

Venous Thromboembolism Prophylaxis in Underweight Hospitalized Patients

Clinical and Applied
Thrombosis/Hemostasis
Volume 27: 1-6
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10760296211018752
journals.sagepub.com/home/cat



Douglas Buckheit, PharmD¹, Amanda Lefemine, PharmD² ,
Diana M. Sobieraj, PharmD, FCCP, BCPS^{1,3} , and Laura Hobbs, PharmD, BCPS¹

Abstract

There is limited evidence about optimal anticoagulant dosing for venous thromboembolism (VTE) prophylaxis in underweight patients. The purpose of this study was to characterize dosing strategies used in underweight patients and compare the incidence of bleeding and VTE to patients receiving a standard dose. This multi-center retrospective study evaluated medicine patients who weighed 45 kilograms or less and received VTE prophylaxis with unfractionated heparin or enoxaparin. We categorized subjects into groups as either standard or reduced dose and compared the incidence of bleeding and VTE between groups. Of the 300 patients included in the outcome analysis, 40.7% received a reduced dose regimen, most often enoxaparin 30 mg daily. Standard dose was associated with major bleeding compared with reduced dose, when adjusted for age, gender and admission hemoglobin (odds ratio 4.73, 95% confidence interval 1.05 to 21.34). Incidence of clinically relevant non-major bleeding (2.4% vs. 1.1%) and VTE (0.6% vs. 0%) were similar between groups. Anticoagulant dose reduction for VTE prophylaxis in underweight hospitalized medicine patients is common practice and associated with less major bleeding.

Keywords

thrombosis prophylaxis, anticoagulants, deep venous thrombosis, pulmonary embolism, bleeding

Date received: 24 March 2021; revised: 16 April 2021; accepted: 30 April 2021.

Introduction

Venous thromboembolism (VTE) is estimated to be the third leading cause of cardiovascular death.¹ Non-fatal VTE also carries significant morbidity, through VTE recurrence or development of chronic venous insufficiency.² Pharmacologic prophylaxis with anticoagulants in higher-risk hospitalized patients is a well-established practice that has been shown to reduce the incidence of VTE and its consequences.³

Selection of appropriate anticoagulant doses for VTE prophylaxis in the extremes of weight is challenging. In patients classified as obese, a higher dose of anticoagulant is required to sufficiently protect against VTE compared to non-obese patients.⁴⁻⁶ In patients weighing less than 55 kg, anti-Xa levels inversely correlate with body weight.⁷ Anti-Xa levels were highest in the subgroup of patients weighing less than 45 kg and the odds of exceeding the recommended anti-Xa level for prophylaxis was 8 times higher in the same subgroup of patients compared with heavier patients.⁷ Whether elevated anti-Xa levels correlate with higher bleeding risk in underweight patients is unknown.⁸⁻¹⁰

Based on this evidence, some advocate for reducing the prophylactic dose of enoxaparin to 30 mg daily.¹¹ Practice

guidelines and drug manufacturers do not make specific recommendations for dose adjustments in underweight patients.^{3,12} Real-world evidence in critically ill, underweight patients who receive VTE prophylaxis suggests bleeding is more frequent compared to the incidence reported in clinical trials although the incidence of major bleeding did not differ significantly between standard and reduced dose groups.^{8,9} Similar observations were made in a population of mixed levels of care.¹⁰ We sought to characterize the dosing strategies used for VTE prophylaxis in underweight patients admitted to general medicine units and to compare the incidence of bleeding, VTE, and length of stay in patients who receive a reduced versus standard dose.

¹ Department of Pharmacy Services, Hartford Hospital, Hartford, CT, USA

² University of Rhode Island College of Pharmacy, Kingston, RI, USA

³ Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, CT, USA

Corresponding Author:

Laura Hobbs, Department of Pharmacy Services, 80 Seymour Street Hartford, CT 06102, USA.

