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Evaluation of Venous Thromboembolism Prevention in High-Risk Trauma Patients: A Prospective, Randomized Trial of Standard Enoxaparin Versus Two Anti-Xa Adjusted Enoxaparin Dosing Strategies

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14. ABSTRACT

The impact of antithrombin III activity (AT-III) and on prophylactic enoxaparin serum trough anti-factor Xa concentration (anti-Xa) has not been evaluated. In addition, the optimal strategy for enoxaparin dose adjustment to attain target anti-Xa trough concentrations is unknown in high-risk trauma patients. The objective of this study was to determine if AT-III activity affects enoxaparin anti-Xa target attainment and to evaluate two enoxaparin dose adjustment strategies in patients with low anti-Xa concentrations. We conducted a single-center, prospective, randomized clinical trial of adult, high-risk trauma patients admitted to a level 1 trauma center over a 2-year period. Patients were eligible for inclusion if prescribed enoxaparin 30 mg subcutaneously every 12 hours for venous thromboembolism chemoprophylaxis based on a Greenfield Risk Assessment Profile score of 5 or more. Coordinated serum AT-III, anti-Xa, and thromboeslastogram samples were drawn 8 hours after the third dose of enoxaparin. Patients with anti-Xa $\geq$ 0.1 IU/mL served as the control group, while patients with anti-Xa < 0.1 IU/mL were the intervention group. Intervention group patients were randomized to one of two dose adjustment strategies: 1) enoxaparin 40 mg every 12 hours with escalation to 50 mg every 12 hours based on repeat anti-Xa (group 1) or 2) enoxaparin 30 mg every 8 hours (group 2). In total, 103 patients were studied. Trough anti-Xa concentrations were subprophylactic in 50.5% of patients. Demographics were similar between control and intervention groups. Initial serum AT-III activity was not statistically different between groups. Median time to anti-Xa trough achievement from initiation of enoxaparin was similar between intervention groups. Goal trough was achieved in 8 (38.1%) patients vs. 9 (50%) patients (P = 0.53), 11 (84.6%) patients vs. 8 (53.3%) patients (P = 0.11), and 15 (71.4%) patients vs. 13 (72.2%) patients (P = 0.76) in group 1 and group 2 at first, second, and overall assays, respectively. No venous thromboembolism occurred when patients were on the study drug. Mean packed red blood cell transfusion requirements after the first 48 hours were similar between all groups vs. intervention. A trend toward reduced AT-III exists for patients with subprophylactic anti-Xa; however, AT-III was not an independent risk factor for low anti-Xa. Although there was no difference overall, a non-significantly higher proportion of patients receiving dose-adjusted enoxaparin Q12H achieved goal anti-Xa concentrations earlier (i.e., at the second anti-Xa after dose adjustment).

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1.0 EXECUTIVE SUMMARY

The impact of antithrombin III activity (AT-III) and on prophylactic enoxaparin serum trough anti-factor Xa concentration (anti-Xa) has not been evaluated. In addition, the optimal strategy for enoxaparin dose adjustment to attain target anti-Xa trough concentrations is unknown in high-risk trauma patients. The objective of this study was to determine if AT-III activity affects enoxaparin anti-Xa target attainment and to evaluate two enoxaparin dose adjustment strategies in patients with low anti-Xa concentrations.

We conducted a single-center, prospective, randomized clinical trial of adult, high-risk trauma patients admitted to a level 1 trauma center over a 2-year period. Patients were eligible for inclusion if prescribed enoxaparin 30 mg subcutaneously every 12 hours for venous thromboembolism (VTE) chemoprophylaxis based on a Greenfield Risk Assessment Profile score of 5 or more. Coordinated serum AT-III, anti-Xa, and thromboeslastogram samples were drawn 8 hours after the third dose of enoxaparin. Patients with anti-Xa $\geq$ 0.1 IU/mL served as the control group while patients with anti-Xa < 0.1 IU/mL were the intervention group. Intervention group patients were randomized to one of two dose adjustment strategies: 1) enoxaparin 40 mg every 12 hours with escalation to 50 mg every 12 hours based on repeat anti-Xa (group 1) or 2) enoxaparin 30 mg every 8 hours (group 2). Intervention group patients had peak anti-Xa assessment 4 hours after the third adjusted dose with coordinated repeat AT-III, trough anti-Xa, and thromboeslastogram assessments 8 hours after the third and sixth adjusted doses.

Primary outcomes were difference in AT-III activity between control and intervention groups and proportion of patients achieving goal anti-Xa and time (days) to goal anti-Xa between intervention groups at first, second, and overall assays after dose adjustment. Secondary outcomes included VTE and bleeding events.

In total, 103 patients (mean age, 41.5 [standard deviation (SD), 16.3] years, 67 men [65%]) were studied. Trough anti-Xa concentrations were subprophylactic in 50.5% of patients. Demographics were similar between control and intervention groups. Initial serum AT-III activity (control, 87% [interquartile range (IQR) 80-98] vs. intervention, 82% [IQR 71-96]; P=0.092) was not statistically different between groups. Median time to anti-Xa trough achievement from initiation of enoxaparin was similar between intervention groups (group 1, 7 days [IQR 5-8] vs. group 2, 2 days [IQR 4-8]; P=0.29). Goal trough was achieved in 8 (38.1%) patients vs. 9 (50%) patients (P=0.53), 11 (84.6%) patients vs. 8 (53.3%) patients (P=0.11), and 15 (71.4%) patients vs. 13 (72.2%) patients (P=0.76) in group 1 and group 2 at first, second, and overall assays, respectively. No VTE occurred when patients were on the study drug. Mean packed red blood cell transfusion requirements after the first 48 hours were similar between all groups (control mean 0.70 [SD 1.74] vs. intervention mean 0.73 [SD 1.28], P=0.94; group 1 mean 0.81 [SD 1.50] vs. group 2 mean 0.64 [SD 1.0], P=0.645).

A trend toward reduced AT-III exists for patients with subprophylactic anti-Xa; however, AT-III was not an independent risk factor for low anti-Xa. Although there was no difference overall, a non-significantly higher proportion of patients receiving dose-adjusted enoxaparin Q12H achieved goal anti-Xa concentrations earlier (i.e., at the second anti-Xa after dose adjustment).

2.0 BACKGROUND

Venous thromboembolism (VTE) is a common complication in hospitalized patients and is associated with increased rates of morbidity and mortality [1]. VTE incidence without prophylaxis is estimated at 40-80% for deep vein thrombosis and approximately 4-10% for pulmonary embolism in the subgroup of critically ill patients [1]. Low molecular weight heparins (LMWHs) have been established as the agents of choice for VTE prevention in high-risk trauma patients, including those with spinal cord injuries and pelvic fractures [2-9].

