

Anti-Factor Xa Activity of Prophylactic Enoxaparin Regimens in Critically Ill Patients

Yigal Helviz MD¹, Ilia Dzigivker MD², David Raveh-Brawer MD³, Moshe Hersch MD^{1,6}, Shoshana Zevin MD^{4,6} and Sharon Einav MD^{5,6}

¹Intensive Care Unit, ²Department of Cardiothoracic Surgery, ³Infectious Diseases Unit, ⁴Department of Internal Medicine and ⁵Surgical Intensive Care Unit, Shaare Zedek Medical Center, Jerusalem, Israel

⁶Hadassah-Hebrew University Medical School, Jerusalem, Israel

ABSTRACT: **Background:** Enoxaparin is frequently used as prophylaxis for deep venous thrombosis in critically ill patients.

Objectives: To evaluate three enoxaparin prophylactic regimens in critical care patients with and without administration of a vasopressor.

Methods: Patients admitted to intensive care units (general and post-cardiothoracic surgery) without renal failure received, once daily, a subcutaneous fixed dose of 40 mg enoxaparin, a subcutaneous dose of 0.5 mg/kg enoxaparin, or an intravenous dose of 0.5 mg/kg enoxaparin. Over 5 days anti-activated factor X levels were collected before the daily administration and 4 hours after the injection.

Results: Overall, 16 patients received the subcutaneous fixed dose, 15 received the subcutaneous weight-based dosage, and 8 received the dose intravenously. Around two-fifths (38%) of the patients received vasopressors. There was no difference between anti-activated factor X levels regarding vasopressor administration. However, in all three groups the levels were outside the recommended range of 0.1 IU/ml and 0.3 IU/ml.

Conclusions: Although not influenced by vasopressor administration, the enoxaparin regimens resulted in blood activity levels outside the recommended range.

IMAJ 2016; 18: 108–113

KEY WORDS: deep venous thrombosis (DVT) prophylaxis, enoxaparin, anti-factor X activity (aFXa), vasopressors, subcutaneous administration, intravenous administration

Critically ill patients are at increased risk of venous thromboembolic (VTE) events [1]. Among the pharmacologic modalities to prevent this disorder are subcutaneously administered low molecular weight heparins (LMWH). They are recommended as an alternative to low dose unfractionated heparin for standard deep venous thrombosis (DVT) prophylaxis in most critically ill patients [2].

Although many intensive care units (ICUs) administer the preventive dose of LMWH as for the general patient population [3], this has not been validated sufficiently in the critically ill. Indeed, several studies demonstrated questionable

efficacy of the preventive standard enoxaparin dose in the critically ill [4-7]. Among the factors that differentiate ICU patients from the general patient population are those that may affect uptake from the subcutis, such as administration of vasopressor.

One way of monitoring LMWH treatment is by measuring anti-factor X activity (aFXa). In the present study we investigated the aFXa levels of enoxaparin preventive regimens in the critically ill and the effect of vasopressors on these levels.

PATIENTS AND METHODS

This randomized prospective controlled study was conducted in the ICU of Shaare Zedek Medical Center in Jerusalem. Both local institutional review board (IRB) and National Institute of Health approvals (NCT00351663) were obtained. Local IRB approval demanded that families be informed of the result of randomization since standard therapy was being waived. In accordance with local IRB demands, informed consent was signed either by a court-appointed legal guardian or by an independent physician and, when available, a first-degree family member.

SAMPLE SIZE CONSIDERATIONS

Based on the assumption that at least 40% of the aFXa levels would be outside the recommended range, we planned to recruit 15 patients for each treatment group. This would have provided the study with a two-sided confidence level and a power greater than 0.9.

INCLUSION/EXCLUSION CRITERIA

All mechanically ventilated patients admitted to the ICU were screened for study inclusion. Inclusion criteria were age \geq 18 years old, mechanical ventilation expected for $>$ 3 days, and an indication for VTE prophylaxis therapy. Exclusion criteria were treatment with low dose unfractionated heparin (LDUH) $<$ 8 hours before enrolment, indication for therapeutic anticoagulation, presence of contraindication for anticoagulation, platelet count $<$ 75,000/10³ μ l, international normalization ratio (INR) $>$ 1.7, creatinine clearance $<$ 30 ml/min/m², body

mass index (BMI) > 30 kg/m², or any other condition precluding treatment according to the treating physician.