Email: laura.hobbs@hhchealth.org



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use,

reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Methods

Study Design and Patient Population

This was a multi-center retrospective study approved by our Institutional Review Board. We evaluated patients hospitalized at 1 of 4 hospitals within the Hartford HealthCare system between May 1, 2017 and November 30, 2019. Patients meeting the following criteria were included: age at admission between 18 and 89 years (inclusive), admission to a medicine floor or medical stepdown unit, weight at admission ≤ 45 kg, length of hospitalization ≥ 72 hours, and received VTE prophylaxis for at least 48 hours with unfractionated heparin (UFH) $\leq 15,000$ units subcutaneously (SC) per day or enoxaparin ≤ 40 mg SC per day. Patients were excluded from our analysis if they were admitted with a suspected VTE or bleed, had a creatinine clearance [CrCl] < 30 mL/min, received hemodialysis during their admission, or were admitted for obstetric treatment.

The primary objective was to characterize VTE prophylaxis regimens prescribed to underweight patients. The secondary objectives were to compare outcomes of bleeding, VTE and length of stay in patients receiving standard versus reduced dose VTE prophylaxis. Patients were categorized into the standard dose group if they received UFH 5000 units 3 times daily or enoxaparin 40 units per day; regimens with total doses less than this were considered to be a reduced dose. We excluded patients from analysis of health outcomes if they received more than one VTE prophylaxis regimen during their admission, described as a change in anticoagulant, dose, and/or frequency at any point during the admission compared to the initial order.

We verified inclusion criteria and collected data using a combination of reports and manual review of the electronic medical record. For included patients, we collected patient demographics, comorbidities, VTE prophylaxis dosing regimens, time to first dose of anticoagulant, therapy duration, concurrent use of antiplatelet agents, estimated creatinine clearance using actual body weight, International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score,¹³ and data used to assess bleeding and VTE outcomes of interest.

Outcome Definitions

Bleeding events were considered related to VTE prophylaxis if they occurred within 24 hours of the last dose of pharmacologic VTE prophylaxis. Bleeding events were considered major bleeding if the bleed was fatal, hemoglobin decreased by ≥ 2 g/dL, the patient required transfusion of ≥ 2 units of packed red blood cells or whole blood in 24 hours, or bleeding occurred in any critical organ (retroperitoneal, intracranial, intraspinal, intraocular, intra-articular, pericardial, or intramuscular with compartment syndrome).¹⁴ Hemoglobin decreases ≥ 2 g/dL that occurred within the first 24 hours of admission in patients who received ≥ 30 mL/kg of intravenous fluids were considered dilutional and were not considered a bleeding event.^{8,15,16} Clinically relevant, non-major bleeding (CRNMB)

was defined as any bleeding that did not meet the criteria for major bleeding, but required medical intervention by a health-care professional, or led to an increased level of care. An acute VTE was defined as any VTE event occurring within 24 hours of VTE prophylaxis administration. Patient encounters with an ICD-10 code for a VTE or bleeding event underwent a manual chart review to confirm the event. Any DVT in the popliteal, femoral, or iliac veins was considered clinically relevant, while VTE occurring elsewhere was considered asymptomatic.

Statistical Analysis

Data were reported descriptively to characterize patient demographics. Subjects were categorized into either the “standard dose” group or “reduced dose” group based on the dose of VTE prophylaxis prescribed. Normality for the study population was tested with the Kolmogorov-Smirnov test. Continuous variables were presented as medians with interquartile ranges, and comparisons between groups were analyzed using the Mann-Whitney U test. Dichotomous variables were presented as values and percentages and comparisons between groups were analyzed using Chi-squared tests or Fisher’s exact test. Multivariable logistic regression using backward elimination was used to calculate an odds ratio with accompanying 95 percent confidence interval for the association of VTE prophylaxis dosing with major bleeding. The analysis was adjusted for gender, age (65 years of age and older) and low hemoglobin on admission (lower than 13mg/dL for males and 11.5mg/dL for females).¹⁷ A *P*-value < 0.05 was considered significant. Analyses were conducted with IBM SPSS Statistics Version 26.

Results

We assessed 2793 patient records for eligibility and 2251 did not meet the inclusion criteria (Figure 1). Of the 541 remaining patients, 200 were subsequently excluded because of a CrCl < 30 mL/min ($n = 180$, 33.2%), suspected VTE or bleed on admission ($n = 18$, 3.3%), or obstetric treatment ($n = 2$, 0.4%). We included 341 patients and describe the prescribing patterns observed. Of the 341 patients, 300 received 1 VTE prophylaxis regimen and we present the demographics and analysis of health outcomes in this group.

