ENOXAPARIN VERSUS UNFRACTIONATED HEPARIN FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS IN CRITICALLY ILL PATIENTS: A PROPENSITY SCORE-ADJUSTED ANALYSIS

Hasan M. Al-Dorzi[1], Hani M. Tamim[2], Shmeylan A. Al Harbi[3] and Yaseen M. Arabi[1]

Abstract

Background: There is limited evidence that guides the choice between heparins for thromboprophylaxis in critically ill patients. The objective of this study was to compare enoxaparin with unfractionated heparin (UFH) as a prophylactic strategy in the intensive care unit (ICU).

Methods: This was a prospective cohort study (N=798) that evaluated the incidence of symptomatic venous thromboembolism (VTE) in a medical-trauma-surgical ICU patients (7/2006-1/2008). Thromboprophylaxis was given routinely according to established evidence-based guidelines. First, a propensity score was derived from a multinomial logistic regression model to adjust for baseline imbalances. Then Cox proportional regression analysis was used to estimate hazard ratio adjusting for the generated propensity score.

Results: Of the 798 patients in the cohort, 639 (80.0%) patients received a heparin for thromboprophylaxis: 174 patients received enoxaparin and 465 patients received UFH. There was no difference in VTE incidence during ICU stay in the two groups: 8.0% (3.1 per 1000 patient-days) for patients on enoxaparin and 7.5% (3.6 per 1000 patient-days) for those on UFH. Additionally, VTE incidence was 7.3% for patients on UFH 5000 units 12 hourly and 7.6% for those who received 5000 units 8 hourly (p=0.89). The VTE rates were similar in medical, trauma and surgical patients. Enoxaparin was associated with similar VTE risk compared with UFH (propensity score-adjusted hazard ratio, 0.95; 95% CI, 0.46-1.96). This finding was observed in medical, trauma and surgical patients.

Conclusions: In a medical-trauma-surgical ICU, the use of enoxaparin was associated with similar VTE incidence and adjusted VTE risk compared with UFH.

Keywords: Critically ill, venous thromboembolism, heparin, low-molecular weight heparin**,** prophylaxis.

1 Intensive Care Department, King Saud Bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center - Saudi Arabia.

2 Epidemiology and Biostatistics, King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center - Saudi Arabia and Department of Internal Medicine, American University of Beirut- Medical Center, Beirut-Lebanon.

Department of Internal Medicine, American University of Beirut- Medical Center, Beirut-Lebanon.

3 Pharmaceutical Care Department, King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center - Saudi Arabia.

Corresponding Author: Yaseen M. Arabi, MD, FCCP, FCCM, Intensive Care Department, King Saud Bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center. Mail code 1425, P.O. Box 22490, Riyadh, 11426, Saudi Arabia. Phone: +966(11) 8011111 Ext 18855/18877. arabi@ngha.med.sa

Introduction

Critically ill patients have multiple risk factors for venous thromboembolism (VTE)[1] leading to deep venous thrombosis (DVT) incidence that ranges between 9.6 and 33%[2-4]. The 2012 Antithrombotic Therapy and Prevention of Thrombosis 9th edition (AT9) guidelines recommended routine assessment for VTE risk and thromboprophylaxis and suggest pharmacologic prophylaxis using unfractionated heparin (UFH) or low molecular weight heparin (LMWH)[5]. The evidence clearly favors heparins over no prophylaxis to prevent DVT with a recent systematic review of seven trials involving 7,226 patients in adult medical-surgical intensive care units (ICUs) showing that a heparin (UFH or LMWH) thromboprophylaxis compared with placebo reduced the rates of DVT (pooled risk ratio, 0.51; 95% confidence interval [CI], 0.41-0.63; p< 0.0001; I^2=77%) and pulmonary embolism (PE) (risk ratio, 0.52; 95% CI, 0.28-0.97; p=0.04; I^2= 0%)[6]. The evidence that compared LMWH with UFH for thromboprophylaxis in ICU patients is less conclusive. A randomized controlled trial in major trauma patients compared LMWH with UFH and found that DVT incidence was significantly lower in the LMWH (enoxaparin) group (31% versus 44% in UFH group, p=0.01)[7]. Three subsequent randomized controlled trials in medical[8,9] and surgical[10] ICU patients compared enoxaprin (30 mg twice daily[8,9] or 40 mg once daily[10]) with UFH (5000 units twice daily) did not find difference in the incidence of all DVT. The largest multicentre randomized controlled trial to date, compared LMWH (dalteparin, 5000 units subcutaneously once daily) with UFH (5000 units twice daily) in 3764 nontrauma ICU patients and found similar proximal DVT incidence (5.1% versus 5.8%, respectively, hazard ratio [HR], 0.92; 95% CI, 0.68-1.23)[11]. The meta-analysis of these trials found that LMWH reduced rates of PE (two trials, risk ratio, 0.62 [95% CI, 0.39-1.00]; p=0.05; I^2=53%) but not DVT (four trials, risk ratio, 0.90; 95% CI, 0.74-1.08; p=0.26; I^2=0%) compared with UFH[6]. However, a more recent meta-analysis of eight randomized controlled showed LMWH compared with UFH reduced the risk of any DVT (risk ratio, 0.84, 95% CI; 0.71-0.98, p=0.03)[12].

