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Enoxaparin may be associated with lower rates of mortality than unfractionated heparin in neurocritical and surgical patients

Sophie Samuel[1] · Catherine To[1] · Yaobin Ling[2] · Kai Zhang[2] · Xiaoqian Jiang[2] · Elmer V. Bernstam[2,3]

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Abstract
Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are often administered to prevent venous thromboembolism (VTE) in critically ill patients. However, the preferred prophylactic agent (UFH or LMWH) is not known. We compared the all-cause mortality rate in patients receiving UFH to LMWH for VTE prophylaxis. We conducted a retrospective propensity score adjusted analysis of patients admitted to neuro-critical, surgical, or medical intensive care units. Patients were included if they were screened with venous duplex ultrasonography or computed tomography angiography for detection of VTE. The primary outcome was all-cause mortality. Secondary outcomes included the prevalence of VTE, deep vein thrombosis (DVT), pulmonary embolism (PE), and hospital length of stay (LOS). Initially 2228 patients in the cohort were included for analysis, 1836 (82%) patients received UFH, and 392 (18%) patients received enoxaparin. After propensity score matching, a well-balanced cohort of 618 patients remained in the study (309 patients receiving UFH; 309 patients receiving enoxaparin). The use of UFH for VTE prophylaxis in ICU patients was associated with similar rates of all-cause mortality compared with enoxaparin [RR 0.73; 95% CI 0.43–1.24, p = 0.310]. There were no differences in the prevalence of DVT, prevalence of PE or hospital LOS between the two groups, DVT [RR 0.93; 95% CI 0.56–1.53, p = 0.889], PE [RR 1.50; 95% CI 0.78–2.90, p = 0.296] and LOS [9 ± 9 days vs 9 ± 8; p = 0.857]. A trend toward mortality benefit was observed in NICU [RR 0.37; 95% CI 0.13–1.07, p = 0.062] and surgical patients [RR 0.43; 95% CI 0.17–1.02, p = 0.075] favoring the enoxaparin group. The use of UFH for VTE prophylaxis in ICU patients was associated with similar rates of VTE, all-cause mortality and LOS compared to enoxaparin. In subgroup analysis, neuro-critical and surgical patients who received UFH had a higher rate of mortality than those who received enoxaparin.

Keywords Deep vein thrombosis · Pulmonary embolism · Mortality · Venous thromboembolism prophylaxis · Unfractionated heparin · Low molecular weight heparin

Highlights

- Venous thromboembolism remains highly prevalent in hospitalized patients, and often leads to increased mortality.
- Although many studies have been done, results of studies are imprecise with small benefits and even meta-analyses differ with respect to conclusions regarding the benefits UFH vs LMWH.
- Intensive care unit patients have a greater risk of thrombotic events due to additional risk factors such as immobilization, mechanical ventilation, and central catheters.
- In this propensity score matched analysis of patients from Medical, Surgical and Neurological ICUs, Afri-

✉ Sophie Samuel
Sophie.Samuel@memorialhermann.org

[1] Department of Pharmacy, Memorial Hermann-Texas Medical Center, 6411 Fannin Street, Houston, TX, USA

[2] School of Biomedical Informatics, The University of Texas Health Science Center at Houston, 7000 Fannin Street, Houston, TX, USA

[3] Division of General Internal Medicine, The University of Texas McGovern Medical School at Houston, 6431 Fannin Street, Houston, TX, USA

can-Americans were over-represented compared to other studies.
- In spite of multiple studies suggesting benefits of LMWH over UFH in terms of safety and possibly efficacy, 82% of our sample was given UFH and 18% LMWH showing that clinicians are not convinced of the benefit of LMWH over UFH.
- After propensity score matching, we found no differences between UFH and enoxaparin in hospital length of stay, prevention of VTE, PE or all-cause mortality.
- In subgroup analysis, neuro-critical and surgical patients who received UFH had a higher rate of mortality than those who received enoxaparin.

Introduction

The decision between UFH and LMWH for prevention of thromboembolism usually depends on the patient's renal function or risk of bleeding complications [1]. However, the difference between the clinical outcomes associated with these two agents remains unknown. Recent studies have concluded that both UFH and LMWH reduce the risk of VTE, but some studies suggest that enoxaparin might be slightly more effective and/or safer than UFH [2–4]. One meta-analysis of randomized clinical trials (RCTs) found enoxaparin to significantly reduce VTE compared to UFH with a trend toward reduced risk of mortality in hospitalized medical patients [5]. Another (network) meta-analysis of RCTs similarly found that LMWH was associated with a lower risk of DVT, but not PE or all VTE [6]. Similar results were observed in critically ill medical and stroke patients receiving enoxaparin, with small impact on mortality [7, 8]. In most studies, estimates were imprecise with very small benefits. Therefore, the American Society of Hematology 2018 guideline panel suggests using LMWH or fondaparinux rather than UFH with a low or very low certainty (recommendations 1, 2 and 3) [9]. Most studies comparing LMWH to UFH were retrospective without propensity matching performed and therefore potentially included uncontrolled biases or suffered from other substantial limitations. Our objective was to compare the all-cause mortality in critically ill patients receiving either enoxaparin or UFH subcutaneously with particular attention to neuro-critical care, a population with relatively little previous data on this topic. A secondary aim was to report the prevalence of deep vein thrombosis and pulmonary embolism. We hypothesized that unfractionated heparin for thromboprophylaxis is associated with higher in-hospital mortality compared to enoxaparin use in critically ill patients.