STUDY PROTOCOL

Using the online tool (<http://www.randomizer.org/form.htm>) patients were randomized to receive enoxaparin 40 mg subcutaneously (SQ), 0.5 mg/kg SQ, or 0.5 mg/kg intravenously (IV).

On the day of enrolment the patient’s Acute Physiology and Chronic Health Evaluation II (APACHE II) score was documented, as were BMI, levels of blood creatinine blood urea nitrogen (BUN), complete blood count and coagulation profile. Daily follow-up included complete blood count and coagulation profile, documentation of bleeding episodes and thrombotic phenomena, thrombocytopenia below 75,000/10³ µl or the appearance of a rash. In patients receiving vasopressors, both type and dose of vasopressor were documented.

During the first 5 days of treatment, blood samples were drawn for aFXa levels at 30 minutes before enoxaparin injection (trough) and 4 hours after injection (peak). Although the aFXa will peak immediately after the IV administration, we used the 4 hour levels to standardize the comparison between the regimens. After 5 days of treatment, venous duplex ultrasound to rule out the presence of DVT was performed by an experienced operator blinded to the treatment group.

LABORATORY WORKUP OF aFXa SAMPLES

All samples were collected in tubes of trisodium citrate and were coded to maintain laboratory blinding to the drug administration protocol. Samples were analyzed using an enoxaparin-specific aFXa assay (Coamatic Heparin®, Chromogenix, Italy). aFXa levels of 0.1–0.3 IU/ml were considered as representing effective prevention. Although some researchers consider aFXa levels of 0.2 IU/ml to be a safer upper limit, we decided to accept levels as high as 0.3 IU/ml as the upper limit, as also stated by others [8,9]. All laboratory and clinical staff were blinded to the treatment groups and to aFXa levels respectively.

OUTCOME MEASURES

The main outcome measure was the blood levels of aFXa. The secondary outcome measure was the effect of vasopressor therapy on aFXa levels in each treatment protocol.

STATISTICAL ANALYSIS

Analysis of variance (ANOVA) was used to compare the amount of enoxaparin administered and the aFXa levels in the three study groups. Chi-square test was used to compare categorical variables. In addition, linear regression was used to study variables related to aFXa levels before and after administration. The enoxaparin dose was not incorporated in this model due to its strong correlation to the treatment arm and BMI, which were included.

RESULTS

The first patient was recruited on 19 February 2007 and the last on 4 August 2008. Forty-five patients underwent randomization but 6 were withdrawn from the study due to family request, precluding analysis according to intension to treat. The major baseline characteristics of the 39 study subjects are given in Table 1. Most patients were admitted to the ICU for treatment of respiratory dysfunction or after abdominal surgery. Sixteen (41%) had undergone surgery prior to ICU admission. Most were males (27/39, 69%). Their median APACHE II score was 19 (IQR 17–22) and their median length of stay in the ICU was 15 (IQR 6–21) days.

ENOXAPARIN TREATMENT GROUPS [TABLE 1]