The available evidence on LMWH versus UFH for thromboprophylaxis in ICU patients may be criticized by the fact that the trials compared LMWH with UFH given twice daily and used different LMWHs. It is believed that the anticoagulant effect of different LMWHs may not be the same[13]. Michalis et al compared tinzaparin with enoxaparin in non-ST-segment elevation acute coronary syndromes and found lower incidence of the primary end point (recurrent angina, myocardial infarction or reinfarction, or death at day 7) in the enoxaparin group (12.3% versus 21.1% in the tinzaparin group, p=0.015)[14], with sustained benefit at 6 months[15]. The American Heart Association specifies that enoxaparin is preferred to UFH in the noninvasive management of unstable angina and non-ST elevation myocardial infarction as limited data are available for the use of other LMWHs[16].

The aim of this study was to compare enoxaparin with UFH given twice or thrice daily as a VTE prophylactic strategy in a medical-surgical ICU.

Methods

Setting and patients

The ICU was a closed medical-trauma-surgical unit staffed by board-certified intensivists 24 hours per day, 7 days per week. The hospital was a 900-bed tertiary-care academic center in Riyadh, Saudi Arabia and had adapted its own evidence-based thromboprophylaxis guidelines that were based on the 2004 ACCP recommendations[17]. The treating intensivists selected the thromboprophylaxis modality after assessing VTE and bleeding risks. During the study period, the heparins available in the hospital formulary were enoxaparin and UFH.

This prospective observational cohort study was performed to determine the incidence, predictors and outcomes of VTE in critically ill patients[18]. The cohort was comprised of consecutive adult patients (age ≥18 years) admitted to the ICU of King Abdulaziz Medical City between July 2006 and January 2008 and expected to stay in the ICU for >48 hours. Patients were excluded if they had any of the following: Do-Not-Resuscitate order or brain death within 24 hours of admission, chronic anticoagulation with warfarin or heparin, admission to the ICU with acute PE or DVT

diagnosed on admission or within first 24 hours. In this study, patients who did not receive any form of heparin for DVT prophylaxis were excluded. The cohort patients were followed for the development of VTE (both DVT and PE) during ICU stay and up to 5 days after ICU discharge to the wards. Clinically suspected DVT and PE were diagnosed by Doppler compression ultrasound of the extremities and spiral computerized tomography of the chest as requested by their treating team, respectively. The study was approved by the Institutional Review Board of King Abdulaziz Medical City-Riyadh.

Data collection

The following baseline information were noted: patient's demographics including age, gender, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE) II[19], Admitting Diagnostic Category (medical, trauma and surgical [postoperative]), admission Glasgow Coma Scale (GCS) score, admission creatinine, bilirubin, lactate, platelet count, International Normalized Ratio (INR) and partial thromboplastin time and pre-defined VTE risk factors. In addition, the following data were collected on a daily basis for a period of 30 days or until discharge from the ICU to the ward or death in the ICU, whichever earlier: use of pharmacologic thromboprophylaxis (UFH or LMWH [enoxaparin]), the use of mechanical thromboprophylaxis (graduated compression stockings and intermittent pneumatic compression devices), number and location of central lines, and requirement for mechanical ventilation. The primary outcome of this study was the incidence of symptomatic VTE among critically ill patients during the ICU stay and up to 5 days after ICU discharge. The secondary outcomes were VTE prophylaxis practices, ICU and hospital mortality, ICU and hospital length of stay (LOS), and duration of mechanical ventilation.