Methods

Patients

This is a single-center, retrospective cohort study of patients admitted from December 2014 to June 2019. We used data from the Vizient database (Vizient, Inc. Ft. Worth, TX). We included patients 18 years and older, admitted to medical, surgical, or neuro-critical intensive care units (ICUs) that had received VTE prophylaxis with either UFH or enoxaparin and who underwent diagnostic or screening venous duplex ultrasonography (VDU) of at least one extremity. Patients were also included if they underwent chest computed tomography angiography (CTA) with or without VDU. Table 1 describes the baseline characteristics of patients before and after propensity matching. We collected risk of mortality derived from Severity of Illness (SOI), and Risk of Mortality (ROM), which are proprietary outputs of the APR-DRG Grouper (3 M, St. Paul, MN). We defined VTE based on the Agency for Healthcare Research and Quality indicators (AHRQ QI™) ICD-10-CM/PCS Specification Version 6.0 criteria [10]. All perioperative PE or proximal DVT as a secondary diagnosis were included. Patients were excluded from the analysis if they had VTE upon admission, atrial fibrillation, or required therapeutic anticoagulation for a reason other than therapeutic anticoagulation for a new VTE event during admission. Pharmacological VTE prophylaxis was administered within 48 h of admission or surgery in the absence of contraindications [10]. Early mobilization was also initiated as soon as possible. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included the prevalence of DVT, PE, cause of death, and hospital length of stay. This study has been approved by the Committee for the Protection of Human Subjects (the UTHSC-H IRB) under protocol HSC-MH-19–0356.

Statistical analysis

Propensity score matching

In this cohort of 2228 patients, 1836 (82%) patients received UFH, and 392 (18%) patients received enoxaparin. Given the statistically significant differences in baseline characteristics, propensity matching was performed to control for potential confounding factors. The distributions of the patient characteristics were compared using Mann–Whitney *U* or Fisher's exact test. Propensity scores were computed by fitting a logistic regression model on the patients who had complete data. Missing

values were present in-patient type, race, risk of mortality, and mechanical ventilation. All statistical data analyses were performed using R 4.0.3 [11]. The MICE imputation packages in R were used to impute missing values to avoid removing too much data. The proportion of missing values was lower than 0.05%. The following covariates were used for balancing: age, sex, patient type (surgical, medical, stroke, trauma, mechanical ventilation, renal function, risk of mortality, duplex use, doppler extremities, CTA, central vein catheter (CVC). We used nearest neighbor matching with a 1:1 ratio and a caliper of 0.5. After matching, standardized mean differences for the covariates were close to 0, indicating adequate balance. Log link was applied for binary generalized linear model with a binomial family. For continuous outcomes, ordinary linear regression model was used, and log transformation was applied when the outcomes were skewed. A two-tailed test of statistical significance was set at $p < 0.05$.

Kaplan–Meier survival curve and cox proportional hazard model

Overall survival time was defined as the time interval from admission date to the mortality date and was censored at the last day of the hospital stay. Time to DVT and PE was defined as the time interval from admission date to the time of DVT and PE diagnosis and was censored by the last day of the hospital stay; death was treated as a competing outcome. Cox proportional hazard and cause-specific Cox models were used, and Kaplan–Meier survival curves were plotted (Figs. 2, 3, 4).

Results

Baseline patient characteristics

The database had 22,744 patients, 18 years old or older, that were admitted to three intensive care units: neuro-critical ICU, (NICU), surgical ICU (SICU), and medical ICU (MICU). Of those, 11,688 were admitted to NICU; 5251 to SICU, and 5805 to MICU. There were no screening criteria to define the indication for VDU (i.e., screening vs. diagnostic) but 20,102 patients were excluded because they did not undergo CTA or VDUs. Then 236 patients were excluded because they did not receive VTE prophylaxis during the hospitalization period. And additional 178 patients were excluded due to presence of VTE on admission. We analyzed 2228 patients including 1404 in NICU, 313 in SICU, and 511 in MICU (Fig. 1).

The baseline characteristics before and after matching are shown in Table 1. In the original cohort (Table 1), the UFH group was significantly older, with a higher proportion of male patients and patients that required mechanical ventilation. Most medical patients were on UFH compared to patients categorized under trauma or surgery (i.e., who underwent craniectomy, craniotomy, orthopedic, general surgery, spinal cord injury). Patients with $CrCl \geq 30$ mL/min were mainly on enoxaparin, but those with $CrCl \leq 30$ mL/min received UFH. The UFH group had a slightly higher overall VDU utilization compared to the enoxaparin group. VDUs included studies of all four extremities (upper + lower), lower extremities only, upper extremities only and multiple (more than once) VDU studies that were performed either for diagnostic or surveillance purposes. After propensity matching with a 1:1 ratio, 618 patients were included in the cohort for further analysis (with 136 patients in the MICU, 142 patients in the SICU, and 340 patients in the NICU) including 309 patients in the enoxaparin group and 309 patients in the UFH group (Table 2).