Conflicting evidence exists for the optimal enoxaparin dose in critically injured patients. Trough serum anti-factor Xa concentrations (anti-Xa) between 0.1-0.2 IU/mL have been used as a surrogate marker for LMWH prophylactic efficacy when obtained 30 minutes prior to steady state dose of enoxaparin 30 mg subcutaneously every 12 hours [10]. Patients with subprophylactic anti-Xa values have been associated with increased VTE rates [11,12]. Studies have previously attempted to identify predictors for low anti-Xa. Young age, high body weight, edema, and low peak anti-Xa have been associated with low trough anti-Xa [11-13]. Limited data exist evaluating the impact of serum antithrombin III activity (AT-III) on LMWH chemoprophylaxis, especially given relative AT-III deficiency observed in trauma has been demonstrated [14-20]. Reduced AT-III may represent less substrate to which LMWH can bind and exert anticoagulant effect.

The purpose of this study was to compare AT-III between patients with goal trough anti-Xa to low trough anti-Xa. The hypothesis was AT-III will be lower in patients with a low trough anti-Xa. The secondary purpose was to compare two enoxaparin dosing strategies adjusted based on anti-Xa concentration in high-risk trauma patients.

3.0 METHODS

This was an investigator-initiated, single-center, prospective, non-blinded, randomized trial including trauma patients admitted to the University of Cincinnati Medical Center (UCMC), an urban American College of Surgeons-verified level 1 trauma center, between March 2016 and March 2018. Adult patients (18-80 years) with an anticipated length of stay (LOS) of at least 72 hours initiated on enoxaparin 30 mg every 12 hours per trauma team protocol were eligible for inclusion (Figures 1 and 2). Exclusion criteria were creatinine clearance (CrCl) < 30 mL/min or continuous renal replacement therapy, total body weight < 50 kg or > 150 kg, platelet count < 50,000/mm^3, heparin or LMWH allergy, therapeutic anticoagulation required within 24 hours of admission, preadmission therapeutic anticoagulation, isolated intracranial hemorrhage, hyperbilirubinemia (> 6.6 mg/dL), receiving subcutaneous heparin (SQH) prophylaxis for ≥ 72 hours prior to enoxaparin initiation or chemoprophylaxis not started for ≥ 72 hours, pregnancy, or incarceration. Institutional Review Board approval was obtained from UCMC and Wright-Patterson Air Force Base for study methodology. Informed consent was obtained for all subjects at the time of enrollment.

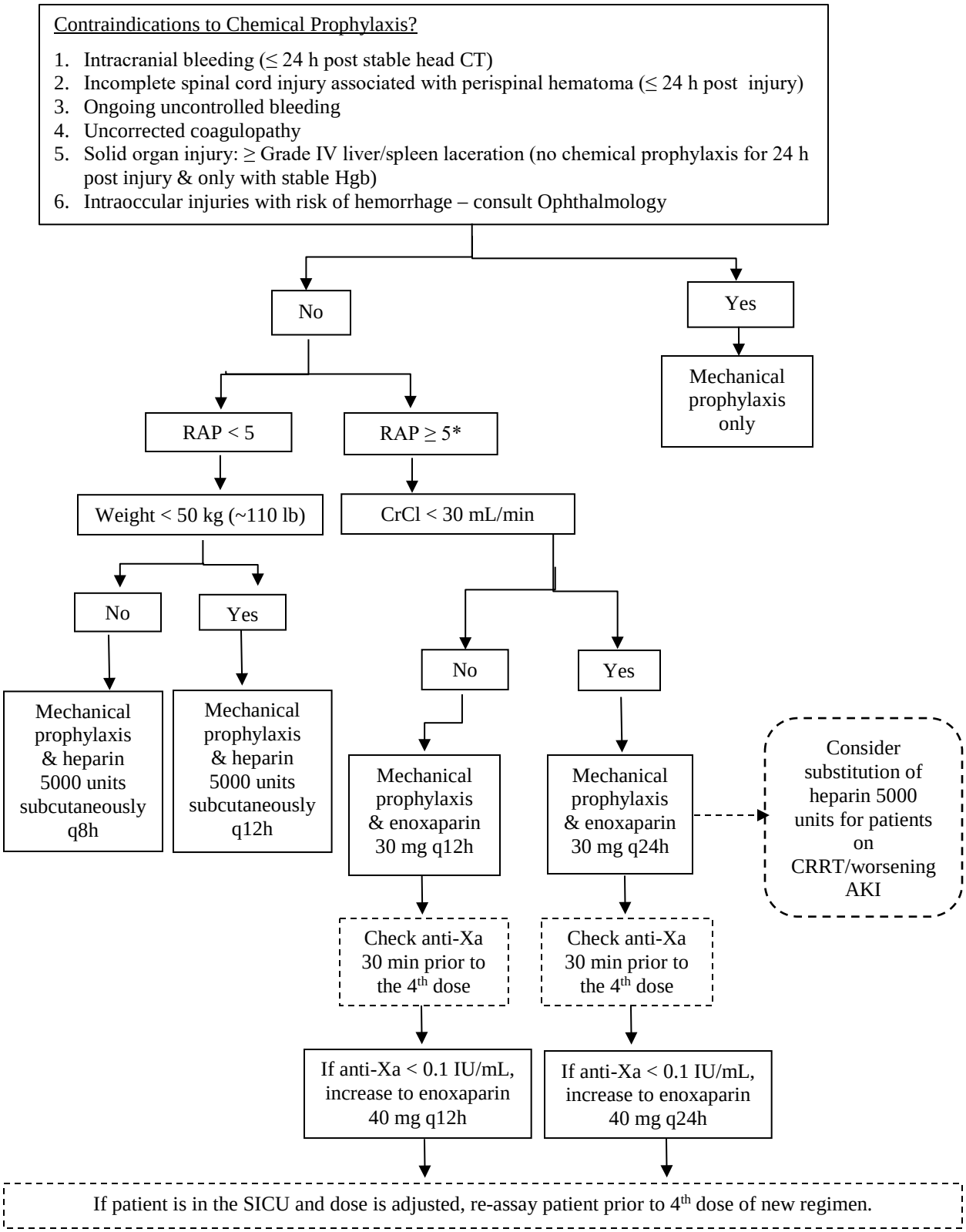

Figure 1. UCMC trauma service VTE prophylaxis protocol: body mass index < 40 or weight < 125 kg. AKI = acute kidney injury; CrCl = creatinine clearance; CRRT = continuous renal replacement therapy; CT = computed tomography; Hgb = hemoglobin; q = every; RAP = risk assessment profile; SICU = surgical intensive care unit. *Consider acute initiation of heparin 5000 units if patient is to have spinal epidural placed (> 2 rib fractures).