Categorization of Patients

In this study, patients were categorized into two groups depending on what was used for pharmacologic prophylaxis. The first group included the patients who received enoxaparin and the second group those who received UFH. Patients who were switched from UFH to enoxaparin or vice versa as decided by the treating intensivist were allocated to the first group if enoxaparin use was used for >50% of thromboprophylaxis duration and to the UFH group if UFH use was for >50%.

Statistical Analysis

Statistical analysis was performed using the Statistical Analysis Software (SAS, Release 8, SAS Institute Inc., Cary, NC, 1999, USA). Baseline characteristics, clinical data and outcomes were summarized by providing the frequencies with percentages for categorical variables and means with standard deviations for continuous variables. The Chi-square test was used to assess differences among the two groups for categorical variables and Student t test for continuous variables. We calculated VTE incidence and incidence rate per 1000 patient-days in the different groups and reported the incidence rate ratio with 95% CI.

Due to the observed imbalances in baseline characteristics, a propensity score was generated using covariates related to exposure (use of UFH or LMWH) and outcome (incident VTE)[20]. Hence, the following variables were entered in the regression model: age, sex, BMI, admission category (medical, surgical and trauma), time spent in the hospital prior to enrolment in the study, admission APACHE II score, Glasgow Coma Scale (GCS) on admission, baseline glomerular filtration rate as estimated by the Modification of Diet in Renal Disease (MDRD) formula[21] (< versus ≥30 ml/hour), platelet count, INR, partial thromboplastin time, spinal cord injury, recent surgery, recent femur or pelvic fractures or knee or hip replacement, bedridden status before ICU admission, presence of malignancy, recent surgery, recent stroke, presence of central venous or hemodialysis catheter, presence of sepsis on ICU admission, and use of mechanical prophylaxis (graduated compression stockings and/ or intermittent pneumatic compression devices). A multivariate Cox proportional regression analysis was performed to compare the effect of heparin type on VTE development adjusting for the calculated propensity score. Stratified analysis was also performed according to the admission category, baseline glomerular filtration

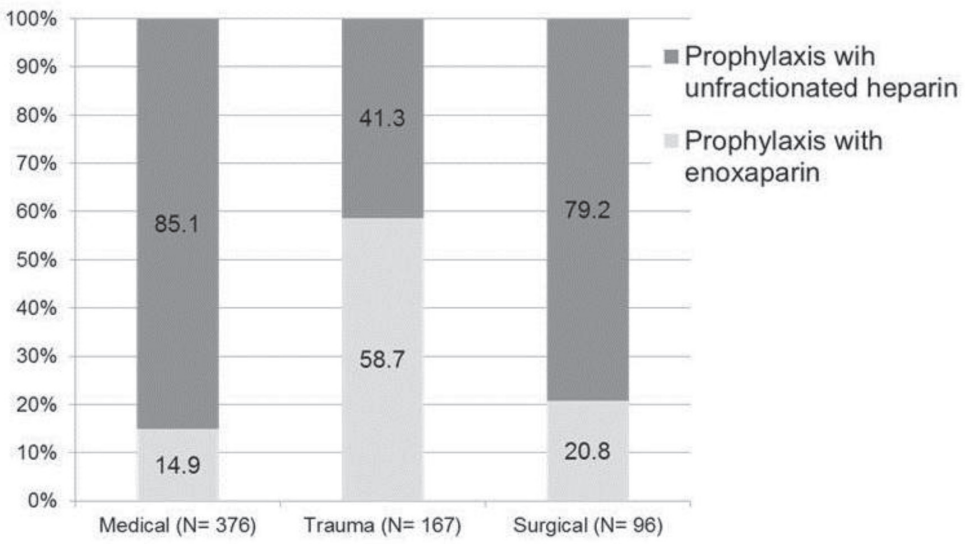

Fig. 1
The use of enoxaparin and unfractionated heparin for thromboprophylaxis in medical, trauma and surgical patients. There was a significant difference in the pattern of heparin use among the three groups (p<0.001) at the end the sentence.

rate (< versus ≥ 30 ml/hour) and the use of graduated compression stockings and of intermittent pneumatic compression devices. The results of the Cox regression analyses were presented as HR with 95% CI. P-values < 0.05 were considered statistically significant for all analyses.