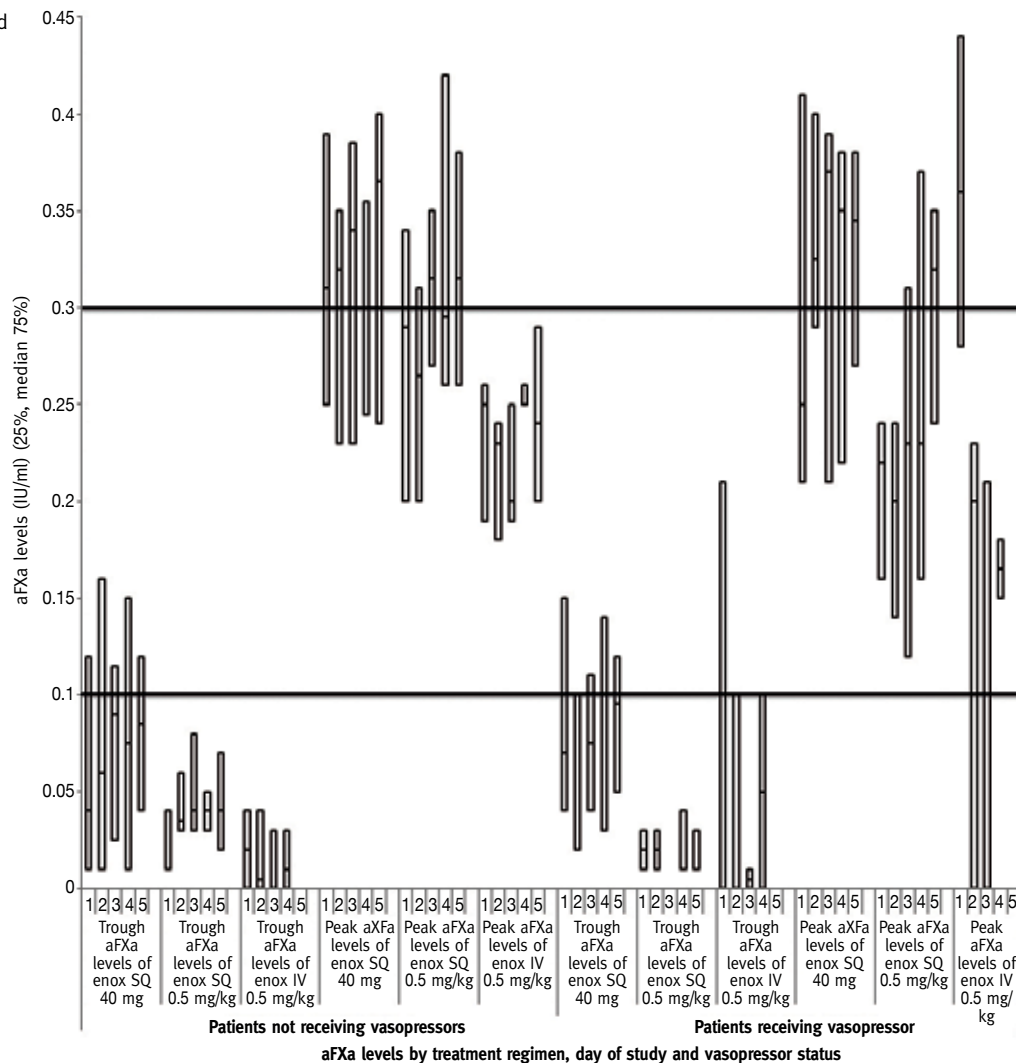
Sixteen patients received SQ 40 mg enoxaparin, 15 received SQ 0.5 mg/kg and 8 received IV 0.5 mg/kg. There was no statistical difference between the three groups in APACHE II score, age, gender, percentage of patients who received vasopressor therapy, BMI, or ICU length of stay. There was also no difference between the groups in the absolute dose of enoxaparin administered.

Table 1. Demographic data of the treatment groups

	Treatment group			Pvalue
	SQ 40 mg n=16	SQ 0.5 mg/kg n=15	IV 0.5 mg/kg n=8	
Age (years) Median (IQR)	73 (62–81)	69 (57–79)	56 (49–73)	0.13
Male gender, n (%)	10 (62.5)	9 (60)	8 (100)	0.10
Surgery, n (%)	5 (31.25)	7 (46.67)	4 (50)	0.58
Body mass index Median (IQR)	25 (24.20–27.57)	25 (24.03–27.68)	26.12 (25.71–27.68)	0.44
APACHE II score Median (IQR)	19.5 (17.00–22.50)	19.00 (17.00–22.00)	18.50 (13.50–20.50)	0.54
Pulse rate Median (IQR)	80 (75–100)	90 (80–100)	75 (64–73)	0.12
Mean blood pressure (mmHg) Median (IQR)	83 (75.5–87.5)	85 (78–88)	85.5 (82–92)	0.35
Temperature (C°) Median (IQR)	38 (37.3–38.55)	38 (37.2–38.2)	37.4 (37.35–37.75)	0.35
Creatinine (mg/dl) Median (IQR)	1.04 (0.84–1.26)	1.16 (0.9–1.38)	0.92 (0.7–1.07)	0.29
Platelets (10 ⁹ /L) Median (IQR)	176.00 (141.50–176.00)	198.00 (154.00–258.00)	180.00 (158.5–220.5)	0.59
INR Median (IQR)	1.35 (1.28–1.44)	1.09 (1.28–1.44)	1.17 (1.13–1.33)	0.19
Vasopressor, n (%)	7 (46.67)	5 (33.33)	3 (20)	0.84

SQ = subcutaneous, IV = intravenous, IQR = interquartile range

Figure 1. Daily peak and trough aFXa levels of enoxaparin (enox)



VASOPRESSOR TREATMENT GROUPS

Almost half the subjects (15/39, 38%) received vasopressors. The only vasopressor used was noradrenaline. There was no difference between patients receiving or not receiving vasopressors in APACHE scores, age, gender and BMI for each treatment group. Patients receiving vasopressors in the weight-based enoxaparin groups had slightly longer length of stay in the ICU (median 10 vs. 7 days, $P = 0.011$).