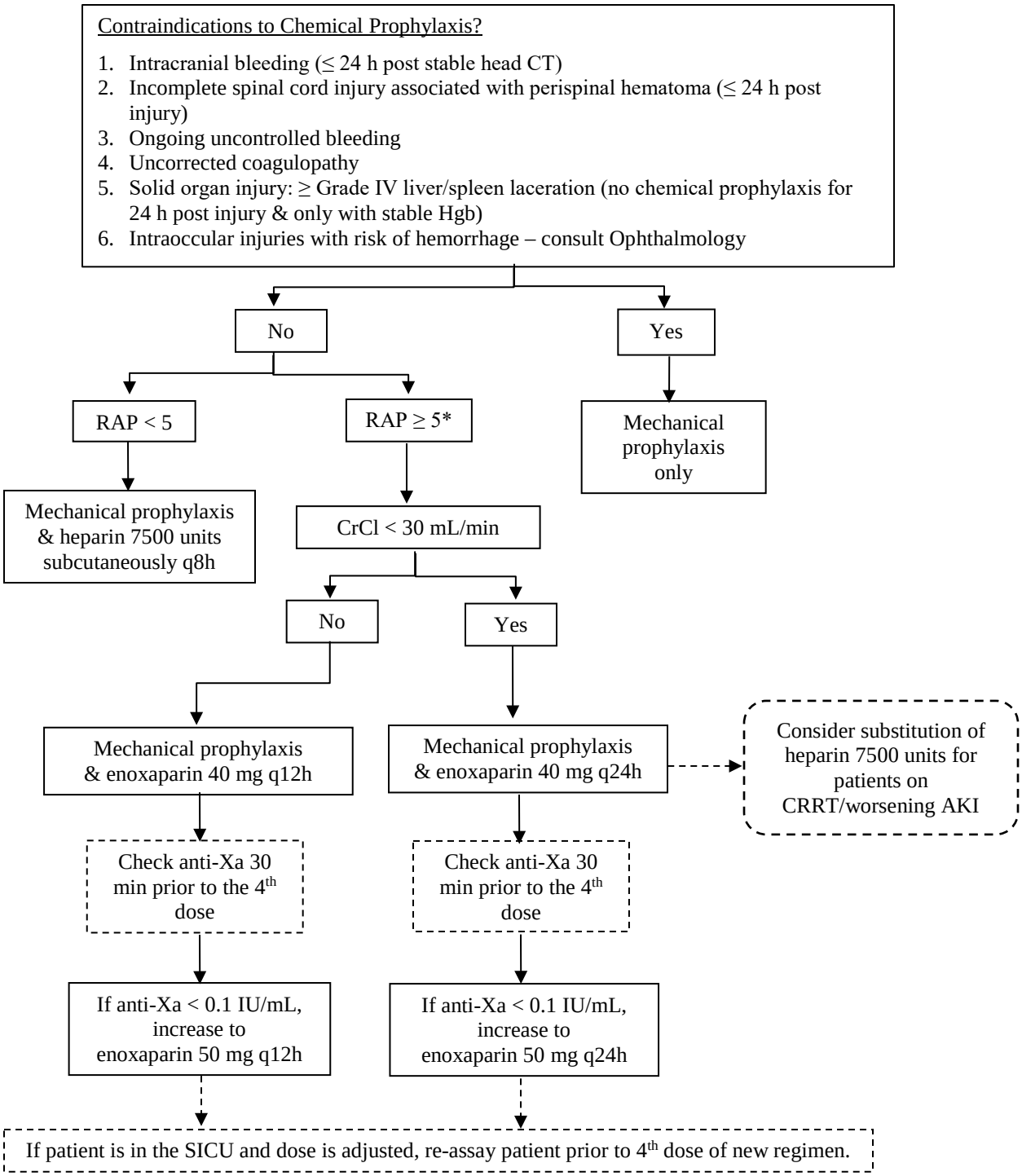

Figure 2. UCMC trauma service VTE prophylaxis protocol: body mass index ≥ 40 or weight ≥ 125 kg.
*Consider acute initiation of heparin 5000 units if patient is to have spinal epidural placed (> 2 rib fractures).

Patients were initiated on enoxaparin 30 mg every 12 hours per standard trauma team protocol based on a Greenfield RAP score of 5 or more (Figures 1 and 2) [21]. Following protocol initiation, trauma protocol changed to weight-based initial enoxaparin dosing: patients weighing ≥ 125 kg or with a body mass index (BMI) ≥ 40 kg/m^2 were started on enoxaparin 40 mg every 12 hours. Bilateral lower extremity compression devices were applied to all patients at admission unless contraindicated. Routine screening bilateral lower extremity duplex ultrasound was performed for patients with RAP ≥ 5 between March 2016 and fall 2016 on post-injury day 3 and every 7 days during admission thereafter or as clinically indicated. During fall 2016, the trauma protocol was modified to perform screening duplex ultrasound on patients with RAP ≥ 8 on admission and weekly thereafter while hospitalized, or as clinically indicated. The trauma attending could elect not to perform routine VTE screening.

Enrolled patients had coordinated serum AT-III, kaolin thromboelastogram (TEG), and anti-Xa drawn 8 hours following the third enoxaparin dose. If the anti-Xa was not collected or was mistimed, an appropriately timed anti-Xa was drawn within 24 hours for assignment to control or intervention groups. Goal prophylactic anti-Xa was defined as a trough serum concentration of 0.1-0.3 IU/mL drawn 8 hours after the third dose of enoxaparin 30 mg every 12 hours. Patients with anti-Xa at goal were assigned to the control group and enoxaparin 30 mg every 12 hours was continued. Patients with subprophylactic anti-Xa were assigned to the intervention group and received 1:1 block randomization to two groups: 1) enoxaparin 40 mg every 12 hours (group 1), or 2) enoxaparin 30 mg every 8 hours (group 2). After the third adjusted dose, peak anti-Xa was obtained at 4 hours post-dose followed by coordinated trough anti-Xa, TEG, and AT-III at 8 hours post-dose. Group 1 dose was adjusted to enoxaparin 50 mg every 12 hours if the anti-Xa level remained subprophylactic (i.e., < 0.1 IU/mL). Group 2 continued enoxaparin 30 mg every 8 hours regardless of anti-Xa, as this regimen has not been previously evaluated. Coordinated trough anti-Xa, TEG, and AT-III were obtained following the sixth overall adjusted dose for all intervention group patients. Weekly anti-Xa and AT-III were collected thereafter up to 28 days. Intervention group doses were decreased to the previous dose if any trough anti-Xa demonstrated bioaccumulation (i.e., ≥ 0.3 IU/mL). Patients were removed from the study if serum creatinine increased 50% from admission or had an absolute change of 1 mg/dL in serum creatinine.

Demographic data including age, sex, weight, BMI, body surface area (BSA), injury mechanism (blunt vs. penetrating), injury severity score (ISS), abbreviated injury score (AIS), and RAP score were collected. Other information collected included admission and highest serum creatinine, admission and lowest CrCl, admission unit (i.e., intensive care unit (ICU) or floor), time to enoxaparin initiation, days and number of doses of SQH prophylaxis administrated prior to enoxaparin initiation, VTE events, ICU and hospital LOS, bleeding events, missed doses of enoxaparin, cumulative fluid balance from admission with each serum assay, and milliliters of packed red blood cell transfusion.