In the 341 patients, 6 different VTE prophylaxis regimens were prescribed initially (Tables 1 and 2). More patients were started on a standard dose regimen ($n = 213$, 62%) as opposed to a reduced dose regimen ($n = 128$, 38%). Overall, initial prescription of enoxaparin ($n = 176$, 52%) and unfractionated heparin ($n = 165$, 48%) was similar. Of the 341 patients, 41 (12.3%) were switched to a second regimen during the study period (Table 2) and most often this was a switch from a standard to reduced dose regimen ($n = 30$, 73%) as opposed to staying in the same dose regimen ($n = 6$, 15%) or increasing the dose ($n = 5$, 12%).

The demographics of the 300 patients who received one VTE prophylaxis regimen are presented in Table 2. Most

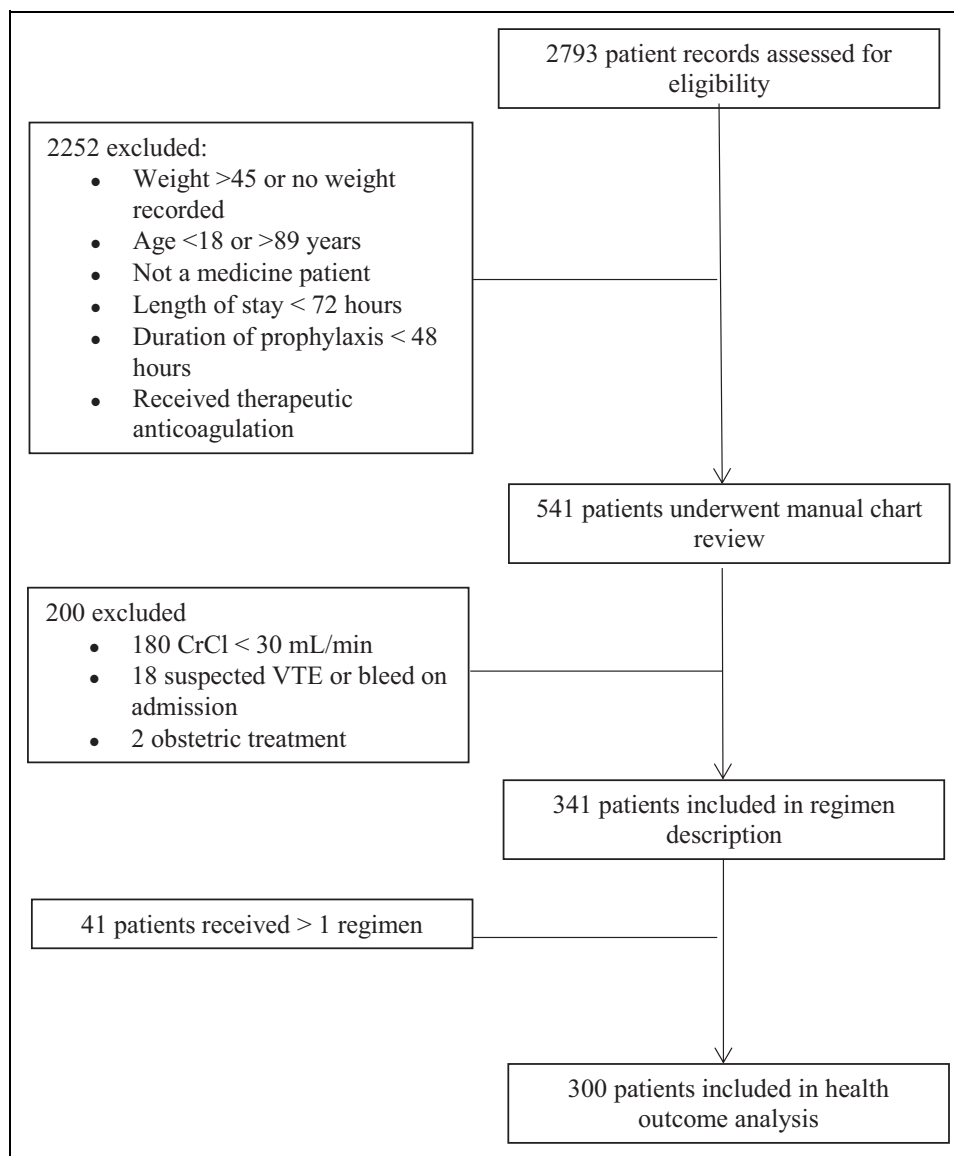


Figure 1. Flowchart of study participants.

