa levels for prophylaxis of 0.2–0.5 IU/mL.

The median trough anti-Xa level, for the 34 patients for whom this was available, was 0.04 IU/mL (IQR, 0.00–0.09). Median trough levels were lower in those receiving once daily dosing of 20 mg, 40 mg or 60 mg, when compared with those receiving 40 mg twice daily (0.01 IU/mL (IQR, 0.00–0.04; $n = 20$) *v* 0.09 IU/mL (IQR, 0.05–0.13; $n = 14$); $P < 0.001$). In addition, when compared with patients receiving 40 mg twice daily, greater proportions of those receiving 40 mg once daily recorded trough anti-Xa levels of 0.00 IU/mL (8/16 [50%] *v* 1/14 [7%]; $P = 0.01$) and

Figure 1. Consort style patient flow chart



DVT = deep vein thrombosis. ICU = intensive care unit.

trough levels below the established therapeutic range (< 0.10 IU/mL) (15/16 [95%] *v* 7/14 [50%]; *P* = 0.002).

In our linear regression analysis of peak and trough anti-Xa levels — which incorporated weight, BMI, eCrCl, and once daily versus twice daily enoxaparin dosing as exploratory variables (Online Appendix, Tables 1 and 2) — we found that none of the included factors were predictive of peak anti-Xa levels. With regard to trough anti-Xa levels, only the use of twice daily rather than once daily enoxaparin dosing was predictive, with an increase in median trough anti-Xa levels from 0.02 (IQR, 0.00–0.04) IU/mL by 0.07 (IQR, 0.04–0.11) IU/mL with twice daily dosing (*P* < 0.001).

Table 1. Baseline demographics of nested cohort patients (for whom anti-Xa levels were obtained) and those weighing ≥ 100 kg for whom anti-Xa levels were not obtained*

	Nested cohort patients, for whom anti-Xa levels were obtained (*n* = 42)	Admitted patients weighing ≥ 100 kg for whom anti-Xa levels were not obtained (*n* = 221)	*P*
Sex (men)	35/42 (83%)	156/221 (71%)	0.09
Age (years)	59.5 (37.0–66.8)	59.0 (45.0–68.0)	0.27
Height (m)	1.76 (0.12)	1.75 (0.12)	0.86
Weight (kg)	112 (106–120)	111 (105–124)	0.54
Body mass index (kg/m^2)	36.3 (32.4–41.1)	36.7 (33.0–42.4)	0.62
Ideal body weight (kg)	70.7 (12.1)	70.3 (11.8)	0.74
APACHE II score	15.5 (11.0–21.0)	13.5 (9.0–18.0)	0.04
ANZROD	0.05 (0.01–0.31)	0.03 (0.01–0.09)	0.02
HAS-BLED score	1 (0–2)	–	–
Active malignancy	2/42 (5%)	–	–
eCrCl (mL/min)	99 (50)	–	–
Serum creatinine (μmol/L)	75 (63–93)	–	–

ANZROD = Australian and New Zealand Risk of Death. APACHE = Acute Physiology and Chronic Health Evaluation. eCrCl = estimated creatinine clearance. HAS-BLED score = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly score. * Data are numerator/denominator (percentage), mean (SD) (data that are normally distributed) or median (interquartile range) (data that are not normally distributed).

Table 2. Processes of care and outcomes for nested cohort patients (for whom anti-Xa levels were obtained) and those weighing ≥ 100 kg for whom anti-Xa levels were not obtained*

	Nested cohort patients, for whom anti-Xa levels were obtained (*n* = 42)	Admitted patients weighing ≥ 100 kg for whom anti-Xa levels were not obtained (*n* = 221)	*P*
Mechanical ventilation	33/42 (79%)	–	–
Received RRT in ICU	2/42 (5%)	–	–
ICU length of stay (days)	6.9 (5.0–10.1)	1.7 (0.9–3.0)	0.001
Hospital length of stay (days)	15.2 (8.8–26.2)	7.83 (3.5–14.1)	0.03
In-hospital mortality	4/42 (10%)	18/221 (8%)	0.76

ICU = intensive care unit. RRT = renal replacement therapy. * Data are numerator/denominator (percentage) or median (interquartile range) (data that are not normally distributed).