The primary outcomes included difference in initial AT-III between control and intervention groups; proportion of patients reaching goal anti-Xa between groups 1 and 2 at any time point, and at first and second repeat assessments; and median time to achievement of goal anti-Xa between groups 1 and 2. Secondary outcomes included a comparison of all VTE events. VTE was defined as pulmonary embolism identified on CT pulmonary angiography or clinically relevant, proximal VTE identified on routine duplex screening or on duplex obtained due to clinical suspicion. Additional secondary endpoints include major bleeding, minor bleeding, total blood transfusion requirements after 48 hours until discharge or day 28 between control and

intervention groups, proportion of patients with enoxaparin bioaccumulation between groups 1 and 2, and assessment of risk factors associated with subprophylactic anti-Xa. Major bleeding while on study medication was defined as hemoglobin decrease of ≥ 2 g/dL in 24 hours requiring two or more units of packed red blood cells, new or worsening intracranial hemorrhage, or repeat surgical intervention due to hemorrhage. Minor bleeding while on study medication was defined as coffee ground emesis with zero to 1 unit packed red cell transfusion, interruption of study drug due to concern of bleeding, or other overt bleeding not characterized as major bleeding. A post hoc analysis was performed comparing the proportion of patients reaching goal peak anti-Xa defined as 0.2-0.4 IU/mL and proportion with undetectable peak anti-Xa defined as < 0.1 IU/mL. Proportion of patients at goal peak and trough was also reported. An additional post hoc analysis evaluating the proportion of patients with AT-III deficiency defined as < 80% was performed between groups on initial and first assay after dose adjustment.

Patient demographic information was with descriptive statistics and compared between groups. Nominal data were analyzed using either Fisher's exact test or chi-square test, as appropriate. Continuous data were compared using Student's t test, Wilcoxon rank sum, or one-way analysis of variance/Kruskal-Wallis analysis of variance, as appropriate. Multivariate logistic regression was performed to identify independent risk factors associated with subprophylactic anti-Xa. All values with P-value < 0.2 were included in the model. Serum AT-III, weight, and age were identified as a priori covariates planned regardless of P-value. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

A power analysis was performed assuming 50% of patients would have anti-Xa < 0.1 IU/mL, a predicted AT-III activity of 70% ± 25% in the intervention group compared to AT-III activity of 80% ± 25% in the control group. To achieve 80% power with alpha 0.05, 200 patients were required initially for enrollment. Secondarily, anti-Xa goal achievement of 50% in group 1 vs. 77% in group 2 required enrollment of 100 patients to achieve 80% power with alpha of 0.05. Fifteen months following study initiation, an unplanned interim power analysis was performed due to slow enrollment. A predicted mean AT-III activity of 80% ± 17.5% and an absolute reduction in AT-III activity of 10% required enrollment of 100 patients to achieve 80% power with an alpha of 0.05. As such, the research team revised its enrollment goal to 100 patients.

4.0 RESULTS

In total, 1496 trauma patients were screened for inclusion and 103 were included (Figures 3 and 4). The study population had the following characteristics: mean age 41.5 years (standard deviation [SD] 16.3), 67 men (65%), mean ISS 20.1 (SD 8.8), mean RAP 10 (SD 3.5), and mean hospital LOS 10.4 (SD 7.3). Trough anti-Xa concentrations were subprophylactic in 50.5% of patients. As such, 51 patients were in the control group and 52 patients were in the intervention group. Intervention group randomization resulted in 26 patients in both group 1 and group 2. Research assays were not collected on 4 control group patients, and 1 intervention group patient (group 1) withdrew consent prior to the first study assays, resulting in 98 patients available for analysis. Two intervention group patients did not have initial AT-III concentrations and were excluded from primary outcome analysis. Control and intervention groups were similar in age, sex, BMI, ISS, AIS, injury type, admitting unit (i.e., ICU), cumulative fluid balance, and CrCls, with RAP score trending toward a significant difference (8 [interquartile range (IQR) 8-11] vs. 10 [IQR 8-12], P = 0.082; Table 1). Intervention group had higher total body weight (79.3 kg [IQR 68.3-90.8] vs. 86.1 kg [IQR 77.1-98.0], P = 0.01) and BSA (1.93 m^2 [IQR 1.80-

2.11] vs. 2.06 m^2 [IQR 1.96-2.21], P = 0.006). Significantly more patients in the intervention group received SQH prior to enoxaparin administration (19 [39.6%] vs. 30 [60%], P = 0.04) and missed at least one enoxaparin dose (9 [18.8%] vs. 20 [40%], P = 0.02). Weight and SQH administration prior to enoxaparin were independent risk factors for low trough anti-Xa on multivariate logistic regression (Table 2). There were no statistical differences in baseline demographics between intervention groups 1 and 2, including cumulative fluid status across all assay time points.