Mortality and prevalence of VTE

Results of the original cohort (before propensity matching)

The use of UFH for VTE prophylaxis in ICU patients was associated with higher rates of all-cause mortality compared with enoxaparin [13% in UFH vs 7% in enoxaparin; RR 0.57; 95% CI 0.39–0.83, $p = 0.001$]. Overall prevalence of VTE was 15% in UFH vs 14% in enoxaparin] [RR 0.93; 95% 0.72–1.22; $p = 0.642$]. In the original cohort, DVT was observed in 12% in UFH vs 8% in enoxaparin [RR 0.66; 95% CI 0.46–0.95, $p = 0.022$] and PE was found in 5% in UFH vs 7% in enoxaparin [RR 1.44; 95% CI 0.96–2.17, $p = 0.084$]. There was no difference in LOS in days between the two groups [10 ± 8 in UFH vs 10 ± 7; $p = 0.656$] (Table 2).

Results of the matched cohort (after propensity matching)

After performing a propensity matching with a 1:1 ratio, no difference in mortality, DVT and PE were observed between UFH and enoxaparin groups. All-cause mortality was 10% in UFH vs 7% in enoxaparin [RR 0.73; 95% CI 0.43–1.24, $p = 0.310$]. Cause of death (cardiac arrest and major bleeding events) were the same between the two groups [RR 1.00; 95% CI 0.38–2.63; $P = 1.00$]. Six percent of the study patients were transitioned to comfort care but without significant difference between the groups [RR 0.64; 95% CI 0.33–1.22; $p = 0.229$]. Overall prevalence of VTE was 12% in UFH vs 15% in enoxaparin [RR 1.28; 95% CI 0.85–1.92; $p = 0.286$]. Similarly, there were no differences in the prevalence of DVT and PE between the two groups. DVT [9% in UFH vs 9% in enoxaparin; RR 0.93;