Table 1. Venous Thromboembolism Prophylaxis Regimens for Patients Receiving More Than One Regimen.

Change in dosing strategy	Regimen 1	Regimen 2	Number of patients
Switched from standard to reduced dose (n = 30, 73%)	Enoxaparin 40 mg QD	Enoxaparin 30 mg QD	17
	Heparin 5000 units TID	Enoxaparin 30 mg QD	8
	Heparin 5000 units TID	Heparin 5000 units BID	5
Remained in same dose category (n = 6, 15%)	Heparin 5000 units TID	Enoxaparin 40 mg QD	3
	Enoxaparin 40 mg QD	Heparin 5000 units TID	2
	Enoxaparin 30 mg QD	Heparin 2500 units TID	1
Switched from reduced to standard dose (n = 5, 12%)	Enoxaparin 30 mg QD	Heparin 5000 units TID	2
	Enoxaparin 30 mg QD	Enoxaparin 40 mg QD	3

Abbreviations: BID, twice daily; TID, 3 times daily; QD, daily.

patients were prescribed standard dose VTE prophylaxis with heparin 5000 units SC 3 times daily (n = 115, 38%) followed by enoxaparin 40 mg SC daily (n = 63, 21%). Among patients

receiving reduced dose prophylaxis, 4 different regimens were used: heparin 5000 units SC twice daily (n = 87, 29%), enoxaparin 30 mg SC once daily (n = 33, 11%), heparin 2500 units

SC 3 times daily ($n = 1, 0.3\%$), and enoxaparin 20 mg SC once daily ($n = 1, 0.3\%$). The IMPROVE score was 2 or higher in 69.6% of the study population, warranting chemical

Table 2. Venous Thromboembolism Prophylaxis Regimens in Patients Receiving One Regimen.

Regimen	Standard (n = 178)	Reduced (n = 122)
Unfractionated heparin, n (%)		
Heparin 5000 units TID	115 (64.6)	0 (0)
Heparin 5000 units BID	0 (0)	33 (27.0)
Heparin 2500 units TID	0 (0)	1 (0.8)
Enoxaparin, n (%)		
Enoxaparin 40 mg daily	63 (35.4)	0 (0)
Enoxaparin 30 mg daily	0 (0)	87 (71.3)
Enoxaparin 20 mg daily	0 (0)	1 (0.8)

Abbreviations: BID, twice daily; TID, 3 times daily; mg, milligrams.

prophylaxis according to our system-wide guidelines. Patients who received a reduced dose were older and had a lower CrCl, a longer time to first dose of VTE prophylaxis, and shorter duration of VTE prophylaxis (Table 3).

Standard dose VTE prophylaxis was associated with major bleeding compared with reduced dose prophylaxis, (odds ratio 4.73, 95% CI 1.05 to 21.34), adjusted for gender, age and low hemoglobin on admission (Table 4). Most major bleeding events (13 of 15 events) were classified as a drop in hemoglobin of ≥ 2 g/dL. Of the 15 patients that experienced a major bleed, 13 received a standard dose (9 received heparin 5000 units TID and 4 received enoxaparin 40 mg daily) while 2 received a reduced dose (heparin 5000 units BID) of VTE prophylaxis.

Five patients experienced a CRNMB, 2 in the standard dose and 3 in the reduced dose groups [2 (1.1%) vs. 3 (2.4%), $P = 0.38$]. No patients in the standard dose group experienced a VTE while 1 patient had a lower extremity DVT

Table 3. Baseline Characteristics of Patients Receiving One Regimen for Venous Thromboembolism Prophylaxis.