Results

Patient Characteristics

The primary cohort consisted of 798 patients and 639 (80.0%) patients who received heparin for VTE prophylaxis were included in this study. Demographics, pertinent laboratory tests and VTE risk factors as presented in table 1. When adjusted for the generated propensity score, all differences between groups became non-significant UFH.. **Figure 1** describes the use of enoxaparin and UFH depending on the admission type. Most medical (85.1%) and surgical (79.2%) patients received UFH whereas most trauma (58.7%) patients received enoxaparin. For patients who received UFH, 192 (41.3%) received 5000 units 12 hourly, 250 (53.8%) patients received 5000 units 8 hourly and the rest (4.9%) received other doses. The use of mechanical prophylaxis in addition to heparin was common (50.4%). Patients on enoxaparin received mechanical prophylaxis more commonly (60.3% versus 46.7% for those receiving UFH; p=0.002).

Incidence of venous thromboembolism

VTE outcomes in the two groups are presented

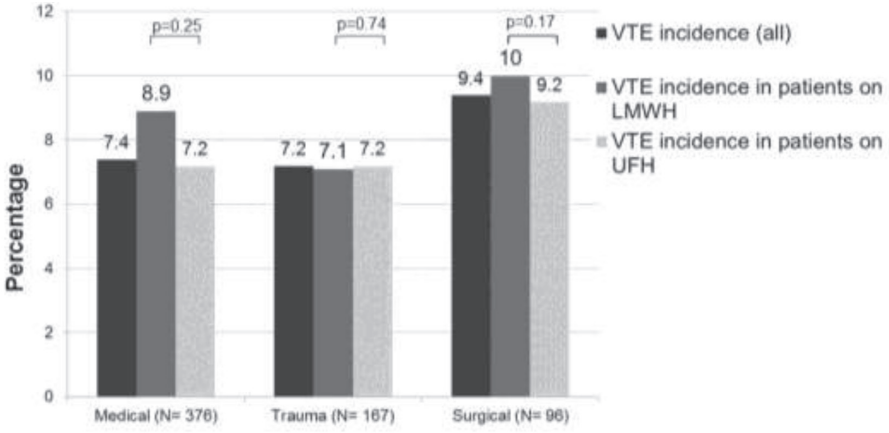

Fig. 2
Incidence of venous thromboembolism in medical, trauma and surgical patients.

Table 1

Characteristics of patients of who received phrmacologic thromboprophylaxis

Variable	Enoxaparin (N=174)	UFH (N=465)	*Crude p*-value	*Adjusted p-value*[#]
Age (years), mean ± SD	36.7 ± 18.5	54.7 ± 20.9	<0.0001	91
Age < 40 years, N (%)	109 (62.6)	124 (26.7)	<0.0001	0.73
Age ≥ 40 years, N (%)	65 (37.4)	341 (73.3)		
Female gender, N (%)	34 (19.4)	173 (37.2)	<0.0001	0.96
Body mass index (Kg/m^2), mean ± SD	27.4 ± 7.2	29.1 ± 11.7	0.04	0.99
Admitting Diagnostic Category, N (%)				
Medical	56 (32.2)	320 (68.8)		
Trauma	98 (56.3)	69 (14.8)	<0.0001	0.68
Surgical	20 (11.5)	76 (16.3)		
APACHE II score, mean ± SD	20.6 ± 7.3	24.4 ± 9.0	<0.0001	0.96
Glasgow Coma Scale score on admission, mean ± SD	7.8 ± 3.9	8.7 ± 4.2	0.01	0.98
Mechanical ventilation, N (%)	156 (89.7)	398 (85.6)	0.18	0.92
Creatinine* (µmol/dL), mean ± SD	96 ± 65	170 ± 154	<0.0001	0.5
Estimated GFR (mL/min), mean ± SD	113.7 ± 165.2	70.2 ± 68.1	0.001	0.51
Lactate* (mmol/L), mean ± SD	2.9 ± 2.5	3.0 ± 3.1	0.63	0.76
Bilirubin* (µmol/L), mean ± SD	23 ± 19	35 ± 74	0.003	0.66
INR, mean ± SD	1.2 ± 0.4	1.3 ± 0.6	0.02	0.99
PTT (seconds), mean ± SD	35.7 ± 38.1	35.6 ± 28.4	0.99	0.98
Platelet count (10^9/L), mean ± SD	252 ± 147	268 ± 157	0.26	0.99
Femur fracture N (%)	34 (19.5)	14 (3.0)	<0.0001	0.87
Sepsis, N (%)	29 (16.7)	212 (45.6)	<0.0001	0.96
Congestive heart failure, N (%)	4 (2.3)	30 (6.4)	0.04	0.84
Recent myocardial infarction, N (%)	0 (0)	7 (1.5)	0.1	0.96
Recent stroke, N (%)	6 (3.4)	78 (16.8)	<0.0001	0.97
Previous VTE, N (%)	2 (1.2)	7 (1.5)	0.73	1
Recent surgery, N (%)	81 (46.6)	112 (24.1)	<0.0001	0.93
Recent spinal cord injury, N (%)	13 (7.5)	5 (1.1)	<0.0001	0.83
Malignancy, N (%)	12 (6.9)	58 (12.5)	0.04	0.98
Bedridden Status for more 3 days before admission, N (%)	51 (29.3)	248 (53.3)	<0.0001	0.93
Central Line, N (%)	130 (74.7)	331 (71.2)	0.38	0.99
Femoral vein	74 (42.5)	191 (41.1)	0.74	0.21
Internal jugular or subclavian vein	110 (63.2)	308 (66.2)	0.48	0.29
Hemodialysis catheter, N (%)	9 (5.2)	67 (14.4)		0.42
Intermittent pneumatic compression devices, N (%)	68 (39.1)	130 (28.0)	0.007	0.98
Compression stocking devices, N (%)	53 (30.5)	108 (23.3)	0.06	0.99
Combination of intermittent pneumatic compression devices and compression stocking devices, N (%)	16 (9.2)	22 (4.7)	0.03	1
Any mechanical prophylaxis, N (%)	105 (60.3)	217 (46.7)	0.002	0.97

