Title

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You're Never Too Old for Optimal Venous Thromboembolism Prophylaxis: Re-Thinking Current Trauma Guidelines

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Authorship Statement

-Johanna M Borst contributed to study design, data acquisition, data analysis and interpretation, and primarily wrote the manuscript.

-Rishi N Modi contributed to study design, data acquisition, and data interpretation, and manuscript review and revisions.

-Tyler N Kirchberg contributed to study design, data acquisition, and data interpretation, and manuscript review and revisions.

-Kevin Box contributed to study design, data interpretation, and manuscript review and revisions.

-Alan M Smith contributed to study design, data acquisition and analysis, and manuscript review.

-Laura N Godat contributed to study design, data interpretation, and manuscript review and revisions.

-Jay J Doucet contributed to study design, data interpretation, and manuscript review and revisions.

-Todd W Costantini contributed to study design, data analysis and interpretation, and manuscript review and revisions.

-Allison E Berndtson led the study design, contributed to data acquisition, data analysis and interpretation, and was the main reviewer and revisionist for the manuscript.

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Trauma patients are at high risk for developing venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). Standard of care to prevent these complications is compression devices and prophylactic enoxaparin; however, the optimal enoxaparin dosing strategy is unknown. Historically, trauma patients received enoxaparin 30mg twice daily (BID), but this was found to be insufficient(1), and recent national guidelines(2, 3) now recommend enoxaparin 40mg BID for most trauma patients.

Increasing age is a significant risk factor for VTE in trauma patients (4), and elderly patients who develop VTE have a higher burden of morbidity and mortality (5). Despite this increased risk of both VTE and VTE-related complications, these same national guidelines (2, 3), recommend 30mg BID for patients 65 years of age and older (65&Up), excluding them from the standard 40mg BID dosage. These recommendations are made due to the lack of data on the safety of higher doses in elderly patients rather than definitive data promoting the use of a lower dosing regimen.

This study assesses the safety of enoxaparin 40mg BID in trauma patients 65&Up when compared to younger patients (Below65). We hypothesized that the dosing regimen's safety profile would be similar regardless of age.

A retrospective review approved by the Institutional Review Board was conducted on patients admitted to our Level 1 trauma center between July 2015 and September 2020. Criteria for inclusion was length of stay >4 days, initiation on 40mg of enoxaparin per our weight-based dosing protocol (50-59kg = 30mg BID, 60-100kg = 40mg BID, >100kg = 50mg BID), and

presence of an appropriately timed (checked 3-5 hours after the administration of at least three consecutive doses) peak anti-Xa level. An in-range prophylactic anti-Xa level was defined as 0.2-0.4 IU/mL. While we dose-adjust enoxaparin to achieve in-range anti-Xa levels, only initial anti-Xa levels are reported here. Patients were excluded if they received initial dosing other than 40mg BID, had renal disease requiring renal replacement therapy, had a CrCl <30mL/min at the time of enoxaparin initiation, or did not receive an appropriately timed anti-Xa assay (SDC 1).

Data on patient's demographics, admission information, injury profile, and VTE/hemorrhagic complications were collected from the trauma registry. Enoxaparin administration data, anti-Xa assay results, and patient weight (kg) and creatinine (mg/dL) prior to enoxaparin initiation were collected by chart review. Patients missing any variables were excluded. Patients received weekly screening lower extremity duplex to assess for DVT per our protocol. For patients with intracranial hemorrhage, enoxaparin prophylaxis is typically initiated 48 hours after a stable repeat CT head.

Data are presented as mean ± standard deviation (SD) or raw percentage score. Continuous variables were analyzed with t-tests; categorical variables were analyzed with chi-square tests. Logistic regression determined whether variables predicted sub-prophylactic anti-Xa levels. Multivariate linear regression identified independent predictors of anti-Xa level. Variables known to impact anti-Xa levels including age, gender, CrCl, and weight were included in our multivariate regression analysis. The Hosmer-Lemeshow goodness-of-fit test was used prior to regression analysis. A p-value of <0.05 was considered statistically significant.