Characteristic	All (n = 300)	Standard (n = 178)	Reduced (n = 122)
Age ^{a, b}	71.50 (60.8, 80.0)	69.50 (58.0, 77.0)	76 (64.3, 83.0)
Age ≥ 65 y n (%)	204 (68)	113 (63.5)	91 (74.6)
Male gender, n (%)	44 (14.6)	27 (15.1)	17 (13.9)
Weight, kg ^a	41.70 (39.2, 43.4)	41.40 (39.0, 43.5)	41.90 (39.7, 43.3)
Hospital ^b n (%)			
Site 1	134 (44.6)	86 (48.3)	48 (39.3)
Site 2	38 (12.6)	23 (12.9)	15 (12.2)
Site 3	81 (27)	58 (32.5)	23 (18.8)
Site 4	47 (15.6)	11 (6.1)	36 (29.5)
Service, n (%)			
Medical floor	251 (83.6)	144 (80.8)	107 (87.7)
Stepdown unit	49 (16.3)	34 (19.1)	15 (12.2)
Ethnicity, n (%)			
Caucasian	220 (73.3)	125 (70.2)	95 (77.8)
Black	29 (9.6)	19 (10.6)	10 (8.1)
Other/unknown	51 (17.0)	34 (19.1)	17 (13.9)
IMPROVE score at admission, n (%)			
Characteristic	All (n = 300)	Standard (n = 178)	Reduced (n = 122)
Low (0-1)	91 (30.3)	52 (29.2)	39 (31.9)
Moderate (2-3)	187 (62.3)	112 (62.9)	75 (61.4)
High (4+)	22 (7.3)	14 (7.8)	8 (6.5)
Charlson Comorbidity Index, n (%)			
0	6 (2.0)	4 (2.2)	2 (1.6)
Low (1-2)	51 (17.0)	34 (19.1)	17 (13.9)
Moderate (3-4)	89 (29.6)	56 (31.4)	33 (27.0)
High (5+)	154 (51.3)	84 (47.1)	70 (57.3)
SCr at admission ^a	0.60 (0.5, 0.8)	0.60 (0.5, 0.8)	0.60 (0.5, 0.7)
CrCl ^{a, b}	40.10 (35.0, 57.1)	41.01 (36.7, 61.0)	38.96 (34.4, 52.4)
Low Hg at admission, n (%) ^c	121 (40.3)	71 (39.9)	50 (41)
Platelets $< 50,000$, n (%)	0 (0)	0 (0)	0 (0)
Hepatic disease, n (%) ^d	1 (1.3)	0 (0)	1 (3.7)
Bleeding disorder, n (%)	0 (0)	0 (0)	0 (0)
Admitted due to anemia, n (%)	2 (0.7)	2 (1.1)	0 (0)
Time to first dose, hours ^{a, b}	11.41 (7.9, 24.4)	10.34 (7.2, 18.8)	14.64 (8.9, 28.7)
Time from first to last dose, hours ^{a, b}	98.40 (72.0, 159.0)	105.6 (76.2, 166.8)	95.5 (65.1, 133.6)

Abbreviations: CrCl, creatinine clearance; SCr, serum creatinine.

^aData presented as n (%) unless otherwise noted. Median, IQR.

^bStatistically significant (P -value < 0.05).

^cDefined as a hemoglobin < 13 mg/dL in males and < 11.5 mg/dL in females on admission.

^dDefined as an INR > 1.5 on admission. Only 78 patients had an INR available on admission, 51 in the standard dose group and 27 in the reduced dose group.

Table 4. Health Outcomes in Patients Receiving One Regimen for Venous Thromboembolism Prophylaxis.

	All (n = 300)	Standard dose (n = 178)	Reduced dose (n = 122)	Standard vs. reduced dose
Major bleed, n (%)	15 (5)	13 (7.3)	2 (1.6)	OR 4.73 (1.05 to 21.34) ^a
Hgb drop ≥ 2 g/dL	13 (4.3)	11 (6.1)	2 (1.6)	
Transfusion of ≥ 2 units	2 (0.6)	2 (1.1)	0 (0)	
CRNMB, n (%)	5 (1.6)	2 (1.1)	3 (2.4)	<i>P</i> = 0.38
VTE, n (%)	1 (0.3)	0 (0)	1 (0.6)	<i>P</i> = 0.23
PE	0	0	0	
DVT, lower extremity	1	0	1	
Length of stay, hours (median, IQR)	161.0 (98.0, 195.3)	147.7 (98.1, 205.3)	131.2 (98.0, 184.3)	<i>P</i> = 0.29

Abbreviations: CRNMB, clinically relevant, non-major bleed; Hgb, hemoglobin; IQR, interquartile range; OR, odds ratio; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.