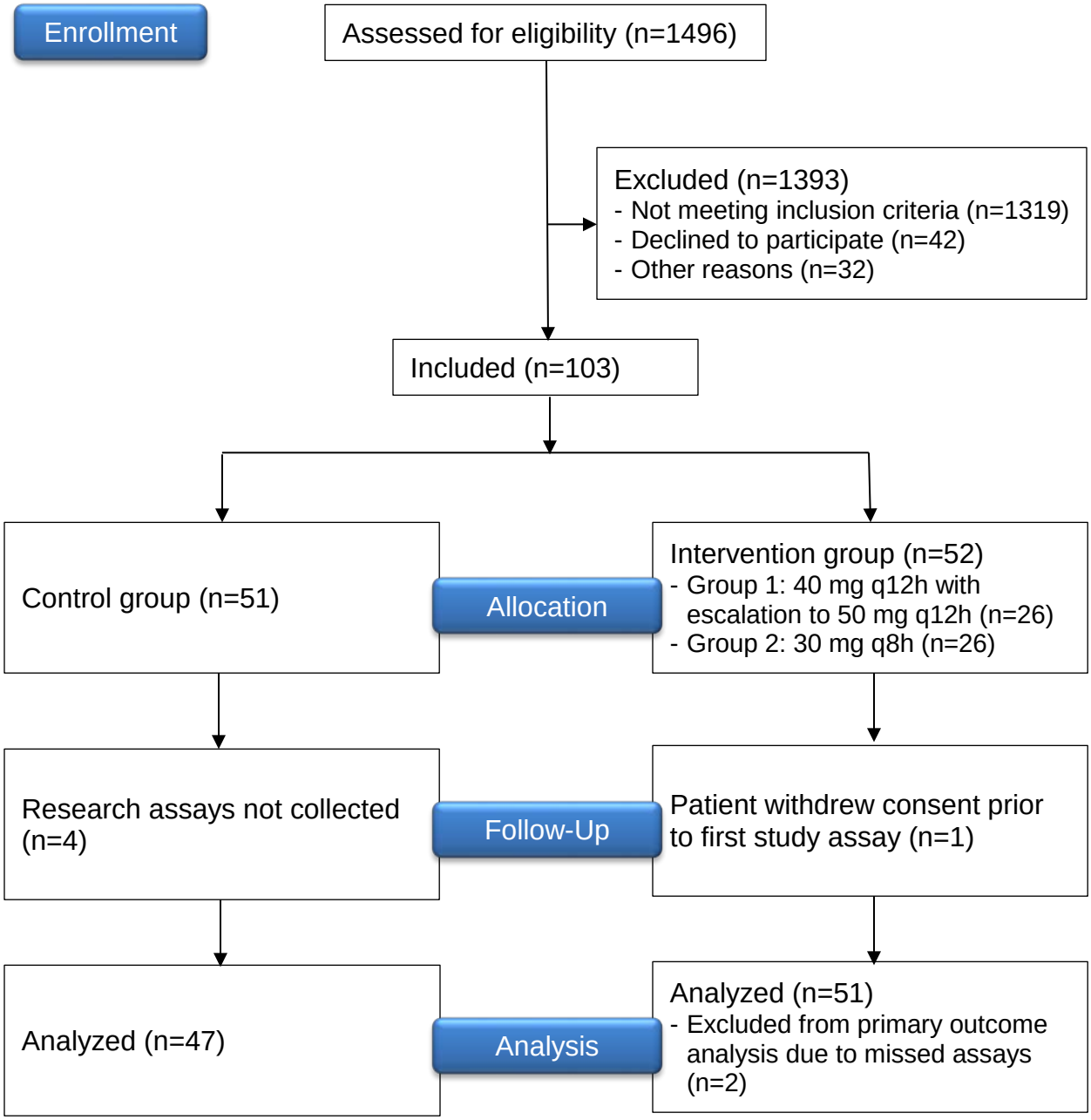

Figure 3. CONSORT 2010 flow diagram.

Excluded (n=1393)

- Not meeting inclusion criteria (n=1320)
  - Age < 18 (n=27)
  - Age > 80 (n=134)
  - LOS < 72 hours (n=259)
  - CrCl < 30 mL/min (n=34)
  - Enoxaparin not started within 72 hours or patient given SQH for > 72 hours (n=47)
  - Prisoner (n=2)
  - Isolated intracranial hemorrhage (n=32)
  - Known hyperbilirubinemia (n=2)
  - Not on chemoprophylaxis (n=2)
  - Continuous renal replacement therapy (n=4)
  - On therapeutic anticoagulation at home (n=65)
  - Platelet count < 50 x 10^3 cells/μL (n=2)
  - Pregnancy (n=2)
  - Required therapeutic anticoagulation within 24 hours of admission (n=32)
  - Enoxaparin 40 mg every 12 hours based on weight ≥ 125 kg or BMI ≥ 40 (n=54)
  - SQH utilized (n=442)
  - Unable to consent (n=25)
  - Unable to consent before received 3 doses of enoxaparin or 4 doses after protocol amendment (n=141)
  - Weight < 50 kg (n=11)
  - Weight > 150 kg (n=3)
- Declined to participate (n=42)
- Other reasons (n=31)
  - Trauma attending declined enrollment (n=6)
  - Enoxaparin started off protocol (n=5)
  - Enrolled in another research protocol (n=9)
  - Consented by anti-Xa not appropriately drawn/not drawn (n=10)
  - Consented by VTE prior to anti-Xa (n=1)

Figure 4. CONSORT 2010 flow diagram: excluded subjects.

Table 1. Comparison of Baseline Characteristics Between Control and Intervention Group

Baseline Characteristic	Control (n = 47)	Intervention (n = 51)	P-value
Age	38 (25-58)	41 (26-56)	0.77
Sex			0.2
Male	29 (61.7)	38 (74.5)	
Weight (kg)	79.3 (68.3-90.8)	86.1 (77.1-98.0)	0.01[a]
BMI (kg/m^2)	26.7 (23.7-31.8)	28.3 (25.7-32.3)	0.11
BSA (m^2)	1.93 (1.80-2.11)	2.06 (1.92-2.21)	0.006 [a]
Injury mechanism			0.63
Penetrating	15 (31.9)	13 (25.6)	
ISS[b]	17 (14-22)	19 (14-22)	0.52
AIS[c]			
Head	0 (0-0)	0 (0-0)	0.897
Chest	3 (2-3)	3 (0-3)	0.40
Abdomen	2 (0-3)	2 (0-3)	0.76
Extremity	2 (0-3)	2 (1-3)	0.24
Cervical spine	0 (0-0)	0 (0-0)	0.84
Thoracic spine	0 (0-0)	0 (0-0)	0.63
Lumbar spine	0 (0-2)	0 (0-2)	0.49
RAP score[d]	8 (8-11)	10 (8-12)	0.082
CrCl (mL/min)[e]			
Admission	78.2 (67.6-90.7)	87.3 (70.4-99.3)	0.12
Lowest	78.2 (63.6-90.3)	86.6 (69.7-92.6)	0.23
Admission to ICU	37 (78.7)	36 (70.6)	0.49
Cumulative fluid balance at initial assay (mL)	1376 (206-2806)	1662 (462-4147)	0.32
Time from admission to enoxaparin initiation (days)	2 (1-2)	2 (2-2)	0.10
Proportion receiving SQH initiated prior to enoxaparin	19 (39.6)	30 (60.0)	0.04[a]
Number of doses before enoxaparin started	2 (2-4)	3 (2-4)	0.705
Missed enoxaparin doses	0 (0-0)	0 (0-1)	0.03[a]
Proportion with at least one missed dose	9 (18.8)	20 (40)	0.02[a]
LOS (days)			
Hospital	7 (5-14)	9 (5-12)	0.69
ICU	2 (1-4)	2 (0-5)	0.86

Note: Continuous data results reported as median (IQR) unless otherwise noted. Nominal data reported as number (%), unless otherwise noted.

[a]Statistically significant.

[b]The ISS ranges from 0 to 75, with the highest score indicating an unsurvivable injury.

[c]The AIS ranges from 1 to 6, with the highest score being currently untreatable.

[d]The RAP score ranges from 0 to 46, with higher scores indicating higher risk.

[e]CrCl calculated using Cockroft and Gault methodology using ideal body weight.

Table 2. Multivariate Logistic Regression Analysis for Independent Risk Factors for Subprophylactic Trough anti-Xa

Variable	Odds Ratio (95% CI)	P-value
Age	1.00 (0.97-1.04)	0.83
Weight, kg	0.96 (0.93-0.99)	0.014
RAP score	0.89 (0.78-1.02)	0.098
On heparin prior to enoxaparin	0.33 (0.13-0.84)	0.02
Admission CrCl	0.98 (0.96-1.00)	0.11
AT-III, %	1.02 (0.99-1.04)	0.16

CI = confidence interval.

Initial serum AT-III activity was 87% (IQR 80-98) in the control group and 82% (IQR 71-96) in the intervention group (P = 0.092; Figure 5). Initial AT-III was not different between groups 1 and 2 (80% [IQR 69.8-87.8] vs. 84% [IQR 73.5-96.5], P = 0.35). There was no difference in AT-III between group 1 and group 2 at the first and second assays following dose adjustments. Intragroup comparison over time revealed a statistically significant increase in AT-III for the intervention group from initial assay (82% [IQR 70-96]) to the first (91% [IQR 75-105], P < 0.01) and second (95% [IQR 81-105], P < 0.01) assays following dose adjustment and from the initial assay to the first repeat assay in group 1 (80% [IQR 70-87] vs. 86% [IQR 75-102], P = 0.02, Figure 5). The proportion of patients with relative AT-III deficiency was 10 (10.4%) patients vs. 20 (40.8%) patients in the control group and intervention group, respectively (P = 0.065). There was no difference in proportion of patients with relative AT-III deficiency between groups 1 and 2 prior to dose adjustment (11 [44%] patients vs. 9 [37.5%], P = 0.86) or at the first assay post-dose adjustment (9 [40.9%] patients vs. 5 [29.4%], P = 0.69).

Anti-Xa trough assessment following dose adjustment in the intervention group was performed in 21 (80.8%) and 18 (72%) patients in groups 1 and 2, respectively. Median time to anti-Xa trough achievement from initiation of enoxaparin was 7 days in both group 1 (IQR 5-8) and group 2 (IQR 4-8, P = 0.29). Goal trough anti-Xa was achieved on first assessment after dose adjustment in 8 (38.1%) patients in group 1 vs. 9 (50%) patients in group 2 (P = 0.53). At second trough assessment, 11 (84.6%) were at goal in group 1 vs. 8 (53.3%) in group 2 (absolute difference 33%, P = 0.11). A similar proportion of patients reached goal across all trough anti-Xa assessments between groups 1 and 2 (15 [71.4%] vs. 13 [72.2%], P = 0.76). Intragroup evaluation of groups 1 and 2 revealed a statistically significant decrease in the proportion of patients who remained subprophylactic at the first vs. second repeat assay following dose adjustment (61.9% vs. 15.4%, P = 0.03); there was no difference in group 2 (50% vs. 46.7%, P = 0.57). Evaluation of detectable trough anti-Xa was no different on first assessment following dose adjustment for enoxaparin 40 mg every 12 hours (0.19 IU/mL [IQR 0.13-0.25]) and enoxaparin 30 mg every 8 hours (0.14 IU/mL [IQR 0.10-0.17], P = 0.21, Figure 6). Overall median trough anti-Xa concentration across all assays was 0.19 IU/mL (IQR 0.14-0.26, n = 29 assays) in group 1 and 0.16 IU/mL (IQR 0.12-0.19, n = 25 assays) in group 2 (P = 0.075). Median trough anti-Xa concentrations for each dose were 0.22 IU/mL (IQR 0.13-0.30, n = 4 assays) for 30 mg every 12 hours, 0.21 IU/mL (IQR 0.18-0.29, n = 15 assays) for 40 mg every 12 hours, 0.15 IU/mL (IQR 0.13-0.17, n = 10) for 50 mg every 12 hours, and 0.16 IU/mL (IQR 0.12-0.19, n = 25 assays) for 30 mg every 8 hours following dose adjustments (P = 0.039; Dunn's method for pairwise multiple comparison showed no statistical difference on ranks).

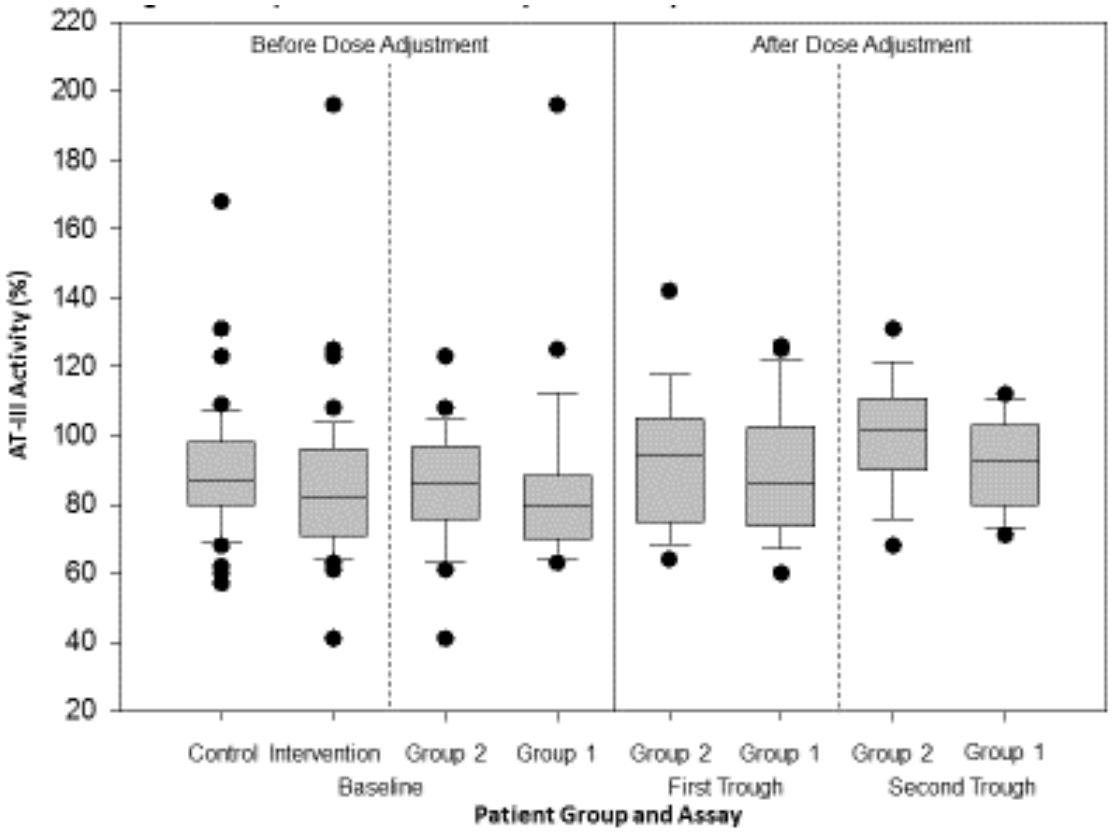

Figure 5. Comparison of AT-III activity at each assay. No statistical difference between groups at each time point.

Peak anti-Xa assessment for enoxaparin 40 mg every 12 hours was 0.20 IU/mL (IQR 0.16-0.31, n = 15) and 0.20 IU/mL (IQR 0.14-0.27, n = 14) for enoxaparin 30 mg every 8 hours (P = 0.21). A post hoc analysis revealed the proportion of patients at goal peak was 7 (38.9%) on 40 mg every 12 hours and 7 (41.2%) on 30 mg every 8 hours (P = 0.84). Three patients in each group had undetectable peak (group 1 16.7% vs. group 2 17.6%; P = 1.00). Eighteen patients in group 1 and 16 patients in group 2 had peak and trough assessments following first dose adjustment. Peak and trough anti-Xa were at goal in 4 (22.2%) patients in group 1 compared to 4 (25.0%) patients in group 2 (P = 1.00). Bioaccumulation requiring dose adjustment occurred in 3 (14%) patients in group 1: 50 mg subsequently decreased to 40 mg and 30 mg on consecutive weekly assessments, 40 mg decreased to 30 mg after second assessment, and 40 mg decreased to 30 mg on first assessment. No patients in group 2 required dose adjustment for bioaccumulation (P = 0.24).

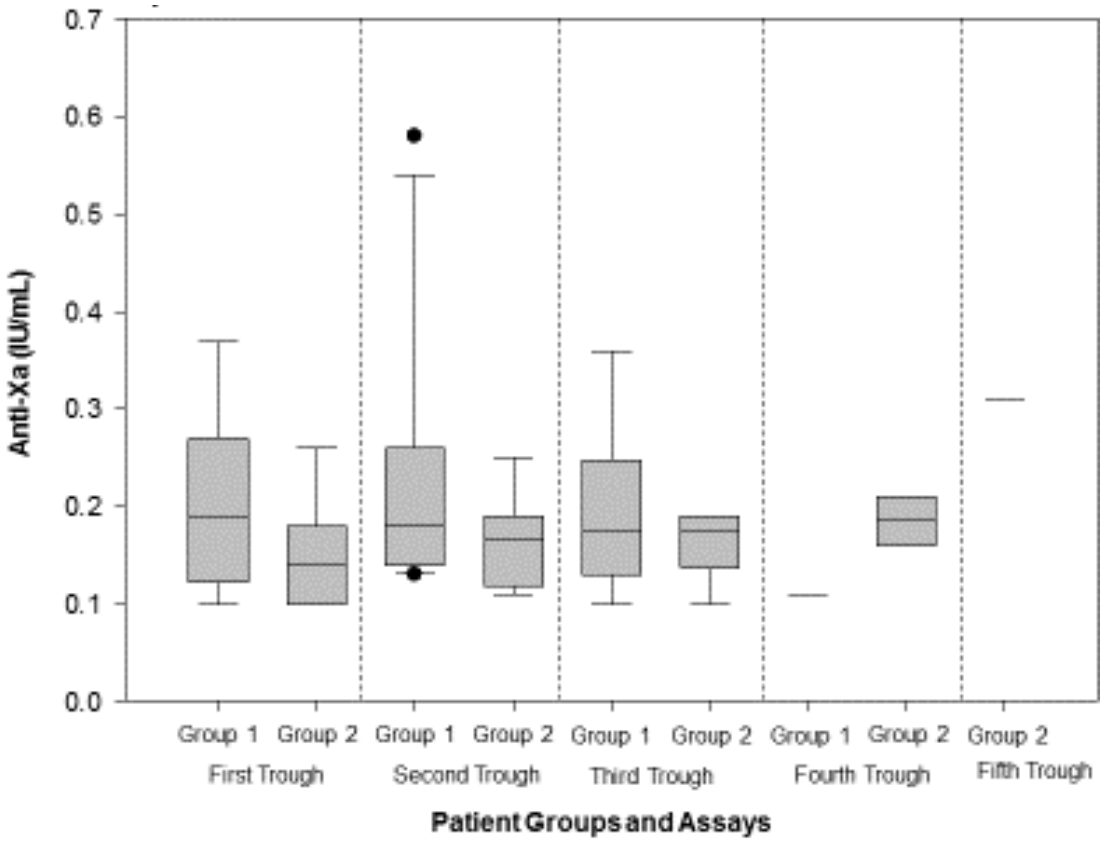

Figure 6. Comparison of anti-Xa trough concentration at each assay following dose adjustment. No statistical difference between groups at each time point.

TEG results demonstrated no difference between patient groups at any time point except maximum amplitude was higher in the intervention group at baseline (66.7 seconds [IQR 63.5-71.6] vs. 70.3 [IQR 66.8-73.1], P = 0.004, Table 3). No VTE occurred in any groups while on protocol enoxaparin doses. Bleeding events and transfusion requirements were similar for control and intervention groups and groups 1 and 2 (Table 4).

Table 3. Thromboelastography Results Between Groups at Each Assay

TEG Component	Control n = 47	Intervention n = 51	P-value	Group 1 (40 BID) n = 26	Group 2 (30 q8h) n = 25	P- value
Baseline						
R time, s	230 (195-265)	250 (195-300)	0.22	240 (195-300)	250 (208-305)	0.95
K time, s	65 (55-75)	65 (55-75)	0.96	65 (55-75)	65 (53-73)	0.94
Angle	77.4 (75.9-78.9)	77.5 (76.5-79.2)	0.61	77.6 (76.4-79.0)	77.4 (76.0-79.5)	0.98
MA	66.7 (63.5-71.6)	70.3 (66.8-73.1)	0.004	69.6 (66.3/73.0)	70.4 (66.7-71.6)	0.96
LY30, %	1.0 (0.5-2.1)	1.2 (0.3-2.5)	0.38	1.3 (0.3-2.1)	1.25 (0.4/2.1)	0.45
At 1st trough after dose adjustment						
R time, s	--	255 (225-285)	--	250 (240-285)	257 (200-285)	0.83
K time, s	--	55 (50-65)	--	55 (50-60)	55 (50-65)	0.74
Angle	--	79.7 (77.8-81.2)	--	79.8 (78.1-81.0)	79.5 (77.8-81.2)	0.63
MA	--	74.7 (70.7-77.9)	--	73.8 (70.7-78.2)	74.8 (71.3-77.8)	0.96
LY30, %	--	0.9 (0.1-2.2)	--	0.9 (0.3-1.6)	1.0 (0.1-2.3)	0.92
At 2nd trough after dose adjustment						
R time, s	--	248 (200-285)	--	252 (235-330)	243 (183-275)	0.41
K time, s	--	53 (50-65)	--	50 (50-65)	55 (50-60)	0.81
Angle	--	79.8 (78.0-80.9)	--	80.3 (77.9-81.2)	79.6 (78.3-80.5)	0.53
MA	--	74.9 (71.7-77.1)	--	75.1 (73.8-77.1)	74.9 (70.1-76.0)	0.35
LY30, %	--	0.4 (0.1-1.7)	--	0.4 (0-0.7)	1.3 (0.3-2.3)	0.09

Note: Continuous data results reported as median (IQR) unless otherwise noted. Kaolin TEG reference ranges: R time 300-600 s, K time 60-180 s, angle 53-72, MA 50-70, LY30 0-8%. BID = twice a day; MA = maximum amplitude; LY30 = thrombolysis at 30 min.

Table 4. Comparison of Bleeding Outcomes

Outcome	Control n = 47	Intervention n = 51	P-value	Group 1 (40 BID) n = 26	Group 2 (30 q8h) n = 25	P-value
Major bleeding events	0 (0-0) 0-4 full range	0 (0-0) 0-2 full range	0.604	0 (0-0) full range 0-2	0 (0-0) full range 0-1	0.41
Minor bleeding events	0 (0-0) 0-4 full range	0 (0-1) 0-4 full range	0.085	0 (0-1) 0-1 full range	0 (0-0) 0-4 full range	0.57
Transfusions						
Entire admission						
Median (IQR)	0 (0-3)	0 (0-3)	0.83	0.5 (0-3)	0 (0-2)	0.80
Mean (SD)	1.94 (3.4)	2.0 (4.6)	0.92	1.65 (2.28)	2.4 (6.23)	0.57
After 1st 48 h until discharge						
Median (IQR)	0 (0-0)	0 (0-1)	0.24	0 (0-1)	0 (0-1)	0.991
Mean (SD)	0.70 (1.74)	0.73 (1.28)	0.94	0.81 (1.50)	0.64 (1.0)	0.645

Note: Continuous data results reported as median (IQR) unless otherwise noted. Nominal data reported as number (%), unless otherwise noted.