ANTI-FACTOR X LEVELS

Peak aFXa levels remained consistent throughout study days 1 to 5, as did trough aFXa levels in all treatment groups. This allowed pooling analysis of the aFXa levels sampled on all the days as one group, providing the study with a greater statistical power.

The aFXa levels measured in most samples were outside the range suggested for VTE prevention [Figure 1], regardless

of treatment group. Levels before administration were consistently lower than recommended and levels after administration were consistently higher. The fixed SQ 40 mg/day enoxaparin protocol provided the highest blood levels of aFXa.

In all three treatment groups, there was no detectable difference in aFXa levels (peak or trough) in patients receiving vasopressors compared to patients not receiving vasopressors [Figure 2].

Multivariate co-factors related to aFXa levels before administration were patient's gender, the treatment arm, and serum creatinine levels. The aFXa levels achieved after administration were related only to BMI and the mode of drug administration [Table 2].

COMPLICATIONS OF TREATMENT

None of the study subjects had pulmonary embolism, but duplex revealed DVT in two subjects (5%). Both were males

with a normal BMI. One was treated according to the SQ weight-based protocol with resultant aFXa levels consistently below 0.1 IU/ml before and above 0.3 IU/ml after enoxaparin administration, respectively. Duplex demonstrated DVT in the distal left leg. This 57 year old patient had been admitted for malignant reperfusion syndrome several hours after carotid endarterectomy and died after developing fulminant brain edema as a complication of the primary diagnosis. The second patient was treated according to the IV weight-based protocol with resultant aFXa levels consistently below 0.1 IU/ml before administration and above 0.3 IU/ml after administration throughout the study period. Duplex demonstrated DVT in the left popliteal vein. The patient, aged 45, had been admitted to the ICU after intubation and mechanical ventilation for respiratory insufficiency as a complication of Duchene’s muscular dystrophy. He had been bound to a wheelchair before hospital admission and was discharged home in a similar condition.

SURVIVAL OUTCOMES

Three deaths occurred during the study period, none of which was secondary to the treatment. One is described above. The APACHE II score of this patient was 18 and he had been receiving a weight-based SQ enoxaparin protocol. The second death was of an 87 year old man who had been admitted for aspiration pneumonia with an APACHE II score of 19. He too received a weight-based SQ enoxaparin dose. The third death occurred in a 79 year old male after chest wall trauma due to a motor vehicle accident; he died of septic shock and multi-organ failure after a stormy ICU course. This last patient had been receiving a weight-based IV enoxaparin protocol and his APACHE II score was 21.

DISCUSSION

The main result of this study was that a daily dose of enoxaparin whether it was SQ or IV, standard or weight-based, led to aFXa outside the suggested levels. The secondary outcome was that noradrenaline administration had no effect on the aFXa blood levels. The aFXa levels may denote the multifactorial nature of the physiology of critical care patients. Moreover, the correlation between the trough levels and co-factors may stem mainly from kidney function, composition of body tissues, and gender. By contrast, the peak levels could demonstrate the pharmacokinetics of the medication, which depends on the volume of distribution and hence on the BMI. A larger study is needed to define these co-factors and their role in different enoxaparin regimens. As for the lack of effect of noradrenaline, it is possible that in this patient cohort the skin perfusion was maintained with the vasopressor and, therefore, its absorption from the subcutis was not impaired.

Previous studies on the recommended dose involved either non-critically ill [9] or less critically ill patients [10,11], included shorter sampling periods [24], or were observational [9,11]. In

Figure 2. aFXa levels in the three treatment groups with and without administration of vasopressors