APACHE, Acute Physiology and Chronic Health Evaluation; GFR, glomerular filtration rate; PTT, Partial Thromboplastin Time; SD, standard deviation; VTE, venous thromboembolism

adjusted to propensity Score

* To convert creatinine to mg/dL divide by 88.4, bilirubin to mg/dL divide by 17.1, lactate to mg/dL divide by 0.111

Table 2
Outcomes of patients

	Enoxaparin (N=174)	UFH (N=465)	*Crude p*-value	*Adjusted p-value*[#]
VTE incidence, N (%)	14 (8.0)	35 (7.5)	0.83	0.73
DVT alone, N (%)	5 (2.9)	20 (4.3)	0.41	0.45
PE alone, N (%)	8 (4.6)	12 (2.6)	0.19	0.41
PE and DVT, N (%)	1 (0.6)	3 (0.65)	0.92	0.08
Hospital Mortality, N (%)	26 (15.0)	169 (36.5)	<0.0001	0.26
ICU Mortality, N (%)	11 (6.3)	95 (20.4)	<0.0001	0.31
Mechanical ventilation duration (days), mean ± SD	10.8 ± 9.3	10.6 ± 14.4	0.86	0.65
ICU LOS (days), mean ± SD	21.5 ± 52.1	16.8 ± 21.7	0.25	0.07
Hospital LOS (days), mean ± SD	99.7 ± 179.1	70.6 ± 104.9	0.046	0.16

DVT, deep vein thrombosis; ICU, intensive care unit; LOS, length of stay; PE, pulmonary embolsim; VTE, venous thromboembolism

in Table 2. Fourteen (8.0%) patients on enoxaparin and 35 (7.5%) patients on UFH developed VTE during ICU stay (p=0.89). The corresponding VTE incidence rates were 3.1 per 1000 patient-days and 3.6 per 1000 patient-days, respectively. The incidence rate ratio in the UFH compared with the LMWH group was 1.18 (95% CI, 0.64-2.19).

VTE incidences depending on the admission type (medical, trauma and surgical) as shown in figure 2. There were no significant differences in this incidence among medical, trauma and surgical patients (p=0.79). The use of either enoxaparin or UFH did not affect VTE incidence in the three admission type groups.

For patients on UFH, VTE incidence was 7.3% for the group of patients who were on 5000 units 12 hourly (incidence rate = 3.4 per 1000 patient-days) and 7.6% for those who received 5000 units 8 hourly (incidence rate = 3.6 per 1000 patient-days) (p=0.89).

Accounting for the differences between the enoxaparin and UFH groups, Cox regression analysis adjusted for the propensity score was performed and showed that LMWH was associated with similar VTE risk compared with UFH (HR, 0.95; 95% CI, 0.46-1.96). The HR for VTE was 2.1 (95% CI, 0.74-5.74) in medical patients, 0.794 (95% CI, 0.24-2.62) in trauma patients and 0.36 (95% CI, 0.05-2.64) in surgical patients.

Other outcomes

Outcomes other than VTE are also reported in Table 2. There were significant differences in ICU of hospital mortalities, which were higher in the group that received UFH for thromboprophylaxis. The hospital LOS was significantly higher in the enoxaparin group compared with the UFH group. All these differences became non-significant after adjusting for the propensity score.

Discussion

The main findings of this study were the following: symptomatic VTE was diagnosed in 7.7% of critically ill patients receiving a heparin for prophylaxis; there were no differences in VTE incidence and propensity score-adjusted VTE risk in the patients receiving enoxaparin compared with those receiving UFH for thromboprophylaxis.

The incidence of VTE in ICU patients has varied in the different studies depending on the employed

methodology and the use of thromboprophyalxis. Earlier studies found a DVT incidence ranging between 23.6%[3] and 33%[2]. More recently, the DVT incidence was 9.6% when lower extremity Doppler ultrasound was performed within 48 hours of ICU admission and then twice weekly with all patients on VTE prophylaxis (pharmacologic prophylaxis for 92.8% and mechanical for the other 7.2%)[4]. In a large multicenter trial that compared dalteparin with UFH and in which DVT was diagnosed on compression ultrasonography performed within 2 days after admission, twice weekly, and as clinically indicated, proximal DVT occurred in 5.1% versus 5.8%, respectively and PE in 1.3% and 2.3%, respectively[11]. In the current observational study VTE, was observed in 7.7% of patients with the incidence being similar in the enoxaparin and UFH groups.

The AT9 VTE prophylaxis guidelines for critically ill patients recommend using LMWH or UFH over no prophylaxis after assessing VTE and bleeding risks[5]. LMWHs and UFHs have different characteristics. The LMWHs are obtained through chemical or enzymatic depolymerization of the polysaccharide chains of UFH leading to complex mixtures of highly sulfated oligosaccharides. There are now at least eight approved originator LMWHs with their own international non-proprietary names, including enoxaparin, dalteparin, nadroparin, reviparin and tinzaparin[22]. Different depolmerization techniques are used in the manufacture of these LMWHs. For dalteparin (weight-average molecular weight= 6,000 Daltons), depolymerisation with nitrous acid leads to 2,5-anhydromannitol residue at reducing ends. For enoxaparin (weight-average molecular weight= 4,500 Daltons), beta-eliminative cleavage of benzyl ester by alkaline hydrolysis results in 2-O-sulfated uronic acid (unsaturated at the 4–5 position) at non-reducing ends[13,22]. These differences lead to diverse physicochemical characteristics and antifactor Xa and anti-thrombin activities. The antifactor Xa activity varies from 83 to 130 U/mg among the different LMWHs (105 for enoxaparin and 130 for dalteparin)[23], while the antithrombin activity varies from 27 to 58 U/mg. Therefore, the different LMWHs cannot be considered the same from biochemical point of view.

Relatively small number of studies were head-to-head comparisons of two LMWHs[14,24-26]. Some studies found similar effectiveness. Tinzaparin was equally effective as enoxaparin in VTE prophylaxis after hip surgery in one trial[24]. Enoxaparin and nadroparin with GP IIb/IIIa inhibitor therapy were found to have similar effects on the development of major cardiac events in an observational study of patients with unstable angina[25]. A non-randomised study involving over 8,000 patients reported that switching from nadroparin to enoxaparin for thromboprophylaxis after major orthopedic surgery did not compromise patient safety[27]. A Canadian study investigated the therapeutic interchange of enoxaparin to dalteparin for VTE prophylaxis in 135 patients with acute spinal cord injury and/or major orthopedic trauma and found that symptomatic VTE was reported in one patient who received enoxaparin (1.6%) and seven patients who received dalteparin (9.7%; absolute risk difference, 8.1%; 95% CI, −0.6-15.6; p=0.103)[28]. Other studies have shown differences in effectiveness. A randomized controlled trial in patients who had colorectal surgery for cancer found that patients treated with nadroparin 2850 IU/day for thromboprophylaxis had a higher incidence of asymptomatic distal DVT compared with those receiving enoxaparin 4000 IU/day[26]. Another trial in patients with non-ST-segment elevation acute coronary syndrome found lower incidence of the primary end point (recurrent angina, myocardial infarction or reinfarction, or death at day 7) in the enoxaparin group (12.3% versus 21.1% in the tinzaparin group, p=0.015)[14]. Hence, the US Food and Drug Administration, World health Organization, American College of Chest Physicians, and the American Heart Association/American College of Cardiology view each LMWH as a distinct medicinal entity[13,16]. There are no studies that compared the different LMWHs for thromboprophylaxis in critically ill patients. The PROTECT trial demonstrated no difference in proximal DVT incidence between the dalteparin and UFH groups; however, the question remains whether other LMWH, and in particular enoxaparin, is more effective than UFH. Our observational study did not show differences in VTE incidence between enoxaparin and UFH in medical, trauma and surgical patients. Additionally, higher UFH dose (5000 units 8 hourly) was not associated with lower VTE incidence than UFH (5000 units 12 hourly).

VTE acquired in the ICU may be associated with

morbidity and mortality. Patients with DVT had longer duration of mechanical ventilation, of ICU stay and of hospital stay and higher hospital mortality (56% versus 38%; p=0.04)[4]. In this study, patients who received UFH had higher mortality than those who received enoxaparin. This is likely related to the differences in the characteristics of patients as the differences became non-significant with propensity-adjusted analysis.

The findings of this study should be interpreted in the light of its strengths and limitations. Strengths include the prospective data collection. Limitations include the study observational nature and being conducted at a single center. Moreover, the study was conducted between July 2006 and January 2008. However, thromboprophylaxis options in the ICU setting remain practically the same since then. UFH and LMWH are most commonly used pharmacologic agents in the ICU setting. The few number of VTE events in this study may have led to type II error. Although we used propensity score adjustment to reduce biased estimates of treatment effect, the influence of unmeasured confounders cannot be excluded. Additionally, unlike the PROTECT trial, there were no surveillance ultrasound performed; and VTE diagnostic tests were only performed at the discretion of the treating team when clinically suspected, which may lead to under-diagnosis; however, this simulates the day-to-day ICU care as routine DVT screening is not recommended for most critically ill patients[29,30]. Moreover, the economic effect of enoxaparin versus UFH was not evaluated in the current study. A recent study found similar or lower total costs associated with the use of dalteparin than UFH[31].

In conclusion, our observational study found that enoxaparin for thromboprophylaxis was associated with similar incidence and risk of symptomatic VTE compared with UFH in medical-surgical ICU patients. Three-times daily dosing of UFH (5000 units 8 hourly) was also associated with similar VTE incidence compared with lower dosing (5000 units 12 hourly). However, conclusive answers these important questions require sufficiently powered randomized controlled trials.

Acknowledgements

Financial support: The study was sponsored in part by an unrestricted grant from Sanofi-Aventis.

Competing interests: The authors declare that they have no conflict of interest.

Author contribution

HMD: Conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, approved the final version to be published.

HMT: Statistical analysis and interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version to be published.

SAH: Data collection, interpretation of data, critical revision of the manuscript for important intellectual content, approved the final version to be published.

YMA: Conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, approved the final version to be published.