1066 patients met inclusion criteria (SDC 1). Patients were predominantly male (79.5%) with a mean ISS of 15.1 ± 10.5. There were 793 (74.4%) patients in the Below65 age group, and 273 (25.6%) in the 65&Up age group (Table 1). The age groups had similar mean weights

(65&Up = 78.1 ± 10.8kg, Below65 = 79.5 ± 10.5kg, p=0.059), but the 65&Up patients were more often female (30.8% vs. 16.9%, p<0.001) and had a lower mean CrCl (89.0 ± 32.2 vs. 153.5 ± 45.2mg/dL, p<0.001). The 65&Up patients had a higher rate of intracranial hemorrhage (33.7% vs. 25.6%, p = 0.013).

Rates of anti-Xa levels in the prophylactic range and below-range were similar between age groups (p=0.472 & p=0.162). Patients 65&Up more frequently had above-range anti-Xa levels (17.2% vs. 11.1%, p=0.009) (Table 1); however, on multivariate regression, age was not a significant risk factor for above-range anti-Xa levels (p=0.95)(Table 2). Female sex was a risk factor for above-range levels (OR 3.78 [2.52, 5.65], p<0.001) while increasing weight was protective (OR 0.94 [0.92, 0.96], p<0.001). The Hosmer-Lemeshow goodness-of-fit test was appropriate, with no evidence of poor model fit (p=0.838 and p=0.286 per model).

A total of 6 patients had expansion of an existing intracranial hemorrhage (ICH) or a new ICH after starting enoxaparin; four were 65&Up (of 92 with baseline ICH; 4.35%) and two were Below65 (of 203 with baseline ICH; 0.99%) (p = 0.138). All had in-range anti-Xa levels at the time of ICH expansion. Four of the six had stable head CTs after starting enoxaparin and before increased hemorrhage was detected. One Below65 patient required an intervention after re-hemorrhage, and one 65&Up patient died from re-hemorrhage.

Three patients had gastrointestinal hemorrhages; all had in-range anti-Xa levels (Table 1). No clinically significant post-operative bleeding complications occurred in either group.

No difference was found in overall VTE rates (65&Up = 4.0% vs Below65 = 5.0%, p=0.498), DVT rates (3.7% vs 4.5%, p=0.539) or PE rates (0.7% vs 1.1%, p=0.570) between age groups. Patients of all ages with below-range anti-Xa levels were more likely to have a VTE (8.7% vs 3.9%, p=0.004).

Despite prior data showing that enoxaparin 30mg BID is inadequate to achieve target prophylactic anti-Xa levels in patients of all ages, recent guidelines exclude patients ≥ 65 years of age from recommendations to start at 40mg BID. Our study demonstrates enoxaparin 40mg BID has a similar safety profile in patients 65&Up compared to Below65, indicating that elderly trauma patients over 60kg without intracranial hemorrhage can be included in standard dosing protocols.

We did not find a statistically significant difference in the rate of expanding or new ICH after starting enoxaparin between the 65&Up and Below65 groups; however, there was a trend in this direction that may be clinically relevant. Many current guidelines suggest starting all patients with ICH on a lower dose of enoxaparin 30mg BID regardless of age. Our findings favor cautious use of enoxaparin in patients with ICH, and further study is needed before expanding dosing protocols in this patient population.

Initiating elderly patients on lower dose enoxaparin is based on the concern that enoxaparin is more likely to accumulate due to age-related decline in renal function and a lower volume of distribution due to age-related changes in body-weight composition. However, our study found no difference in hemorrhagic complications between 65&Up and Below65 patients.

While we did find that patients 65&Up were more likely to have above-range anti-Xa levels on univariate analysis, this relationship disappeared on multivariate regression. The lack of relationship between age 65&Up and anti-Xa levels is consistent with prior literature. Costantini et al.(1) found no difference in age between sub-prophylactic patients and prophylactic patients. Similarly, Chapman et al.(6) shows no difference in reaching target anti-Xa levels based on age. Most recently, two retrospective reviews found that age was not a predictor of out-of-range anti-Xa levels after regression analysis (7, 8). These studies align with our findings that age alone is

not predictive of lower enoxaparin requirements and initiating enoxaparin at 30mg BID in all patients 65&Up may be unwarranted.

When we evaluated the relationship between anti-Xa levels and VTE incidences, there were higher rates of VTEs in patients with sub-prophylactic initial anti-Xa levels regardless of age. This is consistent with multiple other studies that show higher VTE incidence is higher in patients with sub-prophylactic anti-Xa levels (9, 10), and further supports efforts to get all patients to an appropriate anti-Xa level as quickly as possible by optimizing initial dosing.