^aAdjusted for gender, age ≥ 65 years and low admission hemoglobin.

in the reduced dose group (0% vs. 0.56%, *P* = 0.23). Median length of stay was similar between groups (148 vs. 131 hours, *P* = 0.29).

Discussion

In general medicine practice, a reduced dose of UFH or enoxaparin for VTE prophylaxis was used in 38% of patients studied. This practice was associated with a lower odds of major bleeding; the incidence of VTE was rare. No cases of critical bleeding into a major organ occurred. Most bleeding events were due to a hemoglobin drop of at least 2 g/dL but were not always further documented in the medical record as an active bleed or clinically relevant.

Darzi et al identified several demographic and clinical factors that are associated with bleeding risk in hospitalized medical patients.¹⁷ By nature of our exclusion criteria, several of these characteristics were excluded in our population including admission to the intensive care unit, active bleeding on admission, creatinine clearance of 30 mL/min or less, and body mass index of 40 or greater. Furthermore, our health-system guideline for prescribing VTE prophylaxis suggests exclusion of patients with platelets less than 50,000 cells/mcL. Other predictive variables including history of blood disorders, history of hepatic disease, active gastrointestinal ulcer, or anemia as the reason for admission were close to absent in our population. Therefore, we consider our study population to have an overall low risk of bleeding. Despite this, we found that using standard doses of VTE prophylaxis was associated with major bleeding.

We did not observe signals of potential harms with reducing VTE prophylaxis doses. Our observed incidence of VTE events was low (0.3%) overall and in comparison to prior evidence suggesting a frequency of approximately 1% among the general population receiving VTE prophylaxis.^{11,18} Underweight patients may have a lower risk of VTE since an elevated body mass index increases VTE risk.¹⁹ Underweight patients express higher anti-Xa levels upon standard dose anticoagulation which may have been protective against VTE.⁷

Dose reduction of VTE prophylaxis in underweight patients was common in our population of general medicine patients. This practice has been studied in the past, but in different

populations with differing risk for VTE and bleeding, making it difficult to compare our findings to prior research. Dybdahl et al studied all hospitalized patients (medicine, trauma and surgery) with a weight less than 45 kg that were prescribed enoxaparin for VTE prophylaxis and found 37.1% of regimens in underweight patients were dose reduced (less than 40 mg daily).¹⁰ There were no VTE events and the risk of bleeding was not associated with enoxaparin dose although this analysis wasn't adjusted for confounders. In critically ill patients where regimens using unfractionated heparin predominated, 15.3% of underweight patients received a reduced dose and a numerically higher number of bleeding events occurred in patients who received standard vs. reduced doses.⁸ Betterhauser et al studied patients in the neurology critical care unit where 87% of patients received a reduced dose of VTE prophylaxis, consistent with our definition.⁹ No statistical difference in overall bleeding events was observed based on dose, but a significantly higher proportion of intracranial hemorrhages occurred in underweight patients given standard versus reduced doses.⁹

Our study had several limitations. Being retrospective, we originally planned to conduct a propensity score weighted analysis of major bleeding using previously identified predictors of bleeding in our population. Due to the absence of most of these characteristics within our population, we were unable to do so. We did not further classify doses of anticoagulants, beyond categories of overall standard or reduced dose. We did not assess anti-Xa levels of patients in this study as this was a retrospective study and measuring anti-Xa levels is an uncommon practice in our health system. Even still, our analysis of major bleeding remains robust and adjusted for the predictive variables that were present. Finally, the accuracy of our data is dependent on the accuracy of documentation in the electronic health record therefore we cannot rule out misclassification bias. However, we carefully assessed for the presence of bleeding and VTE outcomes throughout the medical record and thus have confidence in our findings.

