If some is good, more is better: An enoxaparin dosing strategy to improve pharmacologic venous thromboembolism prophylaxis

Allison E. Berndtson, MD, Todd W. Costantini, MD, James Lane, PharmD, Kevin Box, PharmD, *and* **Raul Coimbra, MD, PhD**, *San Diego, California*

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From the Division of Trauma, Surgical Critical Care, Burns and Acute Care Surgery (A.E.B., T.W.C., R.C.), Skaggs School of Pharmacy and Pharmaceutical Sciences (J.L.), and Department of Pharmacy (K.B.), University of California, San Diego, San Diego, California.
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Address for reprints: Raul Coimbra, MD, PhD, FACS, 200 W Arbor Drive, Mail Code 8896 San Diego, CA 92103; email: rcoimbra@ucsd.edu.

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BACKGROUND: Empiric enoxaparin dosing is inadequate for most trauma patients, leading to below target initial anti-Xa levels and requiring dose adjustment for optimal venous thromboembolism prophylaxis. We hypothesize that patient factors affecting initial anti-Xa levels can be identified based on drug pharmacokinetics, allowing creation of a new dosing protocol that will provide a higher percentage of in-target (0.2–0.4 IU/mL) patients at initial anti-Xa level assessment.

METHODS: Records of 318 trauma patients were evaluated, and NONMEM and PSN software were used to analyze 11 variables for their effects on anti-Xa levels. Computer modeling was used to select a new dosing protocol, which was implemented on the trauma service as a quality improvement project. The first 145 patients appropriately enrolled were assessed for response and complications.

RESULTS: Only 29.5% of the pre-intervention group had initial anti-Xa levels in the appropriate prophylactic range (Fig. 1). Levels were most strongly influenced by patient weight, outweighing contributions from all other variables. A new regimen for initial dosing was therefore designed with three weight-defined categories for ease of administration. The post-intervention group showed an increase in in-target initial anti-Xa levels to 74.5% ($p < 0.001$), with a corresponding decrease in subprophylactic patients from 68.0% to 20.7%. There was an increase in supraprophylactic levels to 4.8%, but no supraprophylactic patients had hemorrhagic complications.

CONCLUSIONS: Implementation of a new, categorized, weight-based enoxaparin dosing protocol was safe and significantly improved the percentage of trauma patients with in-target anti-Xa levels on initial assessment. Further studies are needed to determine whether such dosing decreases venous thromboembolism rates. (*J Trauma Acute Care Surg.* 2016;81: 1095–1100. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic/care management study, level II.

KEY WORDS: Venous thromboembolism; prophylaxis; enoxaparin; low molecular weight heparin; pharmacokinetics.

Despite widespread awareness and increasing use of prophylaxis, venous thromboembolism (VTE) remains one of the most common causes of morbidity and mortality after traumatic injury. Results vary by series and screening strategy used, but most estimates put current deep venous thrombosis (DVT) rates between 3% and 44% of trauma admissions.[1–5] Geerts et al. initially reported DVT rates of 58% in a population of trauma patients not receiving prophylaxis,[6] demonstrating the effectiveness of modern VTE protocols.

Traumatic injury is a known independent risk factor for venous thromboembolism. Prophylaxis with low molecular weight heparin (LMWH) has thus become standard in many trauma centers. It has repeatedly been shown, however, that LMWH requires dose adjustment guided by plasma anti-Factor Xa (anti-Xa) levels to ensure adequate DVT prophylaxis.[7,8] Although 30 mg subcutaneous twice daily has been the standard starting dose in many centers, research has shown that this dosing may be inadequate for many patients.[7,9]

The pharmacokinetics of LMWH, and thus its effects on anti-Xa levels, are influenced by many patient factors.[10–13] Obesity in particular has been shown to have an outsized effect, with these patients requiring significantly higher absolute doses of LMWH to achieve appropriate anti-Xa levels.[14,15] Renal impairment can prolong drug clearance, leading to higher bioaccumulation over time. Although dose adjustment is critical to ensure patients are receiving adequate prophylaxis, patients starting at an inappropriate dose are at risk of a prolonged period of subprophylactic levels before correction, leading to an increased risk of thrombosis. We hypothesized that a new patient-specific enoxaparin dosing protocol would more efficiently achieve target anti-Xa levels for venous thromboembolism prophylaxis.

