The utility of thromboelastography in monitoring low molecular weight heparin therapy in the coronary care unit

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Low molecular weight heparins (LMWHs) are used for prevention and management of vascular thrombosis. In general, monitoring of anticoagulant activity is not required, however, certain populations may be susceptible to overdosing or underdosing. As anti-activated factor X(anti-Xa) activity testing is not readily available, it was our aim to investigate the usefulness of thromboelastography (TEG; Haemoscope Corporation, Skokie, Illinois, USA) for the assessment of coagulation in patients on LMWH. All patients admitted to the coronary care unit on therapeutic dose of enoxaparin were included (1 mg/kg twice daily). Blood samples were collected 4 h after the morning dose of enoxaparin once the participant had received at least three doses. When anti-Xa activity was classified as low (0–0.5), correct (0.5–1.0) or high (>1.0), the distribution of reaction time (R) and dose per kg showed little association with anti-Xa activity. The difference between mean R for the high anti-Xa group and the correct anti-Xa group was statistically nonsignificant using two-sample t-test ($P = 0.26$). A linear regression model showed no evidence of association between dose per kg and anti-Xa ($P = 0.95$). However, there was evidence of positive association between dose per kg and R ($P = 0.011$) wherein a 10% increase in dose per kg was associated with an increase in R of 2.7 (95% confidence interval 0.6–4.7). There was no evidence of association between R and anti-Xa ($P = 0.38$). TEG was unable to be used to predict anti-Xa activity. However, TEG R was prolonged in more than 90% patients and correlated with dose of enoxaparin. As enoxaparin dose correlated poorly with anti-Xa activity, a more global test might be necessary to adjust dosing of LMWH in sick, hospitalized patients. *Blood Coagul Fibrinolysis* 23:304–310 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

Low molecular weight heparins (LMWHs) are commonly used both in prophylaxis and treatment of vascular thrombosis. A major advantage of managing anticoagulation with LMWHs is that a weight-based dosing nomogram can be used, with no requirement for monitoring in most patients. However, in the critically ill population, in whom pharmacokinetics may be altered by both comorbid conditions and severity of illness, monitoring may be required to ensure adequate, but not over anticoagulation [1].

LMWHs consist of fragments derived from unfractionated heparin by chemical or enzymatic depolymerization. These fragments consist of four to 25 distinct molecular fragments varying in weight from 4000 to 9000 Da. LMWHs mediate their anticoagulant effect through antithrombin (AT). Unlike unfractionated heparin, which produces conformational change in AT resulting in equal binding to and neutralization of activated thrombin (IIa) and activated factor X, LMWH bound AT preferentially binds to Xa. The relative IIa:Xa activity varies between the different LMWHs, depending on the mean molecular weight of the drug [2].

Enoxaparin, which is a relatively small molecule of 4000–6000 Da, demonstrates a Xa:IIa inhibition of approximately 3–4:1. Therefore, theoretically, the principal (although not exclusive) anticoagulant effect of enoxaparin is via the inhibition of Xa.

Accordingly, the standard assay used for monitoring enoxaparin is via the inhibition of Xa. A number of kits are available for measuring anti-Xa activity, although there is some concern relating to interassay variability [3]. Despite a lack of outcome studies, guidelines recommend a therapeutic anti-Xa range of 0.6–1 U/ml (treatment dose) [2]. The accuracy of the assay rests on the correct timing of the sample in relation to dose administration. Although the anti-Xa effect predominates, enoxaparin influences the coagulation cascade in other areas including tissue factor pathway inhibitor (TFPI), direct inhibition of thrombin and platelet function and as such, a more global assessment of coagulation might provide a better guide to monitoring patients in whom comorbid conditions such as renal failure, obesity or thrombocytopenia might impact on both pharmacokinetics and phamacodynamics [1,4,5].

Despite generally encouraging in-vitro data, a number of in-vivo studies have demonstrated a lack of consistency between LMWH dose and anti-Xa activity and anti-coagulant effect. Al Dieri *et al.* [6] demonstrated the coefficient of variation of area under the curve for anti-Xa and anti-IIa activities to range from 22 to 37% for LMWHs. They noted that fixed dosage of LMWH led to underdosage in 10–13% of samples and overdosage in 5–11%, which was only partially explained by body weight and independent of the type of LMWH. Similarly, Mayr *et al.* [7] recorded a significant number of anti-Xa activities outside the therapeutic range while investigating the correlation between anti-Xa activity and standard doses of enoxaparin in the critically ill population. This may partially explain the poor correlation noted in some studies between anti-Xa activity and efficacy and/or safety of LMWH [6,8,9]. For example, in a perioperative bridging study, Hammersting *et al.* [10] demonstrated that 52.8% of patients were found with anti-Xa levels more than 0.5 U/ml despite having ceased the drug 14 h previously. The relationship between anti-Xa activity and clinical complications (both thrombotic and hemorrhagic) requires further elucidation [9,11,12].