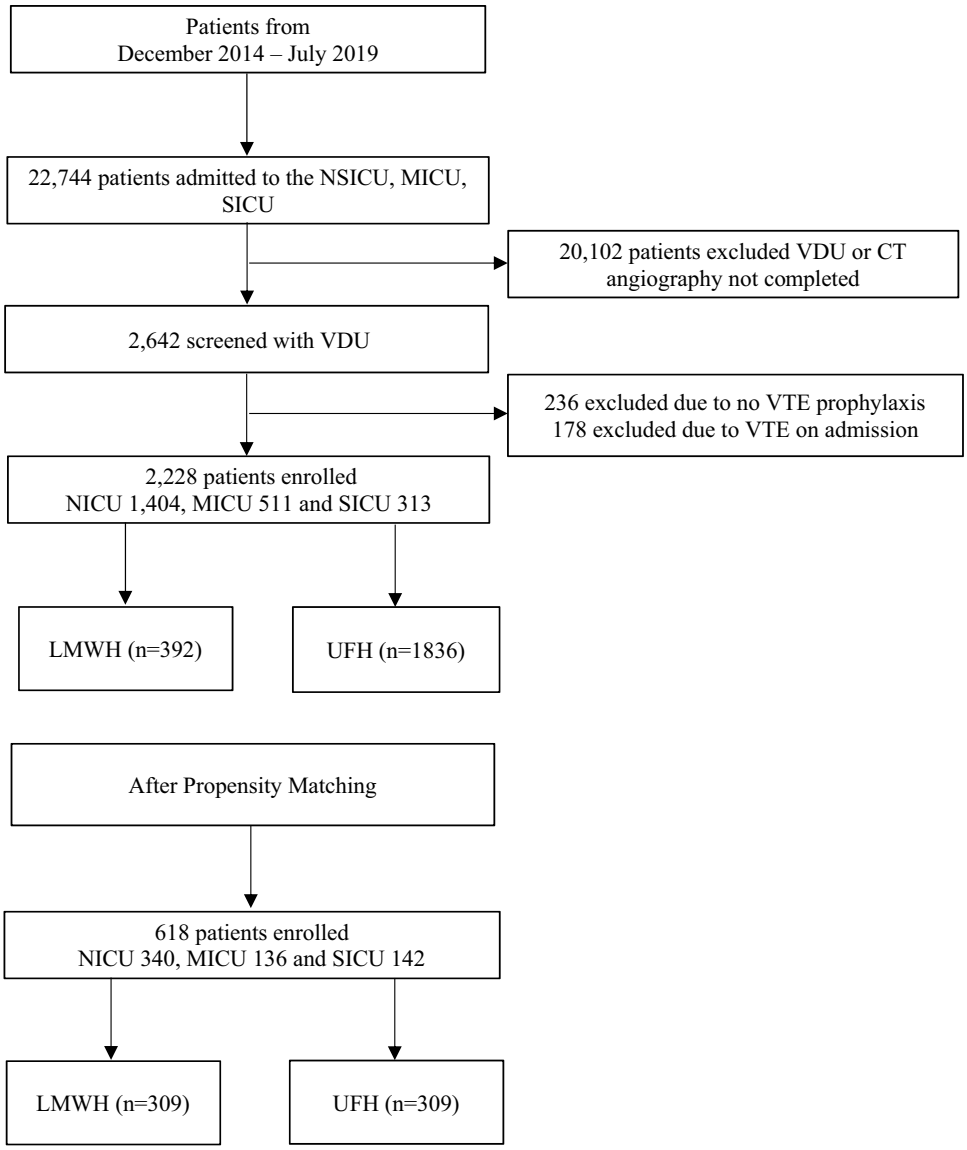

Fig. 1 Flowchart of patient selection

95% CI 0.56–1.53, p = 0.889] and PE [5% in UFH vs 7% in enoxaparin; RR 1.50; 95% CI 0.78–2.90, p = 0.296]. There was no difference in LOS in days between the two groups [9 ± 8 in UFH vs 9 ± 8 in enoxaparin; p = 0.857] (Table 2).

Subgroup analysis of the three intensive care units and by patient type

Neurocritical ICU, (NICU), surgical ICU (SICU), and medical ICU (MICU) (before propensity matching)

In NICU and SICU, a higher rate of mortality was observed in the UFH group [9% in UFH vs 3% in enoxaparin; RR 0.31; 95% CI 0.13–0.75, p = 0.003] and [18% in UFH vs 9% in enoxaparin; RR 0.52; 95% CI 0.28–0.95, p = 0.035], respectively. The DVT rate was significantly higher for UFH compared to enoxaparin in NICU patients [12% in UFH vs 5% in enoxaparin; RR 0.38; 95% CI 0.19–0.76, p = 0.002] and non-significantly higher in SICU patients [14% in UFH vs 7% in enoxaparin; RR 0.54; 95% CI 0.26–2.68, p = 0.099]. Prevalence of PE was higher in the MICU for patients who received enoxaparin during hospitalization [2% in UFH vs 7% in enoxaparin; RR 2.84 95% CI 1.06–7.62, p = 0.043] (Table 3).

Medical, surgical and trauma (before propensity matching)

Medical patients, including stroke patients without surgical intervention, had lower mortality rates with enoxaparin compared to UFH [14% in UFH vs 6% in enoxaparin; RR 0.40; 95% CI 0.21, 0.77, p = 0.003]. There was a trend toward mortality benefit in surgical patients [12% in UFH vs 7% in enoxaparin; RR 0.61; 95% CI 0.35–1.07, p = 0.090].

Table 1 Baseline characteristics before and after propensity matching

Category	Cohort before matching (n = 2228)			Cohort after matching (n = 618)		
	Enoxaparin (n = 392)	Heparin (n = 1836)	p-value	Enoxaparin (n = 309)	Heparin (n = 309)	p-value
Age	49 (20)	58 (18)	< 0.001	51 (20)	50 (19)	0.536
Gender, male	267 (68)	1061 (58)	< 0.001	203 (66)	197 (64)	0.674
Weight (kg)	86 (27)	87 (31)	0.567	86 (28)	84 (27)	0.381
Mechanical ventilation	291 (74)	1495 (81)	0.001	231 (75)	234 (76)	0.852
Patient type	–	–	< 0.001	–	–	0.556
All surgery	192 (49)	877 (48)	–	182 (59)	170 (55)	–
Medical	84 (21)	835 (46)	–	88 (28)	100 (32)	–
Trauma	106 (27)	64 (4)	–	39 (13)	39 (13)	–
Risk of mortality	–	–	< 0.001	–	–	0.930
Minor	21 (5)	56 (3)	–	15 (5)	16 (5)	–
Moderate	44 (11)	126 (7)	–	36 (12)	36 (12)	–
Severe	105 (27)	361 (20)	–	81 (26)	74 (24)	–
Extreme	221 (56)	1293 (70)		177 (57)	183 (59)	–
Renal function	–	–	< 0.001	–	–	1.000
CrCl > 30 mL/min	367 (94)	1414 (77)	–	286 (93)	287 (93)	–
CrCl < 30 mL/min or dialysis	25 (6)	422 (23)	–	23 (7)	22 (7)	–
CVC	11 (3)	129 (7)	0.003	10 (3)	10 (3)	1.000
Doppler type	–	–	< 0.001	–	–	0.985
All extremity	61 (16)	643 (35)	–	60 (19)	61 (20)	–
Lower extremity	110 (28)	396 (22)	–	88 (28)	83 (27)	–
Upper extremity	52 (13)	401 (22)	–	39 (13)	42 (13)	–
Multiple dopplers	49 (13)	229 (13)	–	46 (15)	44 (14)	–
Not done	120 (31)	167 (9)	–	76 (25)	79 (26)	–
PE-CTA	184 (47)	562 (31)	< 0.001	128 (41)	136 (44)	0.569
Doppler indication	–	–	< 0.001	–	–	0.883
Surveillance	167 (43)	890 (49)	–	135 (44)	141 (46)	–
Diagnostic	127 (32)	775 (42)	–	116 (38)	111 (36)	–
Neither	98 (25)	171 (9)	–	58 (19)	57 (18)	–

Results are presented as n, (%) or mean, (SD) where appropriate

VTE venous thromboembolism, *CVC* central venous catheter, *PE* pulmonary embolism, *CTA* computed tomography angiography, *Crcl* creatinine clearance, *Kg* kilogram

Fewer DVTs occurred in surgical patients receiving enoxaparin [12% in UFH vs 5% in enoxaparin; RR 0.42; 95% CI 0.22–0.81, p = 0.004]. However, there were more pulmonary emboli in surgery patients who received enoxaparin compared to UFH [4% in UFH vs 8% in enoxaparin; RR 1.86 95% CI 1.05–3.29, p = 0.040 (Table 3).

NICU, MICU and SICU (after propensity matching)

After propensity matching, differences in the prevalence of DVT and PE disappeared for all three ICUs. However, a trend toward higher mortality rate was observed in NICU patients receiving UFH [8% in UFH vs 3% in enoxaparin; RR 0.37; 95% CI 0.13–1.07, p = 0.062] (Table 3).

Medical, surgical and trauma (after propensity matching)

All patient types had similar rates of DVT and PE after propensity matching. Similar to the NICU, a trend towards higher rate of mortality was present in surgical patients receiving UFH [9% in UFH vs 4% in enoxaparin; RR 0.43; 95% CI 0.17–1.02, p = 0.075] (Table 3).

Kaplan Meier survival curves and Cox proportional hazard model

Additional analysis was performed to assess the impact of UFH and enoxaparin for VTE prophylaxis on mortality. We plotted Kaplan–Meier survival curves for mortality, DVT and PE to show the survival rate in the matched and

Table 2 Primary and secondary outcomes before and after propensity matching

Category	Cohort before matching (n = 2228)				Cohort after matching (n = 618)			
	Enoxaparin (n = 392)	Heparin (n = 1836)	RR (95% CI)	p-value	Enoxaparin (n = 309)	Heparin (n = 309)	RR (95% CI)	p-value
Primary outcome								
All-cause mortality	28 (7)	231 (13)	0.57 (0.39–0.83)	0.001	22 (7)	30 (10)	0.85 (0.67–1.09)	0.310
Secondary outcomes								
Comfort care	18 (5)	176 (10)	0.48 (0.30–0.77)	0.001	14 (5)	22 (7)	0.64 (0.33–1.22)	0.229
Other[a]	10 (3)	55 (3)	0.83 (0.43–1.61)	0.743	8 (3)	8 (3)	1.0 (0.38–2.63)	1.000
Prevalence of VTE	56 (14)	281 (15)	0.98 (0.93–1.03)	0.642	46 (15)	36 (12)	1.16 (0.90–1.50)	0.286
Prevalence of PE	28 (7)	91 (5)	1.08 (0.97–1.20)	0.084	21 (7)	14 (4)	1.26 (0.83–1.91)	0.296
Prevalence of DVT	31 (8)	220 (12)	0.93 (0.88–0.98)	0.022	27 (9)	29 (9)	0.96 (0.74–1.26)	0.889
Length of stay	9.8 (7)	9.6 (8)	–	0.656	9.3 (9)	9.4 (8)	–	0.857

Results are presented as n, (%) or mean, (SD) where appropriate

VTE venous thromboembolism, *PE* pulmonary embolism, *DVT* deep vein thrombosis

[a]Other causes of death include cardiac arrest, and hemorrhagic causes

unmatched cohorts over time. The outcomes for the original and matched cohorts are presented in Figs. 2, 3 and 4.

Discussion

In this propensity matched analysis of critically ill patients, mortality, the prevalence of DVT, prevalence of PE, hospital length of stay and all-cause mortality were similar in patients that received unfractionated heparin or enoxaparin for VTE prophylaxis. Notably, most patients in our study (82%) received UFH. We further evaluated the potential benefit of enoxaparin in subgroup analyses after propensity matching and found that patients in the neuro-critical ICU [8% in UFH vs 3% in enoxaparin; RR 0.37; 95% CI 0.13–1.07, p = 0.062] and those who had surgery [9% in UFH vs 4% in enoxaparin; RR 0.43; 95% CI 0.17–1.02, p = 0.075] may benefit from enoxaparin.

Strengths of our study include a relatively large sample. This allowed us to effectively perform propensity matching on multiple variables to minimize confounding factors. Our study was performed at a level I trauma center and comprehensive stroke center consisting of a variety of critically ill patient populations from three different ICUs and enrolled a wide variety of patients from medical, stroke (ischemic and hemorrhagic), general surgery, neurosurgery and trauma services. We were able to include a large number of patients in the NICU, which is a patient population not well studied. Propensity matching was performed to control for potential confounding factors. We evaluated outcomes in subgroups based on ICU location, comorbidities (including renal insufficiency) and patient type. This study reflects real-world experience and diverse population with respect to race as most previous studies included mainly white patients [5, 8]. Our study included mixed patient population where African Americans (20%) were relatively over-represented compared to the national average [12].

Our study has several important limitations. First, this is a single-center retrospective observational study with a potential risk for bias. As seen in Table 1, the original cohort had significant baseline differences. To account for these differences, we chose to perform a 1:1 propensity matching ratio to minimize bias compared to 1:n which would have generated a larger sample size but may also have increased bias and the potential for overestimating the effects [13]. As is the case with any statistical analysis, we cannot exclude the possibility that unmeasured or excluded characteristics could have altered the results. Another potential source of bias is the large number of patients that were excluded due to the absence of VDU. Although we could not distinguish screening from diagnostic VDU, screening VDU may have been common compared to future cohorts because the clinical benefit of screening VDU has recently been questioned [1, 14]. Lastly, we did not evaluate for bleeding complications in both agents. However, prior studies found both agents to be safe [1, 5, 14].

Laporte et al. reported on an individual patient-level meta-analysis comparing to UFH for VTE prophylaxis in medical patients of four randomized controlled trials [5]. Two of the studies specifically included stroke patients and two were double-blinded studies [4, 15–17]. The median age was 71 years, 49% female, 17.5% were classified as obese, and 31% had renal insufficiency defined as creatinine clearance < 50 mL/min. Overall, baseline characteristics were similar. The results from the study demonstrate that rates of

Table 3 Outcomes for subgroups by ICU location and patient type

Category	Cohort before matching (n = 2228)				Cohort after matching (n = 618)			
	Enoxaparin (n = 392)	Heparin (n = 1836)	RR (95% CI)	p-value	Enoxaparin (n = 309)	Heparin (n = 309)	RR (95% CI)	p-value
Location								
MICU	n = 89	n = 422	–		n = 75	n = 61	–	
Mortality	10 (11)	79 (19)	0.60 (0.32–1.11)	0.123	8 (11)	6 (10)	1.08 (0.40–2.96)	1.000
PE	6 (7)	10 (2)	2.84 (1.06–7.62)	0.043	4 (5)	2 (3)	1.62 (0.31–8.58)	0.691
DVT	13 (15)	40 (9)	1.54 (0.86–2.76)	0.179	11 (15)	4 (7)	2.24 (0.75–6.67)	0.173
SICU	n = 137	n = 176	–		n = 96	n = 46	–	
Mortality	13 (9)	32 (18)	0.52 (0.29–0.96)	0.035	10 (10)	8 (17)	0.60 (0.25–1.42)	0.284
PE	13 (9)	13 (7)	1.28 (0.62–2.68)	0.540	11 (11)	4 (9)	1.32 (0.44–3.92)	0.774
DVT	10 (7)	24 (14)	0.54 (0.26–2.68)	0.099	8 (8)	5 (11)	0.77 (0.27–2.21)	0.757
NICU	n = 166	n = 1238	–		n = 138	n = 202	–	
Mortality	5 (3)	120 (10)	0.31 (0.13–0.75)	0.003	4 (3)	16 (8)	0.37 (0.13–1.07)	0.062
PE	9 (5)	68 (5)	0.99 (0.50–1.94)	1.000	6 (4)	8 (4)	1.10 (0.39–3.09)	1.000
DVT	8 (5)	156 (13)	0.38 (0.19–0.76)	0.002	8 (6)	20 (10)	0.58 (0.27–1.29)	0.229
Patient type								
Medical	n = 84	n = 835	–		n = 84	n = 94	–	
Mortality	11 (13)	146 (17)	0.74 (0.42–1.32)	0.363	11 (13)	11 (12)	1.12 (0.51–2.45)	0.822
PE	4 (5)	28 (3)	1.42 (0.51–3.95)	1.000	4 (5)	3 (3)	1.49 (0.34–6.47)	0.709
DVT	9 (11)	95 (11)	0.94 (0.49–1.80)	0.688	9 (11)	7 (7)	1.44 (0.56–3.69)	0.601
All surgery	n = 192	n = 877	–		n = 177	n = 162	–	
Mortality	7 (4)	70 (8)	0.45 (0.21–0.98)	0.043	7 (4)	15 (9)	0.43 (0.17–1.02)	0.075
PE	14 (7)	54 (6)	1.18 (0.67–2.09)	0.518	13 (7)	7 (4)	1.70 (0.70–4.15)	0.259
DVT	17 (9)	116 (13)	0.67 (0.41–1.09)	0.116	16 (9)	18 (11)	0.81 (0.43–1.54)	0.589
Trauma	n = 106	n = 64	–		n = 39	n = 37	–	
Mortality	10 (9)	7 (11)	0.86 (0.35–2.15)	0.795	4 (10)	3 (8)	1.26 (0.30–5.27)	1.000
PE	10 (9)	7 (11)	0.86 (0.35–2.15)	0.795	4 (10)	4 (11)	0.95 (0.26–3.52)	1.000
DVT	5 (5)	6 (9)	0.50 (0.16–1.58)	0.335	2 (5)	4 (11)	0.47 (0.09–2.44)	0.425

Results are presented as n, (%) or mean, (SD) where appropriate

ICU intensive care unit, *VTE* venous thromboembolism, *PE* pulmonary embolism, *DVT* deep vein thrombosis

mortality were similar between the two groups with RR 0.83 favoring the enoxaparin group. Although after propensity matching, our study population had similar baseline characteristics, the average age for our cohort was 51 years in both groups, which was younger than the Laporte study. Prior to propensity matching, our population was mostly male, perhaps due to the inclusion of trauma patients who tend to be disproportionately male, and a majority had creatinine clearance ≥ 30 mL/min, 30% were medical patients, and included neuroscience ICU. Laporte et al., reported a mortality benefit and lower VTE rate associated with LMHW compared to UFH. In contrast, we found no difference in the prevalence of VTE.