However, weight, BMI and eCrCl were not predictive of trough anti-Xa levels, and a large amount of variation was not explained by the model (R^2 = 0.43).

Thrombosis and bleeding complications

Twelve of the 263 admitted patients who weighed ≥ 100 kg (5%) were diagnosed with VTE and developed a pulmonary embolus (with or without deep venous thrombosis), but no patients in this group were diagnosed with an isolated deep venous thrombosis. No major bleeding events related to chemoprophylaxis were recorded for any of the admitted patients who weighed ≥ 100 kg. Of the 88 patients in the study cohort, five patients (6%) were diagnosed with a pulmonary embolus. In the nested cohort, four of 42 patients (10%) were diagnosed with pulmonary embolism; two were receiving 40 mg once daily dosing and two were receiving 40 mg twice daily dosing. Of these four patients who developed a pulmonary embolus, peak anti-Xa levels

Table 3. Age, weight, body mass index and renal function of nested cohort patients (for whom anti-Xa levels were obtained) across different enoxaparin regimens*

	20 mg once daily (*n* = 4)	40 mg once daily (*n* = 21)	40 mg twice daily (*n* = 14)	60 mg once daily (*n* = 3)
Age (years)	71 (64.7–74.5)	59 (37–66)	53 (31.8–62)	71 (45–72)
Weight (kg)	103 (100–106)	110 (106–114)	122 (114–133)	115 (113–117)
Body mass index (kg/m^2)	35.2 (33.9–37.6)	35.1 (32.2–39.3)	33.3 (32.7–51.3)	36.9 (34.1–37.9)
eCrCl (mL/min)	22 (17–36)	87 (73–130)	116 (77–140)	82 (81–111)
Serum creatinine (μmol/L)	276 (163–375)	73 (63–93)	67.5 (59.0–82.5)	76 (74–82)

eCrCl = estimated creatinine clearance.* Data are median (interquartile range).

were within the target range (0.2–0.5 IU/mL) for three of them and trough anti-Xa levels were below target (< 0.10 IU/mL) for all four of them. Median trough anti-Xa levels for those with and without a diagnosed pulmonary embolus were comparable (0.05 IU/mL *v* 0.04 IU/mL, respectively; $P > 0.99$).

Mortality

Twenty-two of the 263 admitted patients weighing ≥ 100 kg (8%) were deceased at time of hospital discharge — five were in the study cohort (6%) and four were in the nested cohort (10%) (Table 2). When deaths of patients in the study cohort were reviewed, none were deemed to be a result of bleeding or VTE complications.