METHODS

For development of our dosing protocol, a case series with retrospective data collection was assembled after institutional review board approval. The surgical intensive care unit pharmacy database and electronic medical records were queried to identify patients admitted to the trauma service between March 1, 2011 and April 30, 2014, who had at least one measured anti-Xa level during their hospital stay. The study dataset generated was subsequently manually examined by two authors (A.E.B. and K.B.) to include only patients with appropriate enoxaparin dosing and renal function assessment. Our divisional protocol calls for prophylaxis with enoxaparin twice daily (q 12 hours), starting as soon as deemed safe by the attending trauma surgeon. The majority of patients are started at 30 mg twice daily, though a higher dose can be used at the attending's discretion. A peak anti-Xa level is checked 3 to 5 hours after at least three serial enoxaparin doses have been given. Our goal anti-Xa range for prophylaxis is 0.2 to 0.4 IU/mL. Patients were excluded from modeling if less than three equivalent and appropriately timed doses of enoxaparin were given before anti-Xa level assessment, renal function was not assessed during hospitalization, or the patient had acute or chronic renal failure during the anti-Xa level assessment period. The initial study dataset included 318 patients who were used for the creation of the model. Data for each of the variables listed below was collected and included in our modeling sample.

Nonlinear mixed effect modeling (NONMEM version 7.2; ICON Development Solutions, Hanover, MD) and Wings for NONMEM (WFN version 740; wfn.sourceforge.net) were used to develop the base model. We used a one-compartment model with zero-order input (4-hour infusion of each dose) to simulate absorption from a subcutaneous dose of enoxaparin. Perl-speaks-NONMEM (PsN version 4.2; psn.sourceforge.net) software and its stepwise covariate model (SCM) building tool were used to implement Forward Selection and Backward Elimination of covariates to a model. As stated in the PsN manual for SCM, one model for each relevant parameter-covariate relationship was prepared and tested in a univariate manner. In the first step, the model that gives the best fit of the data according to selected criteria ($p < 0.05$, a 3.84 drop in the objective function of an approximately χ^2 distributed variable at 1 degree of freedom) was retained and taken forward to the next step. In the following steps, all remaining parameter-covariate combinations were tested until no more covariates meet the criteria for being included into

TABLE 1. Initial Covariates in Stepwise Covariate Model

Age	Sex
Glomerular filtration rate (GFR)	Presence of spine fracture
History of renal disease	Ventilator requirement
Injury type (blunt vs. penetrating)	History of venous thromboembolism
ISS	Weight (kg)
Race	

Each variable assessed twice—once for drug clearance, once for volume of distribution.

the model. The Forward Selection was then followed by Backward Elimination, which proceeds as the Forward Selection but reversely, using stricter criteria ($p < 0.01$, a 6.65 drop in the objective function at 1 degree of freedom) for model improvement. Eleven variables were evaluated in the aforementioned manner for their association with enoxaparin volume of distribution, clearance, between-subject variability and within-subject variability, and inclusion in the final model (Tables 1 and 2). The final model was then bootstrapped 1,000 times using the bootstrap function of PsN to confirm parameter stability. Bootstrap is a tool for calculating bias, standard errors, and confidence intervals of parameter estimates. It does so by generating a set of new datasets by sampling individuals with replacement from the original dataset and fitting the model to each new dataset. Simulation datasets were then constructed and run through NONMEM to generate expected anti-Xa concentrations of several prospective enoxaparin dosing regimens (Table 3). SAS 9.4 (Cary, NC) was used to manage the data and perform descriptive and inferential statistics. Model 7 was chosen as our new dosing protocol (Table 4), based on our assessment that this provided the best combination of a high percentage of patients in target anti-Xa range without excessively increasing the expected percentage of patients above target range.

The new enoxaparin dosing protocol was then implemented on the trauma service as a quality improvement project. Patients on the trauma service meeting protocol guidelines were enrolled if they had an actual body weight ≥50 kg and creatinine clearance (CrCl) ≥30 mL/min. Patients were excluded if they demonstrated active hemorrhage, significant coagulopathy, intracranial or spinal hemorrhage not cleared for anticoagulation by the neurosurgery service, or trauma attending assessment of prohibitive bleeding risk. Additional thromboprophylaxis standard on our service includes sequential compression devices and early ambulation. Inferior vena cava filters are placed at the discretion of the trauma attending. Timing of peak anti-Xa level assessments and duplex screening protocols were not changed during this pilot study. Trauma patients undergo standardized lower extremity duplex screening within the first 48 hours after hospital admission, followed by a second screen during the first week of hospitalization. They are screened weekly thereafter or at any time if symptoms develop. CT angiography is used to evaluate for pulmonary embolism (PE) as needed based on clinical suspicion. Only DVTs and PEs that arose after the initiation of chemical thromboprophylaxis were collected. The first 145 patients appropriately enrolled after the creation of the model were assessed for anti-Xa level response to the new enoxaparin dosing protocol and for complications including hemorrhage.

