

Original Research

An analysis of in-hospital enoxaparin prescription and bleeding in the predominately middle-, and oldest-old population: insights from a secondary care hospital

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Abstract

Background: Enoxaparin is one of the widely used injectable anticoagulants requiring dose adjustment based on body weight and renal function. Unadjusted or inappropriately adjusted doses can lead to thromboembolic or bleeding events, particularly in patients with advanced age. **Objectives:** This retrospective chart review study primarily aimed to evaluate enoxaparin use, along with exploring factors associated with inappropriate use and bleeding in the elderly population. **Methods:** Baseline characteristics, along with bleeding and thrombotic events, of the patients receiving enoxaparin in the fiscal year 2018-2019 at a secondary care hospital were extracted from the electronic medical record. Prescribed enoxaparin regimens were evaluated against the recommended dose in the package insert, pertinent guidelines, and hospital guidance. Univariate and multivariate analyses were performed to explore factors associated with inappropriate use and bleeding. **Results:** Two hundred and fourteen patients were included. The majority (66.8%) were female, and 39.7% were 80 years or older, with an average age of 74.4 years and a body mass index (BMI) of 24.0 kg/m². Most patients (82.7%) had a creatinine clearance ≥ 30 ml/min. Seventy-six initiations (35.5%) were inappropriate, and 83 problems were found. Underdosing was the most common problem (39.8%), followed by undocumented body weight (22.9%), and inconsistent prophylactic dose per hospital guidance (20.5%). BMI ≥ 25 kg/m² (odds ratio [OR] 2.04 [95% confidence interval [CI] 1.04:3.98]; $p=0.04$) was the only factor associated with inappropriate use. There were 48 bleedings (22.4%), 21 minor (9.8%), and 27 major (12.6%). Hemoglobin (Hb) <10 g/dL was associated with bleedings across all indications (OR 4.25 [95%CI 2.03:8.91]; $p<0.01$). **Conclusions:** In the predominately middle-, and oldest-old population, inappropriate use of enoxaparin was common. Those with BMI ≥ 25 kg/m² and Hb <10 g/dL were at increased risk of underdosing and bleedings, respectively; these patients should be closely monitored.

INTRODUCTION

People are living longer and growth in both the size and the proportion of older persons to the general population occurs in every country.¹ In Asia and the Pacific, the proportion of elderly people, age 60 years or older, was highest in Japan (35.8%). Thailand is ranked eighth in this region (22%).² Living longer typically does not imply living healthier. In one point of view, it is expected that among the elderly, the number of co-morbidities, especially cardiovascular diseases, diabetes,

cancer, chronic respiratory diseases will rise; these non-communicable diseases account for the major causes of elderly hospital admission and death.^{3,4} More comorbidities also correlate with higher drug use and adverse drug events (ADE); a study in the United States found that 48.9% of older patients visited emergency department due to ADE in 2004-2005 required hospital admission.⁵ In another study in South Korea, among the older patients, the middle-old (age 75-84 years) and oldest-old (age ≥ 85 years) groups were more likely to experience ADE when compared to the younger old (age 60-74 years) group.⁶ These data highlight the importance of proper drug use and monitoring for the elderly, especially in certain subgroups, such as the middle-old and oldest old patients.

Enoxaparin is a parenteral anticoagulant approved for the treatment and prevention of thrombosis or embolism in ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), unstable angina (UA), venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism.⁷ In specific populations, including those who are elderly, renally impaired, pregnant, and obese, alteration of pharmacokinetic of enoxaparin requires dosage adjustment.⁸ When compared to other special groups, enoxaparin dosing recommendation in elderly is less clear, and adult dosing is frequently used as reference.^{7,9,10}

While previous studies have revealed various usage patterns of enoxaparin, medication errors, and bleeding in the elderly, these studies largely included the younger old rather than the middle- or oldest-old groups.¹¹⁻¹⁵ We thus set out to evaluate

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the appropriateness of enoxaparin use and bleeding rate in the middle old and oldest old groups, which represented the majority of patients at the Golden Jubilee Medical Center, a secondary care hospital in Thailand.

METHODS

A list of adult patients (≥18 years old) who were prescribed enoxaparin during hospital admission at Golden Jubilee Medical Center between October 1, 2017, and September 30, 2019, or the 2018-2019 fiscal year, was created. Baseline demographics of the patients during the index admission date, such as age, sex, height, body weight, body mass index (BMI), serum creatinine, enoxaparin indication, comorbidities, concurrent medications, and bleeding or thrombosis events were retrospectively extracted from the electronic medical record (EMR). If the necessary baseline data were absent during the index admission, information from the most recent hospital visits, either before or after, was utilized. The rate of inappropriate enoxaparin use was the primary outcome of this study, and the secondary outcomes were in-hospital bleeding and thrombosis events, along with factors associated with inappropriate enoxaparin use and bleeding.

The dose and frequency of enoxaparin therapy were evaluated based on the package insert, drug monograph, drug databases, pertinent practice guidelines. Prophylactic enoxaparin dose was examined in accordance with hospital guidance for VTE prophylaxis. Appropriate therapeutic enoxaparin dose was defined as the dose within the nearest 10-mg to the calculated dose based on actual body weight, appropriate dosing interval was determined based on creatinine clearance (CrCl) calculated by Cockcroft-Gault equation.

In-hospital bleeding and thrombotic events were identified by manual screening for the documented bleeding or thrombosis and change in hemoglobin (Hb) level in the EMR. Major bleeding was defined as clinically evident bleeding with a decrease in the Hb level of ≥2 g/dL or transfusion of ≥2 units of whole blood, occurring at a critical site, or resulting in death,¹⁶ or recorded as “major bleeding” by physician in the progress note. Bleedings, bruises, or hematomas that was documented and did not meet the major bleeding criteria were considered as minor bleedings.

Univariate and multivariate logistic regression analyses were performed to identify factors associated with inappropriate enoxaparin use and bleeding events. Factors with p-value < 0.1 or odds ratio (OR) >1.5, or characteristics of interest in univariate analysis, together with the previously reported significant factors for inappropriate use and bleeding from enoxaparin, such as age, body mass index (BMI), renal failure, platelet count,^{11-13,17,18} were considered for multivariate analyses. Based on the general principle that each covariate added to the model must be supported by at least 10 events,¹⁹ the total number of covariates included was constrained. A multicollinearity test was also carried out to exclude correlated factors from being included in a model.

The sample size of this study was not calculated prior to data

collection, as we intended to evaluate all patients receiving enoxaparin within the 2-year period at our hospital. Descriptive statistics were used to present all baseline characteristics and outcomes; chi-square or fisher’s exact test were used to compare binary outcomes between certain subgroups, univariate and multi-variate logistic regression analyses were performed using IBM SPSS Statistics (Version 23). Two-sided P-value < 0.05 was considered statistically significant. This study was approved by the Institutional Review Board of Siriraj Hospital, Mahidol University (COA.No. Si 703/2020, protocol number 590/2563 [IRB2]).

RESULTS

Enoxaparin was started 214 times during the 2018-2019 fiscal year. The majority of the patients (66.8%) were female, with a mean age of 74.4 years, those aged 80 years or older constituted the largest population group (Table 1). Mean BMI was 24 kg/m², and 82.7% patients had CrCl ≥30ml/min. Prior to the initiation of enoxaparin, 19 patients (8.9%) had no body weight recorded, and 4 patients did not have their serum creatinine levels examined. The most common indication for enoxaparin was VTE prophylaxis (36.0%), particularly in patients who had undergone orthopedic surgeries (knee and hip arthroplasty), followed by NSTEMI/UA (35.5%), VTE treatment (25.2%), and stroke prevention in atrial fibrillation (AF) (3.3%). Aspirin (38.8%) and clopidogrel (33.6%) were commonly used at the time enoxaparin was initiated in the enrolled patients. Thirteen (6.1%) and 39 patients (18.2%) received NSAIDs and PPI, respectively, at the time of enoxaparin initiation.

Table1. Baseline characteristics	
Baseline characteristics	Frequency ; n(%) Total (N :214)*
Sex: female	143 (66.8)
Age (years) ; mean ± SD	74.4 ± 11.3
• <60 years	24 (11.2)
• 60-69 years	45 (21)
• 70-79 years	60 (28)
• ≥ 80 years	85 (39.7)
Body weight (kg) ; mean ± SD†	61.3 ± 15.0
• Undocumented weight	19 (8.9)
• <40 kg	9 (4.2)
• 40-59 kg	88 (41.1)
• 60-79 kg	76 (35.5)
• ≥80 kg	22 (10.3%)
BMI (kg/m ²) ; mean ± SD	24.00 ± 5.4
• BMI ≥ 25 kg/m ²	84 (39.3)
Indications	
• VTE prophylaxis	77 (36.0)
• NSTEMI/unstable angina	76 (35.5)
• VTE treatment	54 (25.2)
• Stroke prevention in atrial fibrillation	7 (3.3)



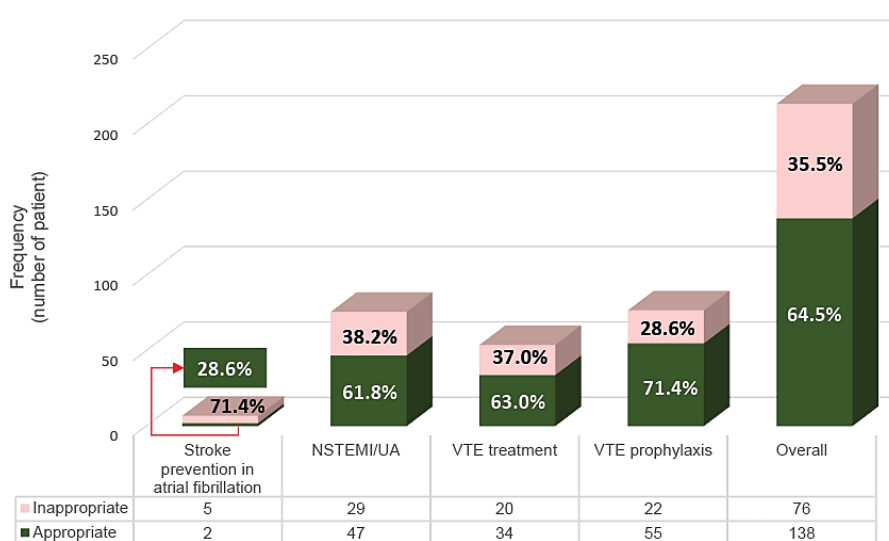
Laboratory parameters	
Creatinine clearance	
• < 15 mL/min	7 (3.3)
• 15-30 mL/min	26 (12.1)
• ≥ 30 mL/min	177 (82.7)
• No record of creatinine clearance	4 (1.9)
Hemoglobin (g/dL ; mean ± SD)	11.3 ± 2.2
Platelet count (x 10 ³ cell/mm ³) ; mean ± SD	253.3 ± 98.5
Significant comorbidities [†]	
• Hypertension	155 (72.4)
• Dyslipidemia	127 (59.3)
• Type 2 diabetes	73 (34.1)
• Cardiovascular diseases [‡]	57 (26.6)
• Stroke or TIA	27 (12.6)
• Cancers	29 (13.5)
Concomitant drugs	
• Aspirin	83 (38.8)
• Clopidogrel	72 (33.6)
• Warfarin	28 (13.1)
• Ticagrelor	7 (3.3)
• Dabigatran	2 (0.9)
• NSAIDs	13 (6.1)
• PPIs	39 (18.2)

* Number of enoxaparin initiation (counts); † Only 195 patients had body weight recorded in the electronic medical record; ‡ Total number exceeds 100 ; as one patient had more than one comorbidities; [‡] Cardiovascular diseases included myocardial infarctions, unstable angina, heart failure
 BMI: body mass index; dL: deciliter; g: gram; kg: kilogram; m²: square meter; min: minute; mL: milliliter; mm³: cubic millimeter; NSAIDs: non-steroidal anti-inflammatory drugs; NSTEMI: non ST-elevated myocardial infarction; PPIs: proton pump inhibitors; SD: standard deviation; TIA: transient ischemic attack; VTE: venous thromboembolism

Of 214 enoxaparin initiations, 138 (64.5%) were considered appropriate for route of administration, dose, and dosing frequency (Figure 1). Among the 76 inappropriate initiations (35.5%), 83 errors were identified, and of which 5 patients had multiple errors. VTE prophylaxis had the highest error prevalence (28 errors, 33.7%), followed by NSTEMI/UA (27 errors, 32.5%) and VTE treatment (22 times, 26.5%). Underdosing was the most common type of error (39.8%) (Table 2), followed by undocumented body weight prior to enoxaparin initiation (22.9%), inconsistent dose per hospital guidance for VTE prophylaxis (20.5%), and improper dosing frequency (10.8%). One patient diagnosed with NSTEMI received an enoxaparin overdose.

At Golden Jubilee Medical Center, during the study period, the recommended prophylactic enoxaparin dose per hospital guidance for orthopedic patients was 40 mg once daily (OD), regardless of renal function. We used this guidance as a reference for evaluation of all prophylactic doses. Consequently, of 17 patients, 3 patients with CrCl <30 mL/min who received a 30mg OD regimen and were initially assessed as receiving inconsistent dose per hospital guidance, were in fact received appropriate dose adjusted for their renal function.⁷ Therefore, the actual prevalence of inconsistent dose per hospital guidance in our study should be slightly lower (6.5% of 214 initiations, and 17.5% of 77 VTE prophylaxis patients). Inappropriate prophylactic doses observed during the study included 20 mg OD, 40 mg twice daily (bis in die, BID), 60 mg OD and BID, and 80 mg OD. For the patient receiving enoxaparin 80mg OD, body weight and renal function were not measured. In addition, 4 patients received enoxaparin for VTE prophylaxis without their renal function examined.

None of the baseline characteristics was significantly associated with inappropriate enoxaparin use in univariate analyses (Table 3). Six covariates were included in the model according to the



NSTEMI = non-ST-elevated myocardial infarction, UA = unstable angina, VTE = venous thromboembolism

Figure 1. Appropriateness of enoxaparin initiation by indication



Table 2. Frequency of inappropriate enoxaparin use by indication of enoxaparin							
Error Indication	Under dosing	Over dosing	Improper frequency	Undocumented body weight*	Hospital guidance inconsistency	Absence of renal function	Total errors
Stroke prevention in AF	4	0	1	1	0	0	6 (7.3%)
NSTEMI / UA	17	1	5	4	0	0	27 (32.5%)
VTE prophylaxis	0	0	0	7	17	4	28 (33.7%)
VTE treatment	12	0	3	7	0	0	22 (26.5%)
Total errors	33 (39.8%) (16.9%) ^Δ	1 (1.2%) (0.5%) ^Δ	9 (10.8%) (4.2%) [¶]	19 (22.9%) (8.9%) [¶]	17 (20.5%) (7.9%) [¶]	4 (4.8%) (1.9%) [¶]	83 (100%) (38.8%) [¶]
AF: atrial fibrillation; NSTEMI: non-ST elevated myocardial infarction; VTE: venous thromboembolism; UA: unstable angina * prior to enoxaparin initiation Some enoxaparin initiation had more than one problem Δ percentage of the errors out of 195 enoxaparin initiation with body weight available ¶ percentage of the errors out of 214 enoxaparin initiations							

Table 3. Factors associated with inappropriate enoxaparin use				
Independent variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	OR (95% CI)	p-value
Sex (Male / female)	1.54 (0.86-2.78)	0.15	1.14 (0.58-2.27)	0.70
Age (years)	1.00 (0.98-1.03)	0.76	1.00 (0.98-1.04)	0.70
Body weight (kg)	0.99 (0.98-1.00)	0.08		
Body mass index	1.05 (0.99-1.11)	0.12		
BMI ≥ 25 kg/m ²	1.83 (1.00-3.34)	0.05	2.04 (1.04-3.98)	0.04
NSTEMI/UA indication	1.20 (0.67-2.14)	0.55	0.43 (0.10-1.80)	0.25
VTE treatment indication	1.09 (0.58-2.07)	0.79	0.36 (0.08-1.55)	0.17
VTE prophylaxis indication	0.62 (0.34-1.12)	0.11	0.27 (0.06-1.18)	0.08
Creatinine clearance				
CrCl < 15 ml/min	0	1.00		
CrCl 15-29 ml/min	1.16 (0.50-2.71)	0.73		
CrCl ≥ 30 ml/min	Ref.	Ref.		
Hemoglobin (g/dL)	1.062 (0.93-1.21)	0.38		
Hemoglobin < 10g/dL	0.91 (0.48-1.73)	0.78		
Platelet count	1.00 (1.00-1.00)	0.07		
Aspirin	0.96 (0.54-1.71)	0.89		
Clopidogrel	1.36 (0.76-2.45)	0.30		
DAPT	1.34 (0.73-2.46)	0.35		
NSAIDs use	0.53 (0.14-1.97)	0.34		
PPI use	1.02 (0.50-2.11)	0.96		
CI: confidence interval; CrCl: creatinine clearance; DAPT: dual antiplatelet therapy; dL: deciliter; g:gram; kg: kilogram; m: meter; min: minute; ml: milliliter; NSAIDs: non-steroidal anti-inflammatory drugs; NSTEMI: non-ST elevation myocardial infarction; PPI: proton pump inhibitor; OR: odds ratio; Ref: reference; UA: unstable angina; VTE: venous thromboembolism				

requirements for multivariate analysis. These covariates were sex, age, obesity status, defined as BMI ≥25 kg/m² ²⁰ⁿ, and NSTEMI/UA, VTE prophylaxis, and VTE treatment indications, given high prevalence of inappropriate use. Obesity (OR=2.04 [95%CI 1.04:3.98]; p=0.04) was the only significant factor associated with overall inappropriate enoxaparin use.

There were 48 bleeding occurrences (22.4% of 214 initiations),

including 21 minor (9.8%) and 27 major (12.6%) bleedings. As shown in Figure 2, the indication with the highest bleeding rate was VTE prophylaxis (29 events), followed by VTE treatment (total 11 events), and NSTEMI/UA (8 events). The group of patients who received appropriate enoxaparin prescription experienced higher bleeding incidents (26.1% versus 15.8%), although the difference was not statistically significant



($p=0.084$). Five thromboembolic events (2.3%), 1 recurrent event in VTE treatment, and 4 events in VTE prophylaxis occurred.

Significant factors for any bleeding events in the univariate analysis included NSTEMI/UA, and VTE prophylaxis indications, hemoglobin (Hb) level, and Hb $<10\text{g/dL}$ status, use of clopidogrel, and dual antiplatelet therapy (DAPT) (Table 4). In multivariate analysis for any bleeding events, VTE prophylaxis indication (OR = 2.75, 95%CI 1.17:6.49; $p=0.02$) and Hb level ($<10\text{g/dL}$ vs $\geq 10\text{g/dL}$) (OR = 4.25, 95%CI 2.03:8.91; $p=0.01$) were the significant predictors of any bleeding events, while NSTEMI indication, DAPT, and inappropriate use of enoxaparin were not significantly associated with bleedings (Table 4). Subsequent analyses, excluding VTE prophylaxis patients, also showed that Hb $<10\text{g/dL}$ remained the only significant predictor (OR=4.99 [95%CI 1.73:14.42]; $p<0.01$) (Supplementary Table 1). For major bleeding events, Hb $<10\text{g/dL}$ was also the only significant predictor, and we also found that VTE treatment was also another significant predictor (OR=23.52 [95%CI 2.06:267.97]; $p=0.01$) after excluding VTE prophylaxis patients. (Supplementary Table 2 and 3) Inappropriate use of enoxaparin was not associated with bleeding in all analyses.

DISCUSSION

This is the first study to provide evidence on patterns of enoxaparin use in the middle-, and oldest-old predominate population group. Underdosing was the most prevalent type of error accounting for approximately 40% of all errors, or 15% of all enoxaparin initiations, notably in those with BMI $>25\text{kg/m}^2$. Bleeding in our mixed enