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Weight-based enoxaparin thromboprophylaxis in young trauma patients: analysis of the CLOTT-1 registry

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ABSTRACT

Introduction Optimal venous thromboembolism (VTE) enoxaparin prophylaxis dosing remains elusive. Weight-based (WB) dosing safely increases anti-factor Xa levels without the need for routine monitoring but it is unclear if it leads to lower VTE risk. We hypothesized that WB dosing would decrease VTE risk compared with standard fixed dosing (SFD).

Methods Patients from the prospective, observational CLOTT-1 registry receiving prophylactic enoxaparin (n=5539) were categorized as WB (0.45–0.55 mg/kg two times per day) or SFD (30 mg two times per day, 40 mg once a day). Multivariate logistic regression was used to generate a predicted probability of VTE for WB and SFD patients.

Results Of 4360 patients analyzed, 1065 (24.4%) were WB and 3295 (75.6%) were SFD. WB patients were younger, female, more severely injured, and underwent major operation or major venous repair at a higher rate than individuals in the SFD group. Obesity was more common among the SFD group. Unadjusted VTE rates were comparable (WB 3.1% vs. SFD 3.9%; p=0.221). Early prophylaxis was associated with lower VTE rate (1.4% vs. 5.0%; p=0.001) and deep vein thrombosis (0.9% vs. 4.4%; p<0.001), but not pulmonary embolism (0.7% vs. 1.4%; p=0.259). After adjustment, VTE incidence did not differ by dosing strategy (adjusted OR (aOR) 0.75, 95% CI 0.38 to 1.48); however, early administration was associated with a significant reduction in VTE (aOR 0.47, 95% CI 0.30 to 0.74).

Conclusion In young trauma patients, WB prophylaxis is not associated with reduced VTE rate when compared with SFD. The timing of the initiation of chemoprophylaxis may be more important than the dosing strategy. Further studies need to evaluate these findings across a wider age and comorbidity spectrum.

Level of evidence Level IV, therapeutic/care management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Three commonly used dosing strategies exist for the use of low-molecular weight heparin (LMWH) in the trauma population: (1) fixed standard dose, (2) weight-based dosing, and (3) anti-Xa-guided dosing. Numerous prospective observational and several systematic meta-analyses of the existing literature have failed to definitively establish the superiority of a particular dosing strategy.

WHAT THIS STUDY ADDS

⇒ In young otherwise healthy trauma patients with at least one risk factor for venous thromboembolism (VTE), weight-based dosing of LMWH is not superior to a standard fixed-dose strategy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Weight-based dosing of LMWH alone is not an appropriate strategy for improving VTE prevention in at-risk trauma patients. Future research should focus on evaluating the efficacy of anti-Xa-guided dosing as an alternative to weight-based administration.

BACKGROUND

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially lethal complication after injury. Endothelial dysfunction resulting from trauma-induced local and systemic inflammatory signals significantly increases the risk of DVT and PE, even in baseline healthy individuals. Risk can be reduced through the use of mechanical and chemical VTE prophylaxis. A 2013 Cochrane database meta-analysis estimated the rate of DVT and PE in trauma patients receiving no prophylaxis at 8.7% and 3.3%, respectively. VTE prophylaxis of any kind (chemical, mechanical, or both) was associated with a significant reduction in DVT (relative risk [RR] 0.52, 95% confidence interval [CI] 0.32-0.84), but not PE.[1] The authors also reported that chemoprophylaxis was more effective than mechanical prophylaxis in reducing overall DVT risk (RR 0.48, 95% CI 0.25-0.95).

Enoxaparin is the preferred agent for chemoprophylaxis in severely injured patients without contraindications for low-molecular weight

heparin (LMWH); however, controversy remains regarding optimal dosing strategies.[2–4] Early administration of LMWH has been associated with lower rates of DVT, PE, and in-hospital mortality when compared with unfractionated heparin (UH).[5–7] These studies typically used one of two fixed dosing regimens: 40 mg daily (once a day) or 30 mg every 12 hours (two times per day).[5 8] Recent recognition that these regimens may not achieve adequate biochemical prophylaxis, as measured by anti-Xa activity level,[9 10] has increased the support for alternative dosing strategies.[3] Obesity has been identified as a possible risk factor for subtherapeutic prophylaxis, leading to the adoption of weight-adjusted dosing schemes.[10 11] Weight-adjusted enoxaparin prophylaxis is clearly linked to increased anti-Xa activity.[12–14] Despite evidence that patients with higher anti-Xa levels have reduced rates of VTE, a large meta-analysis of 24 studies was unable to correlate any type of dosing adjustment aimed at achieving target anti-Xa levels with a reduction in VTE incidence.[14] Additionally, a recent systematic review of 45 studies evaluating the effect of standard fixed-dose and weight-based (WB) chemoprophylaxis regimens on anti-Xa levels and VTE rates in obese trauma and surgical patients was unable to establish the superiority of a particular dosing strategy.[15]

In 2020, the Western Trauma Association (WTA) published updated guidelines for the selection of VTE prophylaxis in trauma patients, advocating for empirical higher doses of LMWH (40 mg two times per day) for young otherwise healthy patients without brain or spinal cord injury.[3] The authors also support the use of WB dosing strategies for the initial dosing of LMWH in patients greater than 100 kg. However, much of the cited literature for this topic relied on anti-Xa targets as a surrogate for VTE risk and did not correlate higher LMWH dosing or adjustment strategies with a reduction in VTE incidence.[11 13 16–18]

At present, it remains unclear whether WB dosing of enoxaparin, when compared with standard fixed dosing (SFD) strategies, reduces post-traumatic VTE in at-risk individuals. Early initiation of prophylaxis has consistently been shown to reduce the incidence of VTE events,[19 20] whereas recent studies have questioned whether delayed dose adjustment effectively reduces risk.[14] Anti-Xa-guided dosing requires numerous doses and laboratory draws over several days, a period during which VTE may have already occurred. Whether an initial WB dosing strategy is superior to SFD dosing has yet to be directly evaluated.

We performed a secondary analysis of the Comparative Effectiveness Analysis of Venous Thromboembolism in Trauma Patients, phase 1 (CLOTT-1) data, a large prospective multicenter study, to evaluate the effectiveness of WB enoxaparin compared with SFD enoxaparin for initial post-traumatic VTE prophylaxis. CLOTT-1 is an observational, multicenter study originally designed to describe and evaluate the clinical spectrum of DVT and PE in a young trauma population. We hypothesized that early initiation of WB dosing would be associated with a decreased risk of VTE when compared with patients receiving SFD enoxaparin prophylaxis.

METHODS

CLOTT-1 population

CLOTT-1 was a multicenter, prospective, observational study of VTE after trauma. Trauma patients admitted to one of 17 participating American College of Surgeons Level 1 trauma centers between January 1, 2018 and December 31, 2020 were screened for enrollment. Inclusion criteria included ages 18–40 years, hospital length of stay (HLOS) ≥48 hours, and at least one post-traumatic risk factor for VTE, resulting in a final cohort of 7903 patients.[21] Patient events and outcomes were recorded until discharge or for up to 30 days from admission.

Patient demographics and risk factors, height and weight, admission vitals, injury characteristics, laboratory values, measures of clinical care, and final disposition were extracted from the electronic medical record by participating sites and housed in the electronic data collection tool REDCap (Research Electronic Data Capture). Twelve post-traumatic risk factors for VTE were defined a priori: major head, chest or abdominal (Abbreviated Injury Scale (AIS) score ≥3) injury; spinal cord injury; pelvic fracture; lower extremity long bone fracture; major venous injury requiring repair; major operative procedure ≥1 hour and requiring general anesthesia; systolic blood pressure <90 mm Hg; mechanical ventilation ≥4 days; femoral venous catheter; and presence of central line.

The type, dose, and date of initiation of pharmacological VTE prophylaxis were extracted, along with dosing changes and missed doses. The data collection tool required that medication type and dosing for VTE prophylaxis was reported separately from medications and dosing intended for therapeutic anticoagulation. Any modification in dosing strategy (ie, agent, dose, etc) was captured along with the time, date, and the reason for the change. Some patients had multiple dosing changes during their hospital course; however, for this analysis the exposure to a dosing modification was simplified to a binary variable (ie, any change vs. no changes). The total number of missed doses of pharmacological prophylaxis was recorded for each patient. Each missed dose was also recorded individually, along with a time and date of the missed medication and the reported justification for holding the dose (eg, patient refusal).

Research by the CLOTT study group is supported by a grant from the Defense Medical Research and Development Program and managed by the National Trauma Institute and the Coalition for National Trauma Research.

Study population and definitions

Patients from the CLOTT-1 registry receiving prophylactic enoxaparin during their hospital stay were identified (n=5539). Those with inferior vena cava filter present at the time of admission or placed during the hospital course, HLOS <3 days, or non-survivable injuries (defined as Injury Severity Score (ISS) of 75 or regional AIS score of 6) were excluded (figure 1). Observations with missing values for height or weight were also excluded due to inability to calculate patient body mass index (BMI). The lower and upper limits for BMI were set at 12 and 200 kg/m^2, respectively. Patients were considered obese if BMI was ≥30 kg/m^2.

Prophylactic dosing strategy was classified post hoc as either WB (0.45–0.55 mg/kg two times per day) or standard (SFD; 30 mg two times per day or 40 mg once a day), based on the first received dose of VTE prophylaxis. Patients weighing between 50 and 70 kg who received enoxaparin 30 mg two times per day were assigned to WB because this is the appropriate WB dose for this weight range. Patients with non-standard, non-WB dosing were censored. Early prophylaxis was defined as receipt of first dose of VTE chemoprophylaxis within 24 hours of hospital admission.

Statistical analysis

The primary outcome was incidence of VTE. The secondary outcomes of interest were incidence of DVT and PE, and rates of in-hospital complications attributable to chemoprophylaxis, including worsening of intracranial hemorrhage, solid organ

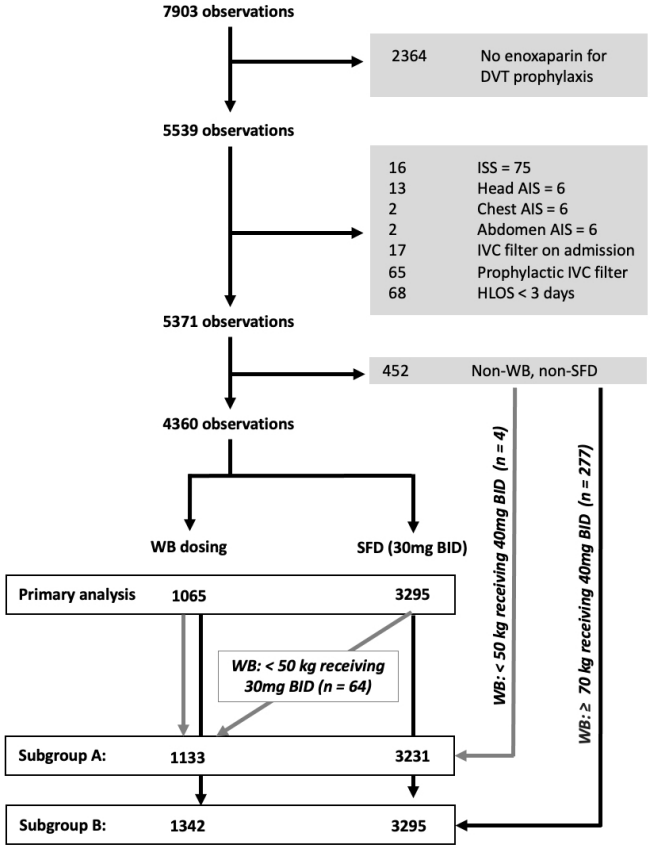

Figure 1 Study flow diagram. AIS, Abbreviated Injury Scale; BID, two times per day; DVT, deep vein thrombosis; HLOS, hospital length of stay; ISS, Injury Severity Score; IVC, inferior vena cava; SFD, standard fixed dosing; WB, weight based.

Table 1 Patient demographics and VTE risk factors

	Weight based (n=1065)	Standard (n=3295)	P value
Age (years; mean, SD)	28 (7)	29 (6)	<0.001
Female*	35.7%	23.8%	<0.001
Race/ethnicity*			0.008
Caucasian	40.5%	45.1%	
African American	32.2%	31.2%	
Latinx	17.4%	13.6%	
Other	9.9%	10.1%	
Obesity (BMI≥30 kg/m^2)	3.4%	30.4%	<0.001
Medical history*			
VTE	0.9%	0.7%	0.687†
Cancer	0.1%	0.3%	0.468†
Blunt mechanism*	74.6%	75.7%	0.436
ISS (mean, SD)	18 (11)	17 (11)	0.002
VTE risk factors			
Head AIS≥3	27.0%	23.5%	0.020
Chest AIS≥3	32.4%	30.8%	0.321
Abdomen AIS≥3	24.1%	21.8%	0.111
Spinal cord injury	4.3%	3.7%	0.339
Pelvic fracture	21.4%	20.2%	0.413
Lower extremity long bone fracture	35.8%	37.4%	0.334
Major venous repair	6.1%	4.5%	0.038
Major operation	81.1%	74.1%	<0.001
SBP<90 mm Hg	7.0%	6.2%	0.379
Ventilator >4 days	12.5%	10.5%	0.076
Femoral venous catheter	6.1%	4.7%	0.077
Central line	11.4%	9.1%	0.030

*Missingness: female n=1; race/ethnicity n=10; history of VTE n=18; history of cancer n=16; mechanism n=2.
†Fisher's exact test.
AIS, Abbreviated Injury Scale; BMI, body mass index; ISS, Injury Severity Score; SBP, systolic blood pressure; VTE, venous thromboembolism.

bleeding, or other sites of new or worsened bleeding (ie, wound, gastrointestinal, genitourinary). Diagnosis of DVT and PE were confirmed by standard imaging techniques. The date and results of extremity duplex ultrasonography and CT chest angiography during the hospital course were recorded. As this was an observational study, no study protocol directed the screening, prophylaxis, or treatment of patients with suspected VTE.

The study was performed on an intention-to-treat basis, with the assignment of WB versus SFD made based on the first recorded dose of prophylactic enoxaparin. Univariate and bivariate analyses used common statistical tests to compare WB and SFD populations. Mean and SD are reported for continuous variables with normal distribution, and differences compared using the independent samples t-test. Non-parametric variables are summarized by median and IQR and evaluated using the Wilcoxon rank-sum test. Categorical variables are reported as percentages and compared using χ^2 test or Fisher's exact test, as appropriate.

Multivariate logistic regression models for VTE, DVT, and PE were developed to explore the effect of WB enoxaparin dosing, after adjusting for known risk factors. All potential risk factors that were significant at $p<0.2$ were entered into a forward stepwise logistic regression model. Clustering at the hospital level was applied to account for institutional differences not otherwise captured by this dataset (eg, VTE screening protocols). Variables retained in the final models are reported in the results, along with model diagnostics, including area under the receiver operating characteristic curve and Hosmer-Lemeshow goodness-of-fit testing. Adjusted ORs (aOR) and 95% CIs are reported.

A substantial number of patients received a non-WB, non-SFD enoxaparin for chemoprophylaxis (n=452, 9.4%). While these observations were censored for the primary analysis, on closer review of the data we noted that 85.0% of this censored cohort received 40 mg two times per day. Recent publications have advocated for higher empirical doses of enoxaparin in trauma patients with moderate or greater risk for VTE and no contraindications to LMWH.[3] As such, we completed two additional analyses in which patients receiving 30 or 40 mg two times per day were classified as WB if (1) reported patient weight was <50 kg (n=68), which represented overdosing for prophylaxis, or (2) reported patient weight was ≥70 kg (n=277), consistent with a weight-stratified approach. The results of these sensitivity analyses did not alter our findings, the details of which can be found in online supplemental tables S1 and S2.

Incorporating feedback from reviewers of the initial article two post hoc analyses were completed; one focusing on the relationship between enoxaparin dosing and VTE risk of obese patients, and the second being a time-to-event analysis of in-hospital DVTs. The subgroup analysis of obese patients (BMI≥30) used stepwise multivariate logistic regression techniques with clustering by hospital site, as previously described. It should be noted that of the 1038 obese patients in this subgroup, only 36 received appropriate WB enoxaparin prophylaxis. Findings of

Table 2 Characteristics of prophylactic enoxaparin dosing by group assignment

	Weight based (n=1065)	Standard (n=3295)	P value
Initial dosing			
40 mg once a day	n/a	31.7%	
20 mg two times per day	0.2%	n/a	
30 mg two times per day	78.1%	68.3%	
40 mg two times per day	20.7%	n/a	
50 mg two times per day	0.9%	n/a	
60 mg two times per day	0.1%	n/a	
Early prophylaxis (≤24 h)	53.2%	53.9%	0.694
Missed doses			
Any missed dose	44.4%	39.5%	0.004
Median (IQR) number of missed doses among those with any missed dose	2 (1, 3)	2 (1, 3)	0.593*
Reasons for missing doses among those with any missed dose			
Procedural intervention	47.0%	42.9%	0.023
Patient refusal	36.6%	38.9%	0.185
Bleeding concern	5.5%	4.8%	0.403
Bleeding complication	1.5%	1.1%	0.323
Regimen changes			
Any regimen change	13.8%	16.3%	0.052
Median (IQR) number of dosing changes among those with any change	1 (1, 2)	1 (1, 1)	0.349*

*Wilcoxon rank-sum test.

this analysis are reported in online supplemental table S3, and again did not significantly alter the conclusions of this study. For the time-to-event analysis, the event was defined as a positive finding of DVT on venous duplex examination at any location. Time to event in days was calculated by subtracting the date of a positive examination from the date of hospital admission, and patients were censored at the time of death or hospital discharge. Differences between groups were evaluated by log-rank test and Cox proportional hazard. The assumption of proportionality was evaluated by log-log plot and Schoenfeld residuals.

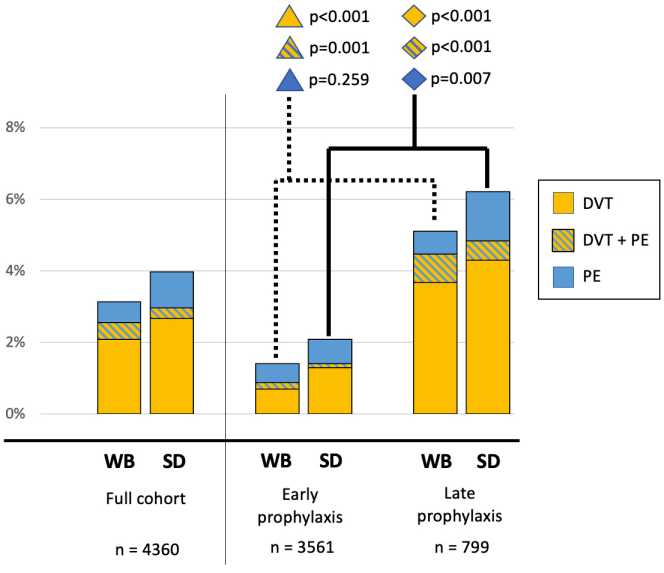

Figure 2 Unadjusted venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) rates by cohort. Early prophylaxis was associated with significantly lower rates of VTE and DVT relative to delayed initiation of prophylaxis for both weight-based (WB) (▲) and standard fixed dosing (SFD) (♦) groups.

Power calculations were completed using a range of incidence rates obtained from published studies, as well as limited data on the patient population used in this study. The purpose of this calculation was to assist in our interpretation of the results, and not to direct the analytical strategy. Previously reported VTE rates in trauma patients have ranged widely; the highest rates are typically among severely injured patients with multiple VTE risk factors and in studies using routine VTE surveillance practices.[5 13] As such, we performed several power calculations with sensitivity analysis to account for this known variation. The expected VTE rate for SFD enoxaparin dosing was evaluated at 4%, 7%, 12%, and 20%.[11 13 15] The hypothesized reduction in VTE with WB dosing was tested at 15%, 30% and 50%, based on reported effects of WB dosing strategies on both anti-Xa levels and VTE rates.[11 18 22] The type 1 error was set at 0.05, and power at 0.80. The 1:3 ratio of WB to SFD patients was used in these calculations based on the observed ratio from initial review of these data. The results of the analysis are included in online supplemental table S4. Based on this evaluation, this study is powered to detect a 30% difference in VTE rate between treatment groups assuming a baseline VTE rate of at least 12% in the SFD group.

Data were cleaned and analyzed using the statistical package Stata for Mac, V.16.1 (StataCorp, College Station, TX). The data collection and initial analysis of the CLOTT-1 registry was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Defense Medical Research and Development Program (award number: W81XWH-17-1-0673). There is no additional funding to report for this secondary analysis. This article was drafted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for retrospective observational studies (online supplemental table S5).

RESULTS

Study population

Of the 7903 patients captured in the CLOTT study, 5539 received prophylactic dosing of enoxaparin during their admission. 727 patients met exclusion criteria (figure 1), and 452 patients were further excluded due to non-standard dosing. The final cohort consisted of 4360 patients: 1065 (24.4%) received WB and 3295 (75.6%) received SFD enoxaparin DVT chemoprophylaxis.

WB patients were younger, more likely to be female, and less likely to be obese (table 1). Mean ISS was statistically higher for the WB cohort. With respect to the 12 predefined VTE risk factors, groups were comparable except head AIS ≥3, major operation, major venous injury, and presence of central line, all of which were more common in the WB group.

Enoxaparin dosing

The majority of patients (78.1%) in the WB group received 30 mg two times per day (table 2). In the SFD group 68.3% of patients received 30 mg two times per day and 31.7% 40 mg once a day. The first dose of chemoprophylaxis was administered within 24 hours of admission for the majority of patients (WB 53.2% vs. SFD 53.9%). Changes to dosing regimens occurred in 13.8% of the WB group and 16.3% of the SFD group. There were 4358 reported missed doses among 1773 patients (mean 2.7, range

Table 3 Multivariable logistic regression model of VTE, DVT, and PE rates

	VTE	DVT	PE
Model diagnostics			
Observations (n)	4268	4268	4226
AUC	0.807	0.805	0.848
Hosmer-Lemeshow GOF	0.124	0.641	0.458
Variables: aOR (95% CI)			
Weight-based dosing	0.75 (0.38, 1.48)	0.86 (0.40, 1.87)	0.73 (0.38, 1.40)
Obesity	1.54 (0.99, 2.39)	1.49 (0.88, 2.53)	1.83 (0.83, 4.03)
Age	**1.03 (1.01, 1.05)**	**1.04 (1.01, 1.06)**	–
ISS	**1.02 (1.01, 1.04)**	**1.02 (1.00, 1.04)**	**1.03 (1.00, 1.05)**
Latinx	–	**1.70 (1.08, 2.66)**	–
Race, other	0.70 (0.41, 1.19)		
Medicare, Medicaid	–	–	0.54 (0.27, 1.06)
Uninsured, self-pay	–	0.49 (0.17, 1.43)	1.66 (0.95, 2.90)
Early prophylaxis (≤24 h)	**0.47 (0.30, 0.74)**	**0.40 (0.25, 0.65)**	0.60 (0.28, 1.28)
Red blood cell (RBC) transfusion	**1.06 (1.02, 1.11)**	**1.06 (1.02, 1.10)**	**1.06 (1.01, 1.12)**
Penetrating mechanism	1.42 (0.92, 2.20)	1.37 (0.87, 2.13)	1.80 (0.87, 3.75)
Tranexamic acid (TXA)	–	1.56 (0.89, 2.71)	–
VTE risk factors			
Head AIS ≥3	–	–	0.51 (0.24, 1.08)
Chest AIS ≥3	1.49 (0.95, 2.34)	**1.51 (1.01, 2.27)**	–
Shock at admission	–	0.65 (0.42, 1.01)	–
Lower extremity long bone fracture	1.34 (0.94, 1.93)	–	1.69 (0.88, 3.25)
Spinal cord injury	1.73 (0.96, 3.10)	–	**2.31 (1.10, 4.43)**
Central venous catheter	**2.55 (1.29, 5.05)**	2.32 (0.99, 5.41)	**3.00 (1.29, 6.95)**
Femoral catheter	**2.07 (1.11, 3.85)**	2.04 (0.94, 4.42)	1.55 (0.89, 2.72)
Prolonged mechanical ventilation (≥4 days)	–	–	2.11 (0.96, 4.63)

Unmeasured variation in institutional practices was controlled for by clustering at the level of the hospital site. Omitted values (–) indicate variables that were not retained in the final stepwise model. Statistically significant values are in **bold**.
AIS, Abbreviated Injury Scale; aOR, adjusted OR; AUC, area under the receiver operating characteristic curve; DVT, deep vein thrombosis; GOF, goodness of fit; ISS, Injury Severity Score; PE, pulmonary embolism; VTE, venous thromboembolism.

1–39), with a significantly higher rate of missed doses in the WB group (44.4% vs. 39.5%). The most common reasons for missed doses were need for procedural intervention and patient refusal, which were more frequent in the WB group (p=0.023; table 2). Concern for bleeding or bleed-related complications were less commonly cited justifications and did not differ by prophylaxis strategy. There was a higher rate of reported regimen changes in the SFD group (p=0.052), but most patients (86.2% for WB and 83.7% for SFD) did not have alterations in chemoprophylaxis agent or dose.

Unadjusted outcomes

The composite VTE rate for the study population was 3.7% (n=162; DVT 2.8%, PE 1.2%). VTE incidence was 3.1% (n=33; DVT 2.5%, PE 1.0%) in the WB group and 3.9% (n=129; DVT 2.9%, PE 1.3%) in the SFD group, which did not differ significantly (p=0.221) (figure 2). Early prophylaxis was associated with significantly lower rates of VTE (1.9% ≤24 hours vs. 5.8% >24 hours, p<0.001), DVT (1.3% vs. 4.7%, p<0.001), and PE (0.8% vs. 1.7%, p=0.004). By dosing strategy, the differences in VTE, DVT, and PE remained significant for SFD patients receiving early prophylaxis, whereas only the rates of VTE and DVT were significantly lower among WB patients with early prophylaxis (figure 2). Among those receiving early prophylaxis, there was no difference in VTE, DVT or PE rates among WB versus SFD cohorts (online supplemental table S6). VTE and DVT were more common among obese patients. Obese patients receiving WB prophylaxis had significantly higher rates of DVT (11.1% vs. 3.0%, p=0.027), but not VTE or PE (online supplemental table S6). In the obese population early prophylaxis was also associated with decreased incidence of VTE (2.7% vs. 7.5%, p<0.001), DVT (1.7% vs. 5.6%, p<0.001), and PE (1.1% vs. 2.8%, p=0.031).

Complications attributable to chemoprophylaxis were uncommon. Enoxaparin exposure was associated with progression of intracranial hemorrhage in seven patients (0.2%), and worsening or new solid organ bleeding in four patients (0.1%). Overall, there was a 1.0% rate of chemoprophylaxis-associated complication within this cohort, and no difference was detected between groups (online supplemental table S6).

Adjusted outcomes

After adjustment, VTE, DVT, and PE rates did not differ by dosing strategy (table 3). For all outcomes, injury severity (ISS) and red blood cell (RBC) transfusion volume were significant positive predictors. Obesity was associated with an increased risk of VTE, DVT, and PE, but this did not reach statistical significance in any model. The variable for missed doses of VTE prophylaxis did not meet prespecified inclusion criteria for any model and was omitted for all outcomes. Early initiation of chemoprophylaxis was associated with a 53% reduction in the likelihood of VTE (aOR 0.47, 95% CI 0.30 to 0.74). This is attributable to a reduction in the odds of DVT (aOR 0.40, 95%

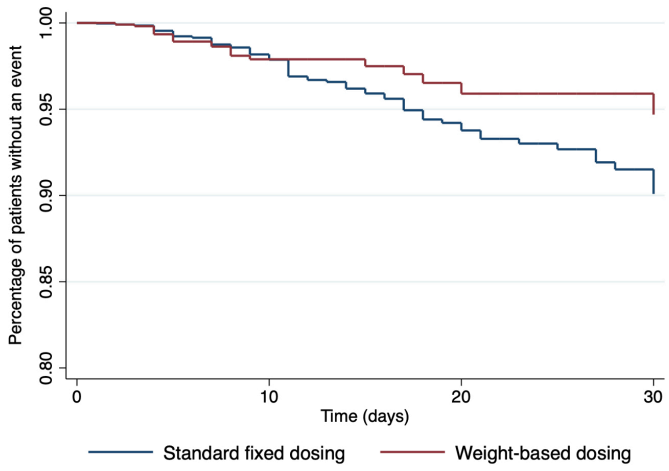

Figure 3 Kaplan-Meier curve of the full cohort showing time to positive venous duplex examination (deep vein thrombosis (DVT) positive) within 30 days of admission. Patients who died or discharged prior to 30 days were censored.

CI 0.25 to 0.65), as early prophylaxis was not an independent predictor of PE on multivariate analysis.

Time-to-event analysis

There were 110 positive venous duplex examinations, which were similarly distributed between groups (WB 2.1% vs. SFD 2.7%; p=0.274). Unadjusted survival curve and log-rank test failed to detect a significant difference in time to event (figure 3; p=0.522). Review of the Kaplan-Meier curve (figure 3) showed a delayed separation of the WB and SFD groups at approximately hospital day 10, raising concern for non-proportional hazard over time. Evaluation of the multivariate Cox model confirmed non-proportionality by log-log plot and Schoenfeld residuals for both the full cohort and for a subgroup of patients with HLOS ≥10 days. The assumption of proportionality was preserved in a subgroup of patients with HLOS <10 days; however, the treatment effect remained non-significant.

DISCUSSION

The results of our study showed no difference in efficacy of WB versus SFD enoxaparin for VTE prophylaxis in young trauma patients. However, early initiation of prophylaxis was protective against VTE regardless of dosing strategy. Other significant risk factors for VTE within this cohort include increased age, obesity, more severe injury (higher ISS, RBC transfusion volume), and two of the 12 predefined VTE risk factors (presence of femoral or other central venous line). Interestingly, missed doses of VTE chemoprophylaxis were more common among the WB cohort, but were not independently predictive of worse clinical outcomes.

Effective prophylaxis against post-traumatic VTE with LMWH may not be dose dependent in young otherwise healthy trauma patients. Subtherapeutic anti-Xa activity is common among patients receiving traditional dosing regimens and has been associated with an elevated risk for VTE.[9 10] New strategies seeking to improve these outcomes include use of higher fixed doses (ie, 40 mg two times per day),[3] WB or weight-stratified dosing,[13 18] and enoxaparin dosing titrated to anti-Xa activity level.[22 23] A shared characteristic of all non-traditional dosing schemes is that most patients ultimately receive larger doses of LMWH. While higher doses do result in a greater percentage of patients achieving biochemical prophylaxis targets by anti-Xa activity level,[11] no single strategy has been proven to lower the risk of post-traumatic VTE relative to traditional dosing.[15] Our evaluation of the CLOTT-1 database offers the largest prospective, observational assessment of initial WB LMWH dosing strategies for VTE prophylaxis in a trauma population. The absence of anti-Xa levels in this dataset precluded biochemical assessment of adequate prophylaxis. However, the lack of evidence to support anti-Xa as an accurate measure of VTE prophylaxis highlights the importance of reporting on clinically relevant events. Our null result is consistent with the conclusions of several recent reviews that found insufficient evidence to back the adoption of non-traditional dosing strategies to achieve the clinical goal of reducing post-traumatic VTE risk.[4 24]

Unlike the controversy surrounding dosing strategies, early initiation of chemoprophylaxis clearly decreases the risk of VTE after trauma.[25] A 2020 evaluation of >79 000 patients from the Michigan Trauma Quality Improvement Program (MTQIP) database used multivariate logistic modeling to optimize the comparison of patients receiving their first dose of VTE prophylaxis <24 hours, 24 to <48 hours, and ≥48 hours after hospital admission.[26] Delays in prophylaxis were associated with increased VTE risk relative to the earliest group (<24 hours). Patients receiving their first dose ≥48 hours from admission had a greater than twofold increased risk of VTE (OR 2.35, p<0.001). Similarly, we found early initiation of prophylaxis with 24 hours of admission to confer a 53% risk reduction in VTE, with the protective benefit persisting regardless of dosing strategy. The 2020 MTQIP study did not exclude patients who received UH, but did adjust for the type of pharmacological agent, finding LMWH to be superior to UH with respect to VTE risk (OR 0.62, p<0.001).[26] Taken together, these findings suggest that both agent and timing may be more important than dosing scheme alone. The low rate of bleeding complications was anticipated based on existing literature and again highlights the safety of early LMWH in trauma populations.[25 27] Our results reinforce current guidelines recommending prophylaxis be started as soon as possible for stable patients without contraindications.[3 4]

Recently, the correlation between post-traumatic DVT and pulmonary clots has been called into question.[28–30] The primary analysis of the CLOTT-1 data sought to characterize post-traumatic pulmonary thrombosis (PT) as an entity that is clinically distinct from DVT and PE.[21] Supported by their findings that patients with PT have specific injury patterns and clinical risk factors, the authors raise intriguing questions as to the ability of post-traumatic VTE prophylaxis to prevent such events. Of the 157 patients with PE on chest imaging, 117 (74.5%) had no evidence of DVT and were thus classified as PT.[21] If a similar proportion of PE-positive patients in our subanalysis are assumed to in fact have PT, we can interpret the lack of effect of early prophylaxis in our risk-adjusted model for PE as further evidence that the pathophysiology of PT is distinct from DVT and PE. As such, future investigations evaluating the effects of VTE prophylaxis should aim to differ between PE and PT when defining clinical outcomes.

Limitations

This study has limitations that are inherent to its observational nature and may limit broad generalizability of our findings. Patients included in this analysis are young and lack many of the comorbidities and risk factors common among older trauma populations. Obesity was uncommon in our WB group. Though we failed to identify a protective benefit of WB dosing in the

obese cohort, our multivariate analysis may be underpowered to detect meaningful differences in dosing strategy that may otherwise exist. Variability in institutional practices with respect to VTE prophylaxis and DVT screening is likely significant across the 17 contributing centers. We attempted to control for the effects of unmeasured site-specific difference in our adjusted analysis. Due to the absence of anti-Xa activity data, we were unable to assess dosing strategy or clinical events with respect to this commonly reported measure. Most importantly, we recognized that 85% of patients who did not classify as either WB or SFD received enoxaparin 40 mg two times per day, an increasingly common fixed prophylactic dose promoted by WTA's 2020 guidelines.[3] As such, we performed two post hoc analyses that considered these patients to have received WB enoxaparin if their weight was (1) <50 kg (overdosed) or (2) ≥70 kg (weight stratified). The results of this additional work did not alter our conclusions and are included in online supplemental tables 1 and 2. Finally, despite this being among the largest prospective evaluations of WB VTE prophylaxis in trauma yet published, due to the low baseline incidence of VTE in patients receiving SFD enoxaparin we may have been underpowered to detect any small incremental benefit that WB dosing might afford.

CONCLUSION

We found no difference in rates of VTE between WB and standard dosing strategy in a young trauma population. Early administration had a significant effect, associated with 53% reduction in odds of VTE. Both dosing strategies appear to be safe, with comparably low risks of bleed progression. Obesity is a known risk factor for VTE; however, our understanding of the complex relationship between higher body mass, post-traumatic physiology, and optimal VTE prophylaxis strategies remains incomplete. Further studies are needed to evaluate the risk-benefit profile of LMWH dosing strategies in older and obese trauma populations, while paying close attention to timing of prophylaxis initiation and other known VTE risk factors.

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