5.0 DISCUSSION

This single center, prospective, randomized clinical trial is the first to compare AT-III activity between patients at goal prophylactic versus subprophylactic trough anti-Xa in high-risk trauma patients. Consistent with previous literature, 50.5% of patients had subprophylactic anti-Xa [10,13,17,22]. Patients with subprophylactic anti-Xa had lower AT-III activity (absolute difference of 5%) and higher proportion with relative AT-III deficiency (absolute difference of 30.4%) compared to patients having goal prophylactic anti-Xa concentrations. To our knowledge, this also is the first study to prospectively randomize patients to different dosing strategies based on 8-hour trough anti-Xa concentration. Enoxaparin 40 mg every 12 hours with potential adjustment to 50 mg every 12 hours resulted in achievement of goal trough anti-Xa in a 33% higher proportion of patients than enoxaparin 30 mg every 8 hours by the sixth enoxaparin dose; albeit not statistically significant, this could be clinically relevant. Importantly,

reassessment of trough assays of both dose adjustment strategies demonstrated low risk of bioaccumulation.

Enoxaparin pharmacodynamic effect is achieved through complexing with endogenous AT-III to augment the binding and decrease the activity of factors Xa and IIa. Theoretically, a relative AT-III deficiency would reduce substrate availability for enoxaparin to exert desired antithrombotic properties. While other studies have observed or reported AT-III deficiency in trauma patients [14-20], this is the first study to evaluate AT-III as a primary endpoint relative to subprophylactic trough anti-Xa concentrations. While the results are not statistically significant and the clinical impact of a 5% absolute difference in AT-III is unknown, the numerical trend toward a greater proportion of patients with relative AT-III deficiency provides credence for future investigations.

Trough anti-Xa timing at 8 hours rather than 12 hours post-dose has not been evaluated previously for dose adjustment. Hass et al. [23] demonstrated 64% and 81% of non-edematous ICU trauma patients with an ISS > 10 had undetectable anti-Xa at 8 and 12 hours. If anti-Xa are undetectable at 8 hours, there is potential for approximately 4 hours without adequate thromboprophylaxis. The choice of an 8-hour post-dose serum anti-Xa concentration was to evaluate clearance and promote safe, pharmacokinetically based administration of enoxaparin with an 8-hour frequency without risking drug accumulation. Berndtson et al. [24] performed modeling based on prior literature that determined weight-based enoxaparin 0.33 mg/kg every 8 hours was predicted to be subprophylactic in 66.67% of patients. No other recent studies have explored an 8-hour dosage interval. With only 53.3% of patients in the current study obtaining goal while receiving enoxaparin 30 mg every 8 hours, the authors would not routinely recommend this dosage in high-risk trauma patients.

Time to goal anti-Xa was 7 days after enoxaparin initiation across intervention groups. Identification of subprophylactic concentrations earlier could reduce the time to goal anti-Xa achievement and may reduce VTE. Ko et al. [25] demonstrated 83.9% of subprophylactic troughs were adjusted to enoxaparin 40 mg every 12 hours with subsequent titration with the majority of patients (65.5%) remaining on enoxaparin 40 mg every 12 hours. Droege et al. [13] evaluated dalteparin concentrations 12 hours after the first dose of 5000 units every 24 hours with a significant decrease in VTE (7% pre- vs. 13% post-anti-Xa dose adjustment protocol initiation, $P = 0.009$) without an increase in bleeding (1.97 [SD 5.8] vs. 2.05 [SD 6.7] packed red cell transfusions per patient, $P = 0.87$). In an era when VTE prophylaxis is advocated within 24 hours of admission in recently hemostatic patients, a pragmatic approach is needed to bridge the safety and efficacy gap by early assessment of anti-Xa on standard enoxaparin doses rather than starting on elevated doses. Further studies are needed to evaluate bleeding risks with anti-Xa assessment following the first enoxaparin dose to allow rapid dose escalation.

No VTE events occurred while patients were on study medication. While the sample size may have contributed to this finding, the proportion of patients that achieved target anti-Xa may suggest maintaining detectable concentrations throughout the dosage interval as a surrogate biomarker for efficacy. Previous studies evaluating 12-hour trough anti-Xa have shown reductions in VTE in patients with appropriately prophylactic concentrations [25]. In contrast, studies evaluating peak-driven dose adjustment strategies have variable impact on VTE reduction [26-30]. Fortunately, all dose adjustment strategies have shown minimal impact on bleeding outcomes [13, 25-30].

There are multiple limitations to this study. First, 8-hour anti-Xa concentrations for a 12-hour dosing regimen are not a true trough concentration. The proportion at goal could be overestimated based on this approach. Nonetheless, it is notable that more than half of patients were subprophylactic at this time point. Second, slow enrollment resulted in early study termination, resulting in an underpowered sample to adequately evaluate the primary outcomes based on the a priori power analysis hypothesizing a larger absolute difference between groups than what was found. Third, the change in trauma team standards of care in fall 2016 to a weight-based approach for patients weighing 125 kg or more or a BMI of 40 kg/m^2 limited enrollment of patients, rather than enrolling up to 150 kg per protocol. Fourth, based on head AIS and exclusion of isolated intracranial hemorrhage, the results of this study may not be extrapolated to a traumatic brain injury population. Fifth, inclusion of patients who received SQH prior to enoxaparin may have resulted in an inducible AT-III deficiency. Although this is unlikely to be a significant clinical effect, further studies are needed to confirm the impact of SQH administration on subsequent anti-Xa concentrations. Finally, the study did not isolate patient-specific variables in patients requiring adjustment to 50 mg every 12 hours versus decrease to 30 mg every 12 hours in group 1. Elucidation of these features may improve the feasibility of starting a weight-based dosage regimen.

6.0 CONCLUSION

A trend toward reduced AT-III exists for patients with subprophylactic anti-Xa. However, AT-III was not an independent risk factor for low anti-Xa. Although there was no difference overall, a higher proportion of patients receiving dose-adjusted enoxaparin every 12 hours achieved goal anti-Xa concentrations earlier. Further investigation is needed to evaluate the link between AT-III deficiency, anti-Xa, and VTE. Additional studies are needed to elucidate additional strategies to improve the time to goal trough anti-Xa obtainment as well as evaluate bleeding risks with anti-Xa assessment following the first enoxaparin dose to allow rapid dose escalation.

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LIST OF ABBREVIATIONS AND ACRONYMS

AIS	abbreviated injury score
anti-Xa	anti-factor Xa
AT-III	antithrombin III activity
BMI	body mass index
BSA	body surface area
CrCl	creatinine clearance
CT	computed tomography
ICU	intensive care unit
ISS	injury severity score
IQR	interquartile range
LMWH	low molecular weight heparins
LOS	length of stay
RAP	risk assessment profile
SD	standard deviation
SQH	subcutaneous heparin
TEG	thromboeslastogram
UCMC	University of Cincinnati Medical Center
VTE	venous thromboembolism