A meta-analysis comparing UFH and LMWH thromboprophylaxis in medical-surgical critically ill patients, there were four randomized trials with 6,165 patients included in the analysis. LMWH was found to reduce rates of PE (RR 0.62; 95% CI 0.39–1.0; p = 0.05) compared to UFH. LMWH did not reduce DVT (RR 0.90, 95% CI 0.74–1.08; p = 0.26) or mortality (RR 0.93; 95% CI 0.82–1.04; p = 0.20) when compared to UFH [18–22]. A more recent network meta-analysis of 13 randomized-controlled trials with a total of 9619 patients found that LMWH was associated with a lower risk of DVT (OR 0.72, 95% CI 0.46–0.98) and heparin-induced thrombocytopenia (OR 0.38, 95% CI 0.15–0.98) but found no significant differences between the two agents with respect to incidence of major bleeding, PE or any VTE; data were insufficient to draw conclusions for other outcomes such as mortality [6]. In a retrospective study, Jacobs et al. used data from the trauma registry in Michigan and included a total of 18,010 patients with 7786 UFH patients and 10,224 enoxaparin patients. This study found that patients administered enoxaparin had a decreased risk of mortality compared with UFH (OR 0.64; 95% CI 0.49–0.83). Patients administered enoxaparin also had a decreased risk in VTE (OR 0.67; 95% CI 0.53–0.84), PE (OR 0.53; 95% CI 0.35–0.79), and

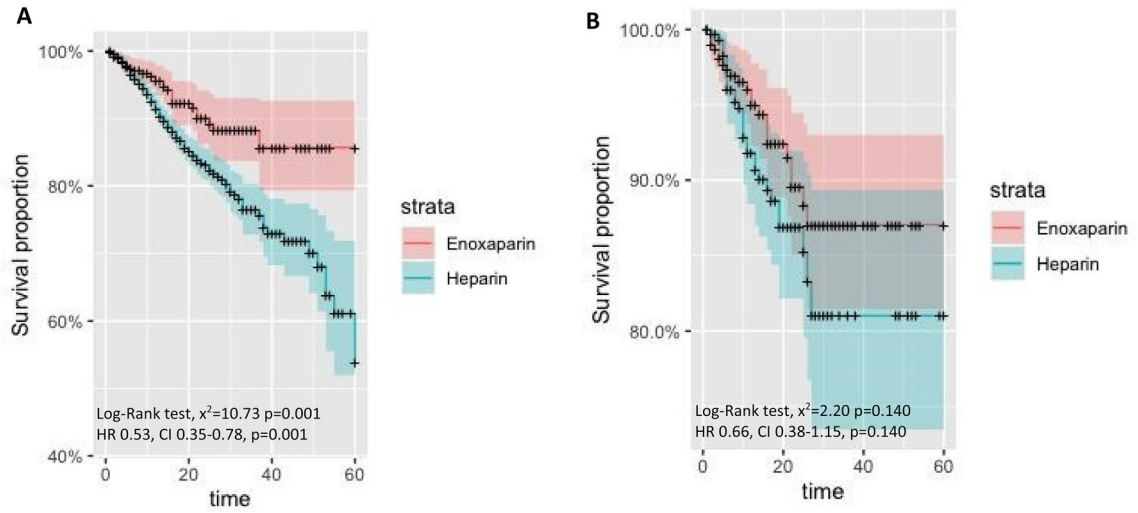

Fig. 2 Kaplan Meier survival curves for primary outcome of all-cause mortality between patients receiving enoxaparin (red) or heparin (blue). **A** Significant difference in increased survival with the enoxaparin group before matching, [HR 0.53, CI 0.35–0.78, P = 0.001] **B** There was no significant difference after matching, [HR 0.66, CI 0.38–1.15, p = 0.140]