While we did not detect any differences in VTE and hemorrhagic events between the Below65 group and the 65&Up group, it is possible that our study size was too small to identify differences due to the low incidences of hemorrhagic complications and VTEs. It is unlikely that any VTE events went undiagnosed due to the comprehensive screening protocol used at our institution.

By analyzing over one thousand patients weighing between 60kg and 100kg who initially received enoxaparin 40mg BID, we found patients 65&Up without intracranial hemorrhage did not have increased hemorrhagic complications compared to patients Below65 on the same protocol. Further study of the safety of 40mg BID dosing in patients of all ages with intracranial hemorrhage is needed. In conclusion, optimal dosing for VTE prophylaxis is crucial in the elderly patient population; initiating enoxaparin at 40mg BID in elderly patients weighing over 60 kg and without ICH is safe and may help reduce VTE rates. National guidelines should reassess select 65&Up patients for inclusion in standard dosing protocols.

Conflict of Interest Statement:

All authors declare that they have no conflicts of interest.

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Table 1: Demographics, Anti-Xa Results, and Outcomes, by Age Group					
	Below65 (N=793)		65&Up (N=273)		p value
Age [y, mean/SD]	40.7	13.8	76.1	8.1	<0.001
Sex [male]	659	83.1%	189	69.2%	<0.001
Weight [kg, mean/SD]	79.5	10.5	78.1	10.8	0.059
Obesity	93	11.7%	35	12.8%	0.632
CrCl [mL/min, mean/SD]	153.5	45.2	89.0	31.2	<0.001
Race					
White	358	45.1%	140	51.3%	0.080
Black	59	7.4%	11	4.0%	0.050
Asian	11	1.4%	2	0.7%	0.395
Other or Unknown	365	46.0%	120	44.0%	0.553
Trauma Mechanism [blunt]	674	85.0%	265	97.1%	<0.001
Injury Severity Score					
Mild (<9)	162	20.4%	58	21.2%	0.774
Moderate (9-15)	297	37.5%	132	48.4%	0.002
Severe (16-24)	191	24.1%	43	15.8%	0.004
Profound (≥ 25)	143	18.0%	40	14.7%	0.201
Intracranial Hemorrhage	203.0	25.6%	92.0	33.7%	0.013
Anti-Xa Level [mean/SD]	0.28	0.1	0.31	0.13	<0.001
Below-Range (<0.2 IU/mL)	152	19.2%	42	15.4%	0.162
In-Range (0.2-0.4 IU/mL)	553	69.7%	184	67.4%	0.471
Above-Range (>0.4 IU/mL)	88	11.1%	47	17.2%	0.009
Venous Thromboembolism	40	5.0%	11	4.0%	0.498
Deep Vein Thrombosis	36	4.5%	10	3.7%	0.539
Pulmonary Embolism	9	1.1%	2	0.7%	0.570
Hemorrhagic Complications					
GI Hemorrhage	2	0.3%	1	0.4%	0.759
ICH Expansion/Pts with ICH	2/203	1.0%	4/92	4.4%	0.138
Post-Op Hemorrhage/Pts with an Operation	0/560	0.0%	0/191	0.0%	-
Hospital Days [mean/SD]	15.3	19.5	11.5	9.4	0.002
ICU Days [mean/SD]	3.9	6.7	4.8	7.2	0.087
Ventilator Days [mean/SD]	2.2	5.5	2.4	6.1	0.044
Mortality	6	0.8%	13	4.8%	<0.001

Creatinine Clearance (CrCl), Gastrointestinal (GI); Intracranial Hemorrhage (ICH); Intensive Care Unit (ICU)

Table 2: Multivariate Analysis of Below and Above Range Anti-Xa Levels

	Below-Range (<0.2 IU/mL)			Above-Range (>0.4 IU/mL)		
	Odds Ratio	95% CI (lower, upper)	p value	Odds Ratio	95% CI (lower, upper)	p value
Age [65&Up]	1.05	(0.66, 1.67)	0.846	1.02	(0.61, 1.7)	0.95
Sex [female]	0.24	(0.13, 0.46)	<0.001	3.78	(2.52, 5.65)	<0.001
Weight [kg]	1.05	(1.04, 1.07)	<0.001	0.94	(0.92, 0.96)	<0.001
CrCl [mL/min/100]	1.24	(0.84, 1.83)	0.289	0.70	(0.43, 1.15)	0.161
Creatinine Clearance (CrCl)						

Supplemental: Figure 1: Patient Inclusion and Exclusion Criteria