TABLE 2. Final Covariates in Stepwise Covariate Model

Variable	*p* Value
Glomerular filtration rate (GFR)	0.000147
Sex	0.000829
Spine fracture	0.000476
Weight (kg)—drug clearance	$1.33e^{-008}$
Weight (kg)—volume of distribution	$5.24e^{-015}$

TABLE 3. Expected Peak Anti-Xa Concentrations of Prospective Enoxaparin Dosing Regimens Based on Computer Modeling

Model	Proposed Regimen	Percent Below Target Range	Percent Within Target Range	Percent Above Target Range
1	30 mg q12 hours	61.64%	35.53%	2.83%
2	40 mg q12 hours	41.51%	45.60%	12.89%
3	0.5 mg/kg q12 hours	38.36%	53.14%	8.49%
4	0.6 mg/kg q12 hours	26.73%	54.40%	18.87%
5	0.33 mg/kg q8 hours	66.67%	31.13%	2.20%
6	0.5 mg/kg q8 hours	32.08%	52.52%	15.41%
7	Fixed dosing 1*	38.99%	51.26%	9.75%
8	Fixed dosing 2†	36.79%	51.89%	11.32%

*30mg, 40 mg, or 50 mg q12 hours by patient weight category, as per Table 4.
†As per Model 7, but replacing 50 mg q12hours with 60 mg q12hours for patients ≥100 kg actual body weight.

RESULTS

Final results of NONMEM and PSN modeling left five variables predictive of anti-Xa levels with standard dosing (Table 2). Actual body weight was found to be the strongest predictor of response, significantly outweighing the contributions from all other variables. Computer simulation was therefore used to design a new regimen for initial enoxaparin dosing based on weight alone; other variables were excluded given their relatively minor contribution. Of the modeled dosing regimens, a model utilizing three weight-defined categories was ultimately chosen (Model 7 in Table 3, further delineated in Table 4) as it was felt to represent the best combination of high in-target rates while minimizing the risk of supraprophylactic results.

Of the 318 patients initially used for modeling analysis, 275 had their initial anti-Xa level drawn as a true peak (3–5 hours after at least the third dose of enoxaparin). This group was labeled the Pre-Intervention Group and assessed for appropriateness of anti-Xa levels at initial assessment. Only 29.5% of the Pre-Intervention Group had initial anti-Xa levels in the appropriate prophylactic range of 0.2 to 0.4 IU/mL. The majority of patients (68.0%) had subprophylactic anti-Xa levels on initial assessment. Statistical modeling predicted that implementation of the new

TABLE 4. Pilot Enoxaparin Dosing Protocol (Model 7 from Table 3)

Patient Weight	Starting Enoxaparin Dose
50–60 kg	30 mg SQ q12 hours
61–99 kg	40 mg SQ q12 hours
≥100 kg	50 mg SQ q12 hours

dosing protocol would increase the number of patients in the appropriate prophylactic anti-Xa range to 51.3% (Table 3).

After initiation of our new dosing protocol, data on the first 145 patients appropriately enrolled were collected and analyzed for response to the new dosing protocol and for any identified complications. The only statistically significant differences between groups were for starting enoxaparin dose, ventilator days, and hospital length of stay (Table 5). The New Dosing Regimen group demonstrated a significant increase in appropriately dosed patients to 74.5% ($p < 0.001$), with a corresponding drop in subprophylactic patients to only 20.7% ($p < 0.001$) (Fig. 1). There was an increase in patients with supraprophylactic levels to 4.8%, though this difference was not statistically significant ($p = 0.261$). One hemorrhagic complication (0.7%) was identified in the New Dosing Regimen group, as compared to 0% in the Pre-Intervention Group ($p = 0.169$). This patient had a previously stable retroperitoneal hematoma, which developed new onset hemorrhage after an enoxaparin dose adjustment. Although there was an absolute change in VTE rate from 4.4% to 2.8% after initiation of the new enoxaparin dosing strategy, this decrease did not meet statistical significance ($p = 0.383$) as this study is not adequately powered to detect a change in VTE rate.