Discussion

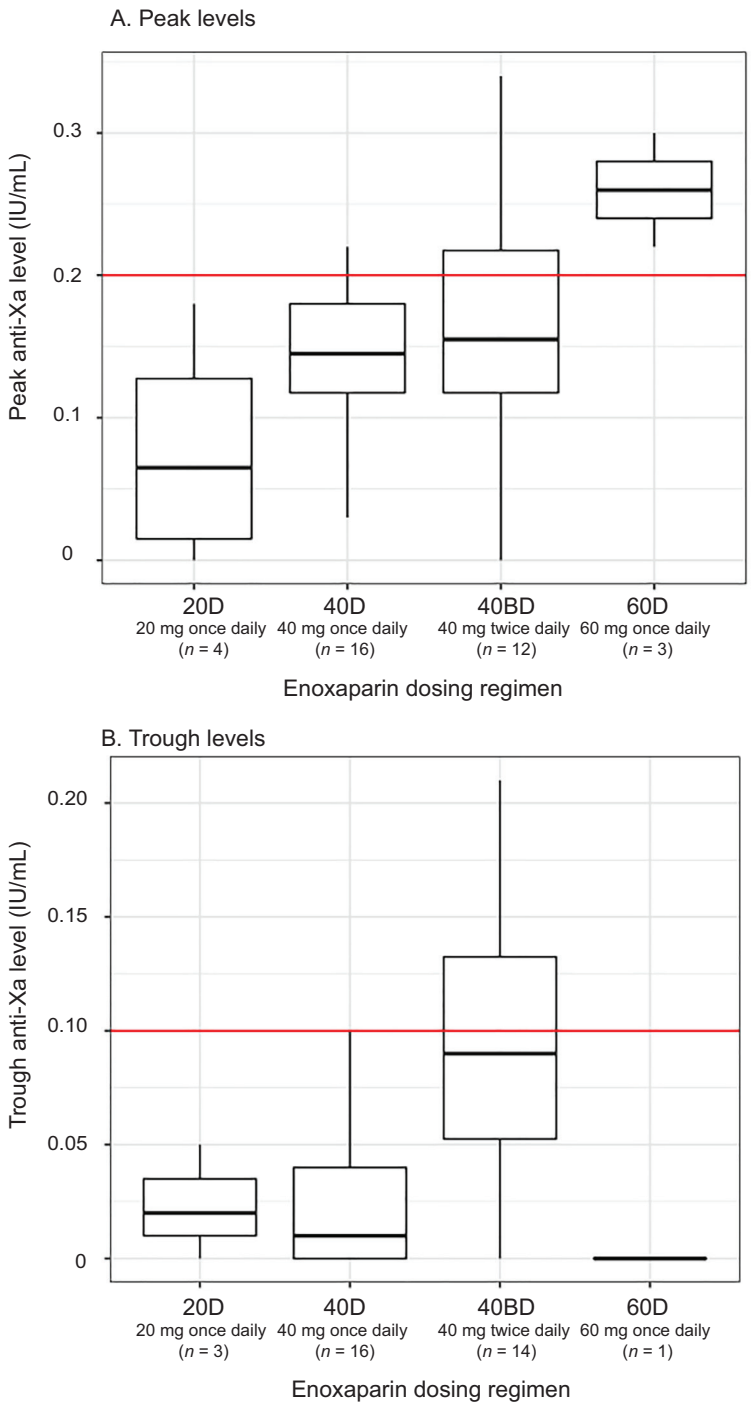
From our results, we made three key observations regarding critically ill patients weighing ≥ 100 kg. First, there was considerable variation in approaches to DVT chemoprophylaxis at the Royal Melbourne Hospital ICU, with only one-third of patients (35%) prescribed enoxaparin according to recommendations in the local guideline. Second, among patients receiving any once daily dosing regimen, trough anti-Xa levels were undetectable in half of the patients (50%) and lower than the recommended level in almost all patients (95%). Third, peak anti-Xa levels were in the suggested therapeutic range in fewer than half of patients receiving 40 mg twice daily (42%) and one-quarter of patients receiving once daily dosing (26%).

Several previous studies have reported anti-Xa levels during prophylactic administration of LMWH to critically ill patients.[9,13,20,25-28] In these studies, the reported proportions of patients with trough anti-Xa levels below target (< 0.1 IU/mL) varied between 5% and 50%. While these studies found proportions of patients with inadequate anti-Xa levels to be lower than in our study, most of them included only critically ill patients with normal weight ranges and were conducted in North America, where the usual approach to chemoprophylaxis is enoxaparin 30 mg twice daily,[9,20,26] whereas the usual Australian practice is 40 mg once daily.[29] Moreover, to our knowledge, only one previous study has measured anti-Xa levels in heavier patients.[28] In this single-centre study of 23 morbidly obese patients (defined as having a BMI ≥ 35 kg/m^2 or weighing ≥ 150 kg) in a North American surgical ICU, the unit policy was to prescribe enoxaparin according to a weight-based regimen (0.5 mg/kg twice daily) and the median prescription was 60 mg (range, 50–120 mg) twice daily. Using this approach, only two patients (9%) had peak anti-Xa levels below the target threshold of 0.2 IU/mL.[28]

In our study, twice daily enoxaparin dosing was predictive of trough anti-Xa levels, with variation between patients not accounted for by weight, BMI or renal function. Although none of these factors predicted peak anti-Xa levels, this does not mean that these factors are not important; for example, clinician choice of the enoxaparin regimen was guided by estimated renal function. Moreover, the narrow spread of weights of those in the nested cohort meant that our ability to assess the relationship between anti-Xa levels and weight was limited. In addition, this meant that we could not extrapolate to more obese patients (ie, those weighing > 140 kg), of whom there were few in the nested cohort. Nonetheless, our results suggest a need for caution in predicting anti-Xa levels in heavier patients using factors that clinicians might intuitively consider likely to determine response.

Our study has several limitations. The major limitation is the reliance on a biomarker of drug efficacy (the anti-Xa level) rather than directly measuring efficacy (eg, by analysing incidence of deep venous thrombosis or pulmonary embolus). However, observational studies in ICU

Figure 2. Peak and trough levels of anti-Xa of nested cohort patients (for whom anti-Xa levels were obtained) by enoxaparin dosing regimen*



* In both panels, median values are represented by a horizontal bar, interquartile ranges by the upper and lower limits of the box, and ranges by whiskers. In panel A, the horizontal line represents 0.2 IU/mL (lower end of the target peak level of 0.2–0.5 IU/mL). In Panel B, the horizontal line represents 0.10 IU/mL (the target trough anti-Xa level of > 0.10 IU/mL). Both peak and trough anti-Xa levels differed significantly between groups ($P = 0.02$ and $P < 0.001$, respectively, by one-way analysis of variance).

populations have shown a threefold increase in the incidence of deep venous thrombosis in patients with trough anti-Xa levels < 0.1 IU/mL[26] and this value is accepted in the literature as representative of inadequate LMWH dosing for thrombosis prophylaxis.[18] While anti-Xa level was used in this study as a biomarker — because it is the preferred method to monitor LMWH dosing in clinical practice[30] — other methods, such as thromboelastography, provide alternative biomarker assessments of in vivo thrombosis risk.[31,32] As testing for venous thromboembolism relies on clinical testing, estimates of efficacy will underestimate the number of patients who develop venous thromboembolism.

Another limitation was that the cohort for whom anti-Xa levels were obtained was small (42 patients). However, the data for these patients add considerably to the evidence base as the previously collected data was limited to 23 patients. Nonetheless, in the cohort of 42, there was variability in enoxaparin dosing schedules which meant that there were few values for each dosing regimen. Recording of dosing regimens was also limited to the ICU, and these may have changed on transition to the ward. Given that the local guideline used a threshold of 100 kg, this was used to identify a cohort of heavier patients rather than the standard definition of obesity using BMI. Also, there are limitations in using the Cockcroft–Gault equation to estimate creatinine clearance and renal function. In a critically ill population, there are often rapid fluctuations in renal function which are poorly reflected in serum creatinine levels measured once daily. Serum creatinine levels will also be falsely lowered by alterations in muscle mass and fluid shifts in this population.[33] Furthermore, while the Cockcroft–Gault formula does take

into account body size, it is unreliable in extremes of weight owing to the use of ideal body weight, which is in itself an estimate for obese patients.[34] Finally, VTE was not routinely assessed. Accordingly, the incidence of thrombosis and embolus only represents those who were diagnosed as part of usual clinical care.

The clinical implication of this study is that there is robust biomarker evidence that once daily dosing of enoxaparin (particularly 40 mg) is inadequate in patients weighing ≥ 100 kg. Furthermore, even when clinicians administered 40 mg twice daily, half of the patients still had biomarker evidence of inadequate dosing. Given this finding, the use of weight-based or fixed dosing with dynamic adjustment using anti-Xa levels has considerable appeal.[13,18,35] Whether such an approach reduces outcomes that are important to patients (pulmonary embolus and mortality) or results in unacceptable risk of bleeding is, however, unknown.

In summary, even within a single centre there was considerable variability when prescribing VTE chemoprophylaxis to patients weighing ≥ 100 kg. Furthermore, when using anti-Xa levels as a biomarker, current static fixed dose approaches, particularly 40 mg once daily, appear to be inadequate in this cohort.

Competing interests

None declared.

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