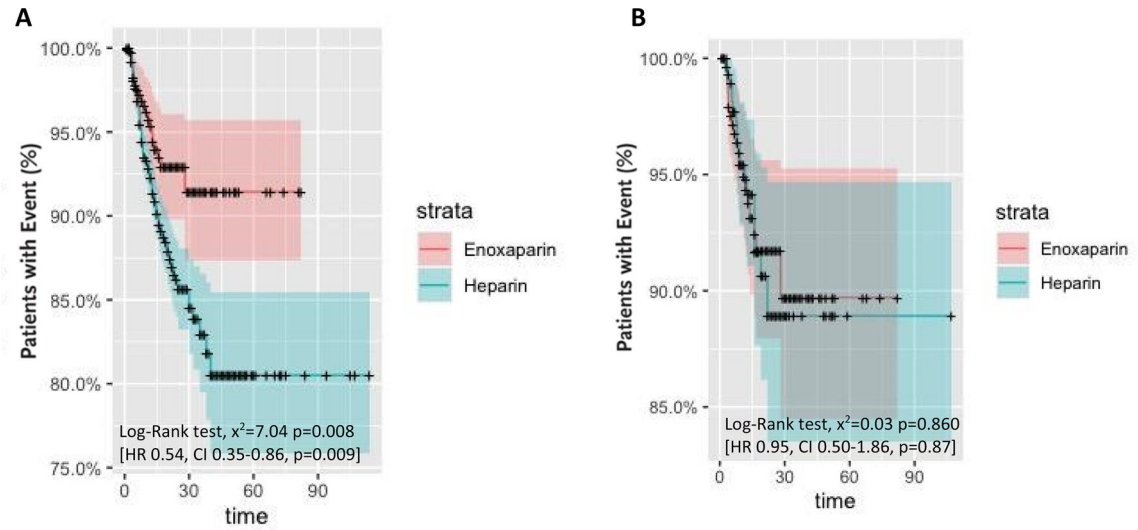

Fig. 3 Prevalence of DVT between patients receiving enoxaparin (red) compared to heparin (blue). **A** There was significant difference in prevalence of DVT before matching [HR 0.54, CI 0.35–0.86, p = 0.009] and **B** There was no significant difference after matching [HR 0.95, CI 0.50–1.86, p = 0.87]

DVT (OR 0.73; 95% CI 0.57–0.95) compared to UFH [18]. Alternatively, other studies had found no difference between the two agents [2–4, 23].

Surveillance duplex may lead to therapeutic anticoagulation for asymptomatic DVTs that may not be clinically significant at the cost of increased bleeding risk. Thus, the role of screening duplex or an optimal screening strategy also remains unclear. Future studies could consider to evaluate the benefit of VTE prophylaxis mainly in those with symptomatic presentation.

Lastly, our study evaluated patients before the COVID -19 pandemic, and our results did not show a difference. A recent study reported a lower 28-day mortality in patients receiving LMWH compared to UFH after controlling for potential confounders in patients with COVID. Although this was a retrospective study, it encourages prospective studies to investigate whether the findings change with COVID-19 patients [24]. Additionally, studies could assess the case-fatality rate for the use of UFH compared to enoxaparin for VTE prophylaxis in critically ill patients.

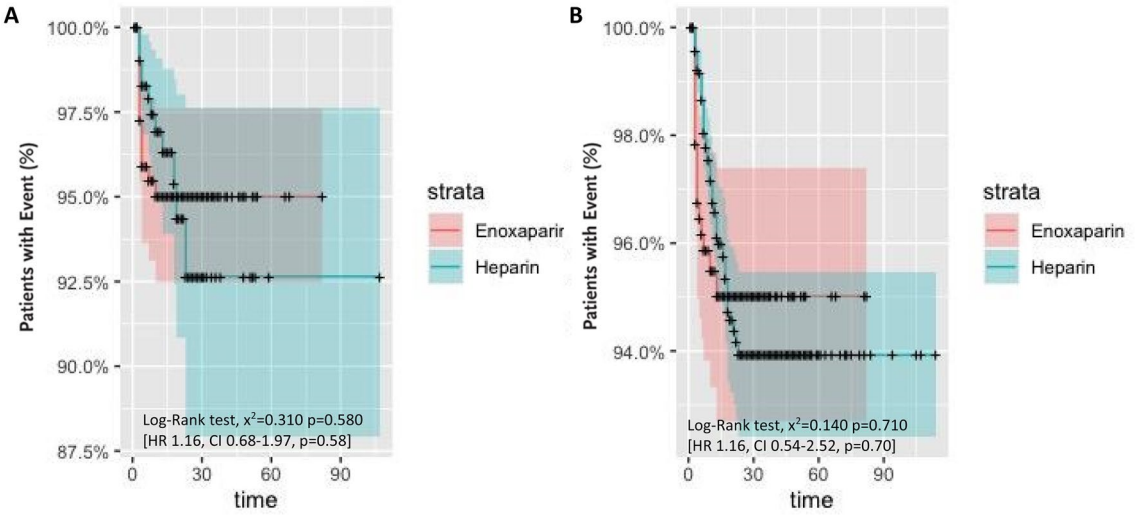

Fig. 4 Prevalence of PE between patients receiving enoxaparin (red) compared to heparin (blue). **A** There was no significant difference in PE before matching [HR 1.16, CI 0.68–1.97, p = 0.58] and **B** after matching [HR 1.16, CI 0.54–2.52, p = 0.70]

Conclusions

There is no significant difference in mortality in critically ill patients who received UFH vs. enoxaparin for VTE prophylaxis. In subgroup analysis, neurocritical unit and patients with surgical intervention had a higher rate of mortality in those who received UFH. Prospective analysis comparing the effectiveness and safety of enoxaparin and UFH in neurological and surgical intensive care units may be warranted.

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Declarations

Conflict of interest Sophie Samuel, Catherine To, Kai Zhang, Xiaoqian Jiang and Elmer Bernstam, declare that they have no conflict of interest.

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