Of the 16 total VTE events (12 Pre-Intervention Group, 4 New Dosing Regimen group), only one was a pulmonary embolism (PE), whereas the remaining 15 were deep venous thromboses. Three DVTs were related to central venous lines. Of the 12 patients in the Pre-Intervention Group, 33.3% (4 patients) had a known low Xa level at the time of VTE diagnosis, whereas 41.2% (5 patients) had an appropriate Xa level. Twenty-five percent (3 patients) had undergone an increase in enoxaparin dose after a previously low anti-Xa level, but had not yet had an anti-Xa level rechecked. Regarding the four patients in the New Dosing Regimen group, 75% (three patients) had an appropriate Xa level at the time of VTE diagnosis, whereas 25% (one patient) had been started on enoxaparin but not yet had an anti-Xa level assessment. The only patient with a PE had received only two doses of enoxaparin before being diagnosed with a subsegmental pulmonary embolism and was transitioned to therapeutic enoxaparin before any anti-Xa level was checked.

TABLE 5. Demographics, Pre-Intervention vs. New Dosing Regimen Groups

	Pre-Intervention Group	New Dosing Regimen Group	*p* Value
Number	275	145	—
Age (years)	46.3 ± 20.2	48.0 ± 19.6	0.399
% Male	72.0%	78.6%	0.140
Weight (kg)	82.0 ± 21.3	82.5 ± 21.2	0.836
Creatinine clearance (mL/min)	160.8 ± 67.4	152.8 ± 76.6	0.292
% blunt trauma	90.5%	91.7%	0.690
Mechanism			0.489
Fall	26.2%	33.1%	
Found down	6.5%	2.8%	
Assault	4.7%	13.1%	
Pedal cycle	4.7%	5.5%	
Motorcycle	10.9%	9.7%	
Motor vehicle accident	16.0%	14.5%	
Pedestrian vs. auto	10.2%	7.6%	
Off-road vehicle	5.1%	0.7%	
Stab wound	5.5%	0%	
Gunshot wound	3.6%	1.4%	
Other	6.5%	11.7%	
Starting enoxaparin dose (mg)	31.2 ± 4.0	40.3 ± 5.3	<0.001
Percent mortality	1.5%	0.7%	0.445
Hospital length of stay (LOS) (days)	16.1 ± 15.8	12.8 ± 17.1	0.036
ICU LOS (days)	6.5 ± 9.8	5.1 ± 7.7	0.105
Ventilator days	4.4 ± 8.6	2.8 ± 7.2	0.042
ISS (median ± IQR)	17 ± 16	14 ± 15	0.079
Venous thromboembolism (%)	4.4%	2.8%	0.383
Hemorrhage	0%	0.7%	0.169

Data presented as mean ± standard deviation unless otherwise specified.

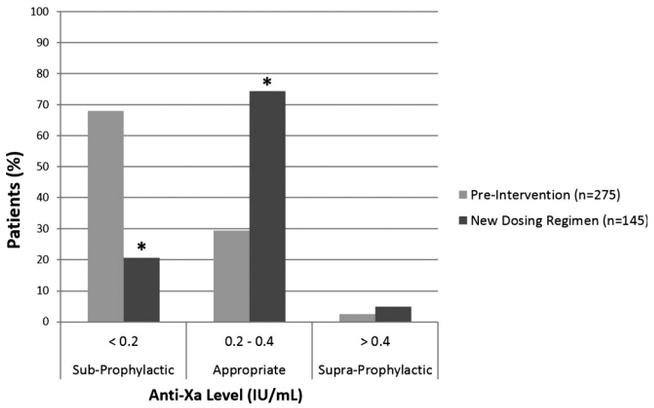

Figure 1. Percentage of patients below, in, and above target anti-Xa levels, by dosing regimen. *Difference pre-intervention to new dosing regimen $p < 0.05$.