Thromboelastography (TEG) measures the viscoelastic properties of blood as it clots under a low sheer stress environment, thus providing a comprehensive evaluation of the process of clot initiation, formation and stability. The purpose of this study was to evaluate the relationship between enoxaparin dose, anti-Xa activity and TEG to determine whether TEG could be used as a guide to enoxaparin therapy in the coronary care population on therapeutic anticoagulation.

Methods
This single-site, prospective, clinical trial was conducted over a period of 6 months to study the correlation of TEG parameters in patients on therapeutic dosage of LMWH with anti-Xa levels and other coagulation parameters. The study setting was a metropolitan coronary care unit. Ethics approval was granted by the Princess Alexandra Hospital Human Research Ethics Committee. The requirement for written informed consent was waived by the institutional review board.

All patients admitted to the coronary care unit (age >18 years) on therapeutic dosage of enoxaparin (1 mg/kg twice daily) were included. Patients greater than 100 kg received 100 mg twice daily and adjustments were made for renal function. Patients receiving other anticoagulants (other than antiplatelet drugs) or enoxaparin only for prophylaxis against deep vein thrombosis were excluded.

Blood samples were collected 4 h after the morning dose of enoxaparin once the participant had received at least three doses. Venous blood was collected by venipuncture from an antecubital vein. Venous samples were obtained simultaneously for thromboelastography, anti-Xa analysis, full blood count, coagulation profile, electrolyte and liver function test and C-reactive protein test.

The TEG sample was collected into a Vacuette 9NC (GBO, Kremsmunster, Austria) coagulation tube containing 3.2% buffered sodium citrate solution and allowed to completely fill the tube. It was gently inverted to ensure it was adequately mixed. Processing of the sample commenced within 30 min of venipuncture.

Enoxaparin was quantitated using a standard chromogenic anti-Xa activity assay (STA-Rotachrom Heparin, Diagnostica Stago, Asnieres, France) on the ACL Futura coagulation analyzer (Beckman Coulter, Sydney, Australia). The assay was calibrated using commercial calibrators (STA-calibrators HBPM/LMWH, Diagnostica Stago), which are referenced against a secondary standard of the 01/608 international standard for LMWH established in 2003.

TEG assays were processed using the Haemoscope TEG 5000 Thromboelastograph haemostasis analyzer (Haemonetics Corporation, Skokie, Illinois, USA). Routine machine quality control and standard calibrations were maintained. An electrical internal quality control (*e*-test) was performed prior to each assay. Haemoscope TEG disposable cups and pins (Haemonetics Corporation) were placed in the analyzer and prewarmed to 37°C. The process was initiated by transferring 20 μl of 0.2mol/l $CaCl_2$ into the TEG test cup to reverse citrate chelation. One millimeter of the citrated blood sample was transferred to a vial of kaolin activator and mixed by gentle inversion. A 340 μl aliquot of this blood sample was added to the cup and further mixed by raising and lowering the TEG pin three times before the analyzer began to automatically process the sample.

Demographic data was collected including participant age, sex and primary diagnosis. The BMI was calculated. Enoxaparin dose and previous administration was detailed. Coagulation profiles, biochemistry data and anti-Xa activity were measured and recorded.

The TEG measures the physical properties of the clot as it forms between the testing cup and pin. Numerous authors have described the technique [13–15]. The TEG haemostasis analyzer provided thromboelastograph test results including reaction time (*R*), clot formation time (*K*), alpha angle, maximum amplitude, time to maximum rate of thrombus generation, maximum rate of thrombus generation (TMRTG) and total thrombus generation (TTG).