References

1. Geerts W, Cook D, Selby R, Etchells E: Venous thromboembolism and its prevention in critical care. *J Crit Care*; 2002, 17(2):95-104.
2. Hirsch DR, Ingenito EP, Goldhaber SZ: Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA*; 1995, 274(4):335-7.
3. Ibrahim EH, Iregui M, Prentice D, Sherman G, Kollef MH, Shannon W: Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. *Crit Care Med*; 2002, 30(4):771-4.
4. Cook D, Crowther M, Meade M, Rabbat C, Griffith L, Schiff D, et al: Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *Crit Care Med*; 2005, 33(7):1565-71.
5. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al: Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*; 2012, 141(2 Suppl):e195S-226S.
6. Alhazzani W, Lim W, Jaeschke RZ, Murad MH, Cade J, Cook DJ: Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med*; 2013, 41(9):2088-98.
7. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, 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(10):701-7.
8. Goldhaber SZ KD, Cusumano CJ, et al: Low molecular weight heparin versus minidose unfractionated heparin for prophylaxis against venous thromboembolism in medical intensive care unit patients: A randomized controlled trial. *J Am Coll Cardiol*; 2000, p. 325A.
9. Shorr AF, Williams MD: Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost*; 2009, 101(1):139-44.
10. De A, Roy P, Garg VK, Pandey NK: Low-molecular-weight heparin and unfractionated heparin in prophylaxis against deep vein thrombosis in critically ill patients undergoing major surgery. *Blood Coagul Fibrinolysis*; 2010, 21(1):57-61.
11. Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, et al: Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*; 2011, 364(14):1305-14.
12. Beitland S, Sandven I, Kjærvik L-K, Sandset PM, Sunde K, Eken T: Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in intensive care patients: a systematic review with meta-analysis and trial sequential analysis. *Intensive care medicine*; 2015, 41(7):1209-19.
13. Garcia DA, Baglin TP, Weitz JI, Samama MM: Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*; 2012, 141(2 Suppl):e24S-43S.
14. Michalis LK, Katsouras CS, Papamichael N, Adamides K, Naka KK, Goudevenos J, et al: Enoxaparin versus tinzaparin in non-ST-segment elevation acute coronary syndromes: the EVET trial. *Am Heart J*; 2003, 146(2):304-10.
15. Katsouras C, Michalis LK, Papamichael N, Adamides K, Naka KK, Nikas D, et al: Enoxaparin versus tinzaparin in non-ST-segment elevation acute coronary syndromes: results of the enoxaparin versus tinzaparin (EVET) trial at 6 months. *Am Heart J*; 2005, 150(3):385-91.
16. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., et al: 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*; 2013, 127(23):e663-828.
17. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al: Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*; 2004, 126(3):338S-400S.
18. Arabi YM, Khedr M, Dara SI, Dhar GS, Bhat SA, Tamim HM, et al: Intermittent Pneumatic Compression and Not Graduated Compression Stockings Are Associated with Lower Incident Venous Thromboembolism in Critically Ill Patients: A Multiple Propensity Scores Adjusted Analysis. *Chest*; 2013.
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. *Crit Care Med*; 1985, 13(10):818-29.
20. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T: Variable selection for propensity score models. *Am J Epidemiol*; 2006, 163(12):1149-56.
21. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*; 1999, 130(6):461-70.
22. Ofosu FA. A review of the two major regulatory pathways for non-proprietary low-molecular-weight heparins. *Thromb Haemost*; 2012, 107(2):201-14.
23. Jeske WP, Walenga JM, Hoppensteadt DA, Vandenberg C, Brubaker A, Adiguzel C, et al: Differentiating low-molecular-weight heparins based on chemical, biological, and pharmacologic properties: implications for the development of generic versions of low-molecular-weight heparins. *Semin Thromb Hemost*; 2008, 34(1):74-85.
24. Planes A, Samama MM, Lensing AW, Buller HR, Barre J, Vochelle N, et al: Prevention of deep vein thrombosis after hip replacement-comparison between two low-molecular heparins, tinzaparin and enoxaparin. *Thromb Haemost*; 1999, 81(1):22-5.
25. Okmen E, Ozen E, Uyarel H, Sanli A, Tartan Z, Cam N: Effects of enoxaparin and nadroparin on major cardiac events in high-risk unstable angina treated with a glycoprotein IIb/IIIa inhibitor. *Jpn Heart J*; 2003, 44(6):899-906.
26. Simonneau G, Laporte S, Mismetti P, Derlon A, Samii K, Samama CM, et al: A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. *J Thromb Haemost*; 2006, 4(8):1693-700.
27. Kistler U, Kramers-de Quervain I, Munzinger U, Kucher N: Bleeding complications after systematic switch of routine thromboprophylaxis for major orthopaedic surgery. *Thromb Haemost*; 2008, 99(6):1049-52.
28. Slavik RS, Chan E, Gorman SK, de Lemos J, Chittock D, Simons RK, et al: Dalteparin versus enoxaparin for venous thromboembolism prophylaxis in acute spinal cord injury and major orthopedic

trauma patients: 'DETECT' trial. *J Trauma*; 2007, 62(5):1075-81; discussion 81.

29. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al: Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*; 2008, 133(6 Suppl):381S-453S.
30. Sud S, Mittmann N, Cook DJ, Geerts W, Chan B, Dodek P, et al: Screening and prevention of venous thromboembolism in critically ill patients: a decision analysis and economic evaluation. *Am J Respir Crit Care Med*; 2011, 184(11):1289-98.
31. Fowler RA, Mittmann N, Geerts W, Heels-Ansdell D, Gould MK, Guyatt G, et al: Cost-effectiveness of dalteparin vs unfractionated heparin for the prevention of venous thromboembolism in critically ill patients. *Jama*; 2014, 312(20):2135-45.