DISCUSSION

VTE remains one of the most common complications after trauma despite protocols for pharmacologic and mechanical prophylaxis in most centers. In addition to causing immediate morbidity and mortality, VTE events contribute unnecessarily to hospitalization costs[16,17] and can lead to long-term complications including post-thrombotic syndrome.[18,19] The standard dosing regimen of enoxaparin 30 mg twice daily results in inadequate pharmacologic prophylaxis for many trauma patients and requires dose adjustment based on anti-Xa levels for optimum results.[7,8] Although this eventually achieves adequate chemoprophylaxis, patients requiring dose adjustment necessarily experience a prolonged initial period of subprophylactic dosing and thus increased thrombotic risk before reaching target anti-Xa levels. Our study identified weight as the single most important predictor of patient response to enoxaparin and developed a new weight-based dosing protocol that increased our percentage of patients achieving an initial in-target anti-Xa level from 29.5% to 74.5%. The number of patients subprophylactic at initial assessment decreased from 68.0% to 20.7%. The proposed protocol significantly decreases the need for dose adjustment, thus reducing the time needed to achieve appropriate anti-Xa levels.

To develop a more efficient dosing regimen and attempt to minimize VTE events, the patients in our modeling group were

analyzed for factors predictive of anti-Xa level response to enoxaparin. Although GFR, gender, and the presence of a spine fracture were ultimately related to final anti-Xa level, patient weight was far more predictive of both enoxaparin drug clearance and volume of distribution, outweighing all other factors. Weight alone was therefore used to create our new dosing model.

Obesity has previously been recognized as a factor influencing anti-Xa level response to enoxaparin, with previous studies evaluating alternative dosing regimens in those patients. Bickford et al.[14] evaluated 86 obese trauma patients (mean admission body weight 113.3 kg) who received enoxaparin 0.5 mg/kg BID, rounded to the nearest 10 mg. Although they reported 86% of patients in the target range, they used a wider goal range of 0.2 to 0.6 IU/mL, compared to 0.2 to 0.4 IU/mL used in the present study. Their mean peak anti-Xa level was 0.42 IU/mL, with most patients outside the goal range being supraprophylactic. Ludwig et al.[15] had previously attempted a similar regimen in 23 obese SICU patients (mean weight 137 kg), administering 0.5 mg/kg enoxaparin rounded down to the nearest 10 mg. They found a mean anti-Xa level of 0.34, lower than the Bickford study, but with 91% of patients inside their goal range of 0.2 to 0.5 IU/mL. Only two patients were outside their goal range, and both were supraprophylactic.

One limitation of both of these studies is their propensity for supraprophylactic levels. Combined with their wider goal anti-Xa ranges, adopting a similar methodology would leave many of our patients at a higher-than-acceptable risk of anticoagulation-related hemorrhage. Additionally, calculating doses by their method necessarily leads to a need for dose rounding, as enoxaparin is provided in a concentrated form making it difficult to accurately draw up small amounts. Finally, this method is limited from broad application by the fact that only morbidly obese patients were included, with a mean BMI higher than even our highest-weight dosing group. It is unclear how the 0.5 mg/kg dosing would translate to nonobese patients, who are also at significant risk of subprophylactic dosing as shown by Costantini et al.[7] Our study was designed to be more inclusive of trauma patients as a whole, excluding only those under 50 kg as the small volumes associated with a 20 mg BID dose are difficult to administer accurately. Given these risks, we felt that defining three distinct dosing categories based on weight presented a potentially safer dosing option than the 0.5 mg/kg dosing strategy, whereas the models performed similarly in our simulation (Table 3). Although we may have been able to create a more perfectly matched model by including more factors or smaller weight categories, the additional complexity would limit accurate protocol implementation with minimal benefit.

Ultimately, our pilot study group outperformed our modeling prediction, with 74.5% of patients in the New Dosing Regimen group appropriately prophylactic at the time of initial anti-Xa level assessment. There was a significant reduction in subprophylactic patients to 20.7% and only a modest increase in supraprophylactic patients to 4.8%. We did have one patient in the New Dosing Regimen group develop a hemorrhagic complication—a patient with a previously stable retroperitoneal hematoma after a fall developed new onset hemorrhage, requiring angioembolization and blood product transfusion. However, although this patient had been started on enoxaparin 40 mg twice daily (appropriate for his 79.1 kg weight), his initial anti-Xa level was low at 0.13. Bleeding developed only after the dose was correctly increased to 50 mg twice daily and before a repeat anti-Xa level was assessed. It is unclear if the hemorrhage was related to enoxaparin or part of the natural history of his disease, particularly given his previously low anti-Xa level. We therefore believe that this complication was unrelated to our new dosing protocol, as previous standards would have led to an identical dose increase. No patient in either group with a supraprophylactic anti-Xa level had a hemorrhagic complication.