Conclusions

A variety of VTE prophylaxis regimens are used in underweight general medicine patients and pre-emptive dose

reduction was common. In underweight medical patients, a standard dose of VTE prophylaxis was associated with major bleeding compared with a reduced dose, which sufficiently provided protection from VTE. Therefore, reducing the dose of VTE prophylaxis in patients who weigh ≤ 45 kg in general medicine units is reasonable; however, these results should be confirmed with prospective studies.

Authors' Note

The data included in this manuscript has been presented at the American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting and Exhibition 2019: Las Vegas, NV; Dec 7 -12, 2019. This study was approved by the Hartford Healthcare Institutional Review Board (HHC-2019-0201).


Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Amanda Lefemine  <https://orcid.org/0000-0001-9694-8346>

Diana M. Sobieraj  <https://orcid.org/0000-0002-5227-0681>

References

1. Wolberg AS, Rosendaal FR, Weitz JI, et al. Venous thrombosis. *Nat Rev Dis Primers*. 2015;1:15006.
2. Office of the Surgeon General (US), National Heart, Lung, and Blood Institute (US). *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism*. Office of the Surgeon General (US); 2008.
3. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e195S-e226 S.
4. Wang TF, Milligan PE, Wong CA, Deal EN, Thoenke MS, Gage BF. Efficacy and safety of high-dose thromboprophylaxis in morbidly obese inpatients. *Thromb Haemost*. 2014;111(1):88-93.
5. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. *Obes Surg*. 2002;12(1):19-24.
6. Vandiver JW, Ritz LI, Lalama JT. Chemical prophylaxis to prevent venous thromboembolism in morbid obesity: literature review and dosing recommendations. *J Thromb Thrombolysis*. 2016;41(3):475-481.
7. Rojas L, Aizman A, Ernst D, et al. Anti-Xa activity after enoxaparin prophylaxis in hospitalized patients weighing less than fifty-five kilograms. *Thromb Res*. 2013;132(6):761-764.
8. Carter C, Bushwitz J, Gowan M, et al. Clinical experience with pharmacological venous thromboembolism prophylaxis in the underweight and critically ill. *Ann Pharmacother*. 2016;50(10):832-839.
9. Betthausen K, Pope H, Gowan M, Human T. Practice patterns of venous thromboembolism prophylaxis in underweight, critically ill patients with neurologic injury. *Neurocrit Care*. 2017;27(1):96-102.
10. Dybdahl D, Walliser G, Pershing M, Collins C, Robinson D. Enoxaparin dosing for venous thromboembolism prophylaxis in low body weight patients. *Clin Med Insights Blood Disord*. 2019;12:1179545X19863814.
11. Sabaaly J, Covert K. Enoxaparin dosing at extremes of weight: literature review and dosing recommendations. *Ann Pharmacother*. 2018;52(9):898-909.
12. Lovenox (enoxaparin) [prescribing information]. Sanofi-Aventis US LLC; May 2020.
13. Rosenberg D, Eichom A, Alarcon M, McCullagh L, McGinn T, Spyropoulos AC. External validation of the risk assessment model of the International prevention registry on venous thromboembolism (IMPROVE) for medical patients in a tertiary health system. *J Am Heart Assoc*. 2014;3(6):1-7.
14. Schulman S, Kearon C. Subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
15. Stamler KD. Effect of crystalloid infusion on hematocrit in non-bleeding patients, with applications to clinical traumatology. *Ann Emerg Med*. 1989;18(7):747-749.
16. Greenfield RH, Bessen HA, Henneman PL. Effect of crystalloid infusion on hematocrit and intravascular volume in healthy, non-bleeding subjects. *Ann Emerg Med*. 1989;18(1):51-55.
17. Darzi A, Karam SG, Charide R, et al. Prognostic factors for VTE and bleeding in hospitalized medical patients: a systematic review and meta-analysis. *Blood*. 2020;135(5):1788-1810.
18. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in medical patients with enoxaparin study group. *N Engl J Med*. 1999;341(11):793-800.
19. Allman-Farinelli MA. Obesity and venous thrombosis: a review. *Semin Thromb Hemost*. 2011;37(8):903-907.