Statistical analysis
Analysis was performed by SAS version for Windows 9.2 (SAS Institute, Cary, North Carolina, USA). Spearman's rho was used to estimate simple correlation between continuous variables; two-sample *t*-test was used to compare continuous variables and least squares regression

Table 1 Descriptive statistics for variables collected on the 50 patients

Variable	N	Mean	SD	Minimum	Maximum
Age	50	60.90	13.86	33.00	88.00
Weight	50	82.62	16.98	53.00	127.00
Height	50	1.67	0.11	1.47	1.93
BMI	50	29.46	4.81	21.61	41.21
Clexane dose	50	80.60	13.50	60.00	100.00
Dose per kg	50	0.99	0.08	0.79	1.31
INR	50	1.08	0.08	1.00	1.30
PT	50	12.16	0.88	10.00	14.00
APTT	50	38.44	5.68	29.00	56.00
FIB	50	6.32	7.75	2.40	47.00
Platelets	50	248.62	68.86	134.00	512.00
CRP	45	18.02	36.94	0.50	189.00
eGFR	50	78.10	12.20	50.00	90.00
Creatinine	50	77.80	18.30	46.00	120.00
Anti-Xa	50	1.00	0.28	0.17	1.86
TEG parameters					
R	49	14.88	6.19	5.90	37.80
K	50	5.24	2.95	1.80	15.20
a	50	38.48	14.16	11.50	64.20
MA	50	57.18	7.83	40.50	70.40
CI	50	−9.55	6.37	−29.40	0.30
MRTG	50	5.59	2.71	1.79	12.99
TMRTG	50	18.74	8.75	0.33	50.67
TG	50	700.43	91.93	513.54	862.44

Anti-Xa, anti-Xa activity; APTT, activated partial thromboplastin time; CI, coagulation index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FIB, fibrinogen; INR, international normalization ratio; MA, maximum amplitude; MRTG, maximum rate of thrombin generation; PT, prothrombin time; TG, total thrombin generation; TMRTG, time to maximum rate of thrombin generation. Clexane (Sanofi-Aventis, Macquarie Park, NSW, Australia).

was used to estimate linear associations between variables with and without adjustment for potential confounders. In addition, logistic regression was used to assess potential predictors of high anti-Xa activity (anti-Xa >1.0).

Results

Descriptive statistics for the variables collected on the 50 patients are provided in Table 1. When anti-Xa activity is classified as low (0–0.5), correct (0.5–1.0) or high (>1.0) the distribution of R and dose per kg shows little association with anti-Xa (Table 2). The difference between mean R for the high anti-Xa group and the correct anti-Xa group is statistically nonsignificant using two-sample t-test (P = 0.26).

A linear regression model shows no evidence of association between dose per kg and anti-Xa (P = 0.95) (Fig. 1).

Table 2 R and dose per kg stratified by anti-Xa classified as high, correct or low

Variable	N	Mean	SD	Minimum	Maximum
Anti-Xa = high					
R	24	15.9	7.62	5.90	37.8
Dose per kg	24	0.99	0.082	0.89	1.31
Anti-Xa = correct					
R	24	13.9	4.41	7.10	20.9
Dose per kg	25	0.96	0.067	0.78	1.10
Anti-Xa = low					
R	1	11.8	–	11.8	11.8
Dose per kg	1	1.23	–	1.23	1.23

Anti-Xa, anti-Xa activity.

However, there is evidence of positive association between dose per kg and R (P = 0.011) in which a 10% increase in dose per kg is associated with an increase in R of 2.7 [95% confidence interval (CI) 0.6–4.7]. There is no evidence of association between R and anti-Xa (P = 0.38) (Fig. 2). Further regression analysis of dose per kg on other TEG parameters shows no evidence of linear association between dose per kg and K, a, maximun amplitude, coagulation index, MRTG or thrombus generation (P > 0.1 for all tests); however, there is evidence of association between dose per kg and TMRTG (P = 0.01) in which a 10% increase in dose per kg is associated with an increase in TMRTG of 3.8 (95% CI 1.0–6.6).

Investigation of association between anti-Xa activity and dose per kg could be confounded by timing of measurement (hours postdose), eGFR or creatinine levels. Therefore, regression analyses for anti-Xa activity were rerun after including hours postdose, eGFR and creatinine as covariates in the models. This effectively adjusts the effect of dose per kg on anti-Xa activity for any differences in hours postdose, eGFR and creatinine between patients. The adjusted analysis shows no evidence of association between dose per kg and anti-Xa activity (P = 0.81) or between R and anti-Xa activity (P = 0.23). However, evidence of positive association between dose per kg and R (P = 0.005) as well as dose per kg and TMRTG (P = 0.003) is unchanged after adjusting for hours postdose, eGFR and creatinine.

When anti-Xa is classified as low to correct (≤1.0) or high (>1.0) logistic regression shows no evidence of association with R (P = 0.25) or dose per kg (P = 0.26). After adjusting for hours postdose, eGFR and creatinine results were similar (R: P = 0.18; dose per kg: P = 0.40).

Discussion

The anti-Xa activity recorded in 50% of our patients was outside the therapeutic range. Furthermore, we failed to find a correlation between the dose of enoxaparin and the anti-Xa activity. A possible explanation could relate to sampling errors, however, the mean time from dose to sampling was 4.17 ± 0.5 h, consistent with recommendations for anti-Xa sampling. A number of other patient factors can affect the relationship between the dose of LMWH and anti-Xa levels. Dose adjustment for obese patients has been the subject of much controversy. Barras et al. [12] noted that dosing regimens based on TBW led to overdosing and increase risk of adverse events, whereras capping at a single dose of 100 mg resulted in subtherapeutic levels. However, the American College of Chest Physicians guidelines still suggest dosing based on TBW up to 144 kg. We included eight patients more than 100 kg [16]. The mean anti-Xa level was 0.93 ± 0.49, although the range of values was from 0.17 to 1.86.

As enoxaparin is largely excreted by the kidneys, decrease renal function will have significant effects on

Fig. 1
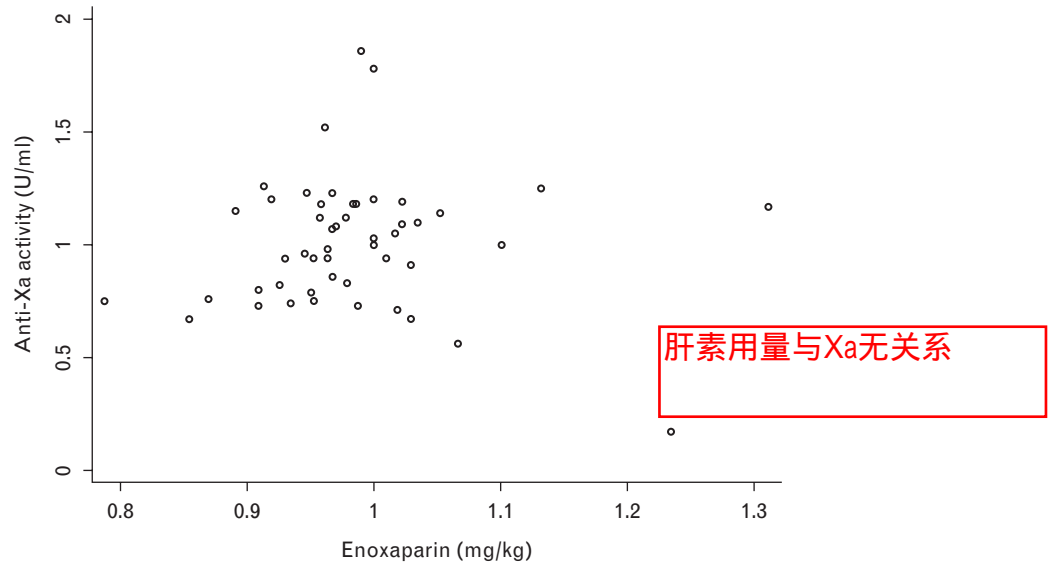
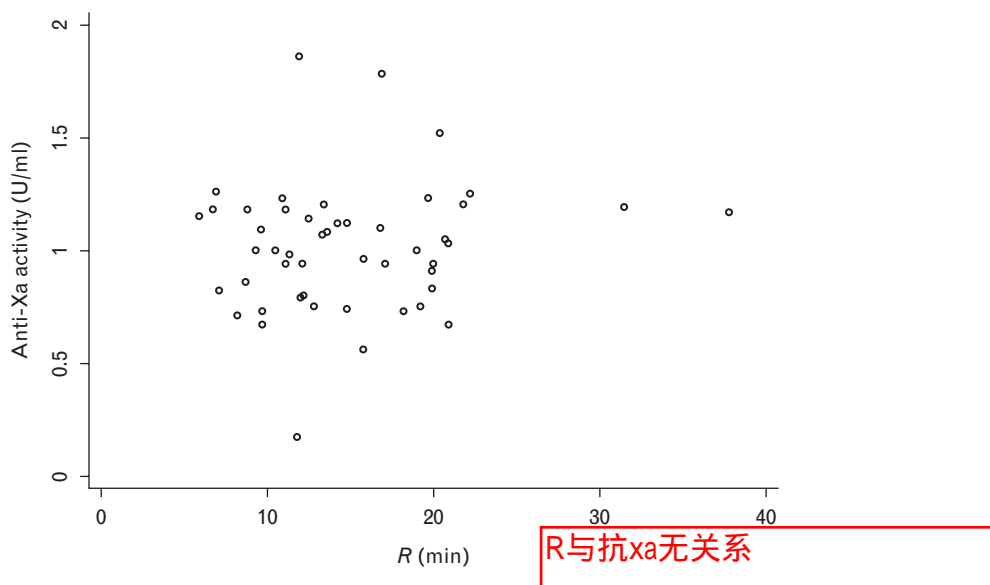Comparison between anti-Xa activity and dose of enoxaparin (mg/kg) ($P = 0.95$).

anti-Xa activity [5]. The mean eGFR and creatinine clearance for our study was 78.1 ± 12.1 and 77.8 ± 18.2, respectively, and there was no association between dose per kg and anti-Xa activity after adjusting for eGFR and creatinine. However, Mismetti *et al.* [17] noted significant accumulation of LMWH (Nadroparin; GlaxoSmithKline, Versailles, France) in elderly health volunteers as compared with young volunteers, despite having normal creatinine clearance. They suggested that even a physiological reduction of renal function in relation to aging has measurable effects on drug clearance, although the clinical relevance of this is unknown. The average age of our patients was 61 ± 14 years, with the oldest being 88 (anti-Xa of 1.08). Although we found a moderate negative correlation between age and eGFR, (Spearman's correlation $= -0.48$, $P = 0.0004$), there was no correlation between age and anti-Xa activity.

Thromboelastography has been employed for a number of years as a point-of-care tool for monitoring the coagulation status of patients in a variety of clinical circumstances, including liver transplantation, cardiac bypass surgery and trauma [18–20]. A number of authors have attempted to use the TEG for the rapid monitoring of anticoagulants [1,21–28]. Assuming that anti-Xa activity is the gold standard for monitoring LMWH use, TEG has been compared with anti-Xa activity using a variety of endpoints including R time, alpha angle and MA and other TEG-related indices. Results, however, have been mixed with some demonstrating a good correlation with TEG, whereas others less so. For example, Klein *et al.* [21] examined the relationship between TEG and anti-Xa activity in orthopaedic surgery patients receiving

prophylactic enoxaparin. They noted that the R value correlates significantly with peak and trough levels of anti-Xa activity ($P < 0.05$) and concluded it could be a useful test to measure LMWH activity. Similarly, in an in-vitro study, Gerotziafas *et al.* [29] noted a significant correlation between tissue factor-triggered TEG R and K value and anti-Xa when comparing the effects of different concentrations of enoxaparin and fondaparinux on clotting of blood specimens taken from health volunteers.

Conversely, Shinoda *et al.* [22] examined the usefulness of TEG for monitoring of LMWH during hemodailysis and failed to find a strong correlation between TEG R and anti-Xa activity. However, when considering the degree of dialyzer clot, they noted a good correlation with the TEG R value, whereas the anti-Xa activity correlated poorly. Similarly, Zmuda *et al.* [23] examined the relationship between TEG parameters and anti-Xa in healthy volunteers administered differing doses and types of anticoagulants. They concluded that TEG parameters did not always coincide with plasma levels of the drug, and therefore TEG did not appear to be an appropriate modality for monitoring enoxaparin therapy. Some authors have attempted to introduce various indices of coagulation based on TEG parameters to monitor anti-Xa activity. For example Artang *et al.* [24] compared anti-Xa activity to a composite TEG parameter called the thrombodynamic ratio and noted a good correlation (using healthy male volunteers). Carroll *et al.* [30] created a measure called delta TEG, which represents the difference between TEG R value performed with heparinase and without. They found a good correlation between anti-Xa activity ($r^2 = 0.806$) and delta R in thrombophilic

Fig. 2

Comparison between anti-Xa activity and R value on Thromboelastography ($P = 0.38$).

pregnancy patients, although considerable scatter was observed at lower values. Interestingly, an ex-vivo titration of normal and thrombophilic pregnancy patient blood samples had a linear dose response of r^2 more than 0.9. This appears to be a common occurrence wherein in-vitro studies and studies using healthy volunteers report good correlations between anti-Xa activity and TEG, whereas in-vivo studies in sick patients fail to show a correlation.

==We were unable to demonstrate a relationship between anti-Xa activity and any TEG parameter.== Even when stratifying patients according to anti-Xa activity, mean R was no different for group with anti-Xa 0.5–1.0 and more than 1.0. This lack of correlation persisted despite correcting for weight and renal function. Significantly, we did find a positive association between enoxaparin dose per kg and R ($P = 0.011$) in which a 10% increase in dose per kg is associated with an increase in R of 2.7 (95% CI 0.6–4.7). Furthermore, 47 out of 50 patients receiving enoxaparin in our group demonstrated a hypocoagulable TEG with R more than 8 min and a decrease in coagulation index, suggesting TEG is able to reflect the anticoagulant effects of enoxaparin in coronary care patients on treatment-dose therapy. This serves to illustrate the fact that tests examining a single point of the coagulation cascade may not represent the overall coagulation picture or patient outcomes. In a randomized controlled trial comparing LMWH with heparin for deep vein thrombosis prophylaxis, Leizorovicz et al. [9] found anti-Xa activity correlated weakly with antithrombotic activity and did not significantly correlate with the incidence of

hemorrhage. The data, however, are inconsistent. Whereas Boneu et al. [31] and Hemker et al. [32] found anti-Xa activity to be a poor parameter to assess quality of anticoagulant effects, Levine et al. [33] found a strong correlation between anti-Xa activity and both hemorrhage and thrombotic events. TEG is a measure of whole blood coagulation and has been shown to associate with clinical outcomes such as bleeding in cardiac and liver transplant patients.

Like Coppell et al. [25], we failed to find a significant correlation between TEG parameters and anti-Xa activity, in contrast to prior in-vivo studies. There are many potential reasons for this finding. First, many studies utilize healthy volunteers to provide samples for in-vitro analysis [6,25–27]. Results from these investigations may not be relevant to sick patients who display altered drug metabolism through changes in drug distribution, biotransformation and excretion. Furthermore, sick patients may display drug interactions that are accentuated by impaired renal clearance, decreased hepatic function, electrolyte and acid–base imbalances. Second, conventional assays use platelet poor plasma, and terminate with the formation of a fibrin clot, therefore possessing a well defined end point that is easily standardized. Segments of the clotting cascade are artificially isolated in these assays, and therefore they do not reflect the cellular contribution to the formation of a stable fibrin clot. Third, enoxaparin stimulates other coagulation factors including inducing the release of TFPI and platelet factor 4 partially neutralizing the anticoagulant activity of LMWH [11]. Fourth, different methods for TEG clot

activation are routinely employed including kaolin and tissue factor, potentially impacting on the generalization of results [34].

Lastly, although the anti-IIa effects of LMWHs are less significant the smaller the molecule, they are not absent entirely. Enoxaparin has been noted to have a Xa:IIa inhibition of approximately 3–4:1. Although relatively insignificant in small doses, the effects may be more important at treatment doses. Gerotziafas *et al.* [26] noted enoxaparin in low concentrations had no significant effect on thrombin generation in whole blood. However, a linear correlation was found between the concentration of enoxaparin and the reduction of thrombin C_{max}, with high concentrations almost completely abrogating thrombin generation. Dieri *et al.* [6] demonstrated a 23–45% (LMWH) variation in the concentration of C-domain (which represents anti-IIa activities) attained in the plasma. Fixed-dose enoxaparin led to large variations in plasma values for both anti-Xa and anti-IIa activity. Furthermore, they noted a large variation in anti-IIa levels between individuals following injection of enoxaparin with both high and low responders. As TEG is a global measure of coagulation activity, it may be more sensitive to the effects of these factors when compared with anti-Xa activity.

In conclusion, we were unable to demonstrate a correlation between enoxaparin dose and anti-Xa activity nor could the TEG be used to predict anti-Xa activity. However, TEG R was prolonged in all but three individuals and was positively associated with dose. This study was too small to evaluate the use of TEG for monitoring enoxaparin treatment in terms of clinical outcomes. However, it seems clear from this and other research that a more global test is necessary to evaluate enoxaparin dosing in sick patient populations as a number of factors other than anti-Xa activity impact on the coagulation system.

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This article describes cohort observational clinical study.

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Conflicts of interest
The authors have no conflicts of interest.

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