Although our current study was not powered to compare VTE rates between groups, we did note an absolute decrease in the rate of VTE after enoxaparin initiation from 4.4% to 2.8%, though this was not statistically significant. There were no deaths in either group resulting from thromboembolic events. Given the comprehensive screening protocol used in our institution, we believe it is unlikely that any VTE events were undiagnosed. Interestingly, of the four Pre-Intervention Group patients with low Xa levels at the time of VTE diagnosis, all would have been started on a higher dose of enoxaparin under the New Dosing Regimen (two at 50 mg and two at 40 mg, when all were actually started on 30 mg twice daily). The three patients who had undergone dose adjustment but not yet had an anti-Xa level rechecked also would have been started on higher doses (40 mg instead of 30 mg twice daily), which may have obviated the need for dose adjustment. In all cases, the new dosing protocol would likely have led to an earlier appropriately prophylactic anti-Xa level, though whether or not this would have prevented the VTE events in question is not proven.

Limitations of our study include a small sample size that precludes definitive assessment for an overall reduction in VTE events. Even with scheduled ultrasound surveillance, the rate of DVT is low enough that an appropriately powered study will require a large number of patients, and thus likely a multicenter trial. It is also not certain that improving anti-Xa levels will reduce the VTE rate, though low trough anti-Xa levels have been shown to correlate with DVT rates.[8] In this study, 8 of 16 patients with VTE events did have appropriate anti-Xa levels at the time of VTE diagnosis. Further analysis of patients who "fail" chemoprophylaxis with dose-adjusted enoxaparin should be undertaken to search for mitigating circumstances that may be addressable. Our own enrollment was limited by an inability to get all eligible patients started on the appropriate new enoxaparin dose and assessed with an appropriately timed anti-Xa level. Our SICU pharmacy staff was empowered to adjust doses and order anti-Xa levels as needed, which increased our enrollment, but patients were still missed despite aggressive resident and nurse practitioner education on the new protocol. Those patients initially sub- or supraprophylactic did undergo dose adjustment, but the majority were subsequently discharged from the hospital before a repeat anti-Xa level could be drawn, limiting our ability to define a final appropriate enoxaparin dose. Regardless, we were able to assess for initial anti-Xa response to enoxaparin, which was our primary goal. The two groups were similar for most demographics, but did differ in terms of ventilator days and hospital length of stay, which could also account for the noted decrease in VTE events.

In conclusion, a categorical weight-based enoxaparin dosing strategy can be used to more rapidly achieve prophylactic anti-Xa levels, while avoiding the need for dose rounding associated with strict milligrams per kilogram enoxaparin

regimens. Using the proposed enoxaparin dosing strategy, supraprophylactic anti-Xa levels were uncommon. Further assessment with a larger study is needed to evaluate for a reduction in VTE complications.

AUTHORSHIP

All authors contributed to the design of this study. A.E.B. conducted the literature search. A.E.B. and K.B. performed data collection. A.E.B., T.W.C., J.L., K.B., and R.C. contributed to data analysis and interpretation. A.E.B. wrote the manuscript, which all authors critically revised.

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DISCLOSURE

The authors declare no conflicts of interest.

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EDITORIAL CRITIQUE

The authors have demonstrated an enoxaparin dosing protocol that effectively and safely improves reaching the target anti-Xa level of 0.2–0.4 IU/mL. A sophisticated computer model was used to create a new weight-based dosing protocol which was then applied clinically. Under the new dosing regimen, a higher percentage of patients reached the goal anti-Xa level with only a small, statistically insignificant increase in supratherapeutic levels. This study has several strengths. It was well-designed and the authors did a nice job of explaining the complicated computer modeling that was used to create the dosing protocol. Patients were adequately matched in the pre- and post-intervention groups. The methods of VTE screening were thorough.

However, there remain some lingering questions regarding the work. Not considered in the covariates used to develop the model was the number of missed doses, which could certainly affect the anti-Xa levels. Missed doses are known to increase the DVT rate significantly. More importantly and more concerning is the finding that half of all patients who developed DVT had anti-Xa levels in the goal range of 0.2–0.4 IU/mL. This finding raises an important question regarding whether this is actually an appropriate target anti-Xa level for trauma patients. Despite these issues, the UCSD group continues to provide useful clinical information on VTE prophylaxis. I certainly agree with their closing comment that a larger, perhaps multicenter, trial is needed to find the "sweet spot" in enoxaparin dosing.

Kimberly A. Peck, MD
Scripps Mercy Hospital
San Diego, California