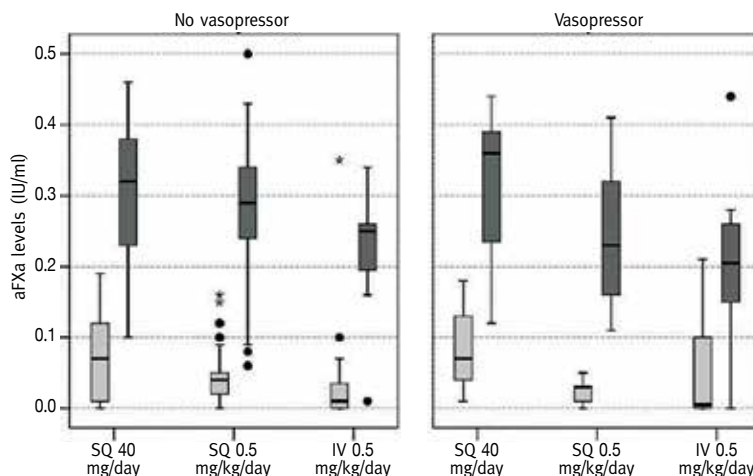


Table 2. Results of the regression model for aFXa levels

Variable	Multiple linear regression model					
	aFXa levels before administration (r ² = 0.26, n=173)			aFXa levels after administration (r ² = 0.14, n=172)		
	Coefficient	95%CI	P value	Coefficient	95%CI	P value
Age	0	0	0.70	-0.001	-0.002	0.27
Gender	0.017	0.002	0.02	0.021	-0.01	0.19
BMI	0.001	-0.001	0.36	0.008	0.003	0.003
Treatment	-0.03	-0.041	< 0.0001	-0.04	-0.062	< 0.0001
Creatinine	-0.029	-0.054	0.025	-0.027	-0.08	0.31

aFXa = anti-factor X activity, CI = confidence interval

contrast, this randomized controlled study deals specifically with the critically ill and uses administration and monitoring methods that are practical for everyday ICU management and are accepted worldwide.

Several studies show similar results. Mayr et al. [8] sampled aFXa levels several times a day in medical and surgical ICU patients treated once daily with SQ 40 mg enoxaparin. Twelve hours after injection the levels were not within the preventive range. Obesity and multi-organ failure correlated with low aFXa levels [8]. Priglinger et al. [10] prospectively compared aFXa levels in medical, medical critical care, and post-cardiac surgery patients and found that aFXa levels were significantly lower in critically ill patients. This decreased efficacy could not be attributed to vasopressor therapy, blood proteins, platelets or leukocyte counts. However, there was a positive correlation with the severity of illness. A study of critically ill trauma patients detected low aFXa trough levels with a standard SQ fixed dose of 40 mg [11]. Higher doses of SQ enoxaparin (e.g.,

60 mg) have been suggested to lead to better aFXa profile in the critically ill patient population [12]. Another study showed low aFXa levels after subcutaneous injection of dalteparin in critical patients with and without edema [13]. Despite the population heterogeneity in these studies of critical care patients, the standard 40 mg SQ enoxaparin dose leads consistently to aFXa levels outside the suggested range. Despite the small size of these studies, it seems that the standard enoxaparin dose may need re-evaluation.

Nevertheless, there are studies that presented opposite results. Dörffler-Melly and co-authors [14] showed that patients receiving vasopressors had lower aFXa levels than patients who had not received these medications. They used nadroparin and not enoxaparin. The size of this study was similar to ours as there were up to 15 patients in the different treatment groups. This different result probably signifies the fact that the critical care population is heterogenic.

Recently, two large prospective trials were published on the subject of DVT prophylaxis in the critically ill. The study by Cook et al. [15] observed no difference in the rate of proximal DVT between critical ill patients receiving another LMWH (deltaparin) and those receiving an LDUH. Although there was a trend toward fewer pulmonary embolisms in the LMWH group, the study concluded that there is no significant change of DVT rates between these treatments. Again the LMWH was given as a SQ dose once a day. In that study the aFXa levels were not measured. In addition, another relatively large study by Robinson et al. [16] indeed checked the levels of aFXa during the first 3 days of administering several weight-based SQ regimens. They concluded that weight-based regimens result in aFXa levels at the target range of 0.1–0.4 IU/ml [16]. In our study this was not observed due to the lack of significant difference in the enoxaparin dosages within the treatment arms.

Our study has some major limitations. The first is the small number of participants. Larger multicenter trials are necessary to validate our findings. Second, our attempt to perform full randomization and analysis by intention to treat was thwarted by the local IRB demand for family approval for study inclusion, which led to selective patient withdrawal from the intravenous administration group. Third, our patients received only noradrenaline as the vasopressor. Although this is a first-line vasopressor [17], other vasopressors should also be studied. In addition, due to the small number of patients in each group, we did not analyze the results according to the noradrenaline dose. Fourth, in this study, aFXa levels were measured only during the first 5 days. It is possible that over a longer period the results would be different and would affect the way we treat patients. Fifth, we studied only non-obese patients, which could mask the necessity of administering weight-based regimens. Sixth, the question whether duplex ultrasonography is sensitive enough to detect DVT in the critically ill must be addressed.

Another major criticism of this study is whether a specific aFXa level should be sought when dealing with DVT prevention. If a specific preventive regimen lowers the rate of VTE on one hand and has no significant level of bleeding on the other, then the aFXa levels are irrelevant. We believe that the ability to monitor treatment by changing enoxaparin dose according to aFXa levels increases patient safety. Furthermore, there is some evidence that low aFXa levels relate to high prevalence of DVT [18].

This study suggests that the current DVT prevention protocol results in aFXa levels not within the suggested preventive range. This does not mean that these protocols are clinically ineffective. Rather, it highlights the need for further research. The effect of vasopressors on the peripheral uptake of subcutaneously administered LMWH also merits additional attention. Despite these unresolved issues, our preliminary data encourage SQ administration in critically ill patients.

Correspondence

Dr. Y. Helviz

Intensive Care Unit, Shaare Zedek Medical Center, Jerusalem 91031, Israel

Phone: (972-2) 655-5564

Fax: (972-2) 655-5846

email: yigalhe@szmc.org.il

References

1. PROphylaxis for ThromboEmbolism in Critical Care Trial Investigators. Failure of anticoagulant thromboprophylaxis: risk factors in medical-surgical critically ill patients. *Crit Care Med* 2015; 43 (2): 401-10.
2. Vincent JL. Give your patient a fast hug (at least) once a day. *Crit Care Med* 2005; 33: 1225-9.
3. Antithrombotic therapy and prevention of thrombosis. 9th edn. ACCP guidelines. *Chest* 2012; 141 (2 Suppl): e195-325S.
4. Michota FA. Venous thromboembolism prophylaxis in the medically ill patient. *Clin Chest Med* 2003; 24: 93-101.
5. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996; 335: 701-7.
6. Palmer AJ, Koppenhagen K, Kirchhof B, Weber U, Bergemann R. Efficacy and safety of low molecular weight heparin, unfractionated heparin and warfarin for thromboembolism prophylaxis in orthopedic surgery: a meta-analysis of randomized clinical trials. *Haemostasis* 1997; 27: 75-84.
7. Geerts W, Cook D, Selby R, Etchells E. Venous thromboembolism and its prevention in critical care. *J Crit Care* 2002; 17: 95-104.
8. Mayr AJ, Dunser M, Jochberger S, et al. Antifactor Xa activity in intensive care patients receiving thromboembolic prophylaxis with standard doses of enoxaparin. *Thromb Res* 2002; 105: 201-4.
9. Levine MN, Planes A, Hirsh J, Goodyear M, Vochelle N, Gent M. The relationship between anti-factor Xa level and clinical outcome in patients receiving Enoxaparin low molecular weight heparin to prevent deep vein thrombosis after hip replacement. *Thromb Haemost* 1989; 62: 940-4.
10. Priglinger U, Delle Karth G, Geppert A, et al. Prophylactic anticoagulation with enoxaparin: Is the subcutaneous route appropriate in the critically ill? *Crit Care Med* 2003; 31 (5): 1405-9.
11. Rutherford EJ, Schooler WG, Sredzienski E, Abrams JE, Skeete DA. Optimal dose of enoxaparin in critically ill trauma and surgical patients. *J Trauma* 2005; 58 (6): 1167-70.
12. Robinson S, Zinck A, Strøm T, Larsen TB, Rasmussen B, Toft P. Enoxaparin, effective dosage for intensive care patients: double-blinded, randomised clinical trial. *Crit Care* 2010; 14 (2): R41.

13. Rommers MK, Van der Lely N, Egberts TC, van den Bemt PM. Anti-Xa activity after subcutaneous administration of dalteparin in ICU patients with and without subcutaneous oedema: a pilot study. *Lancet* 2002; 359 (9309): 849-50.
14. Dörffler-Melly J, de Jonge E, Pont AC, et al. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. *Lancet* 2002; 359 (9309): 849-50.
15. The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 2011; 364: 1305-14.
16. Robinson S, Zincuk A, Larsen UL, et al. A comparative study of varying doses of enoxaparin for thromboprophylaxis in critically ill patients: a double-blinded, randomised controlled trial. *Crit Care* 2013; 17 (2): R75.
17. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41 (2): 580-637.
18. Malinoski D1, Jafari F, Ewing T, et al. Standard prophylactic enoxaparin dosing leads to inadequate anti-Xa levels and increased deep venous thrombosis rates in critically ill trauma and surgical patients. *J Trauma* 2010; 68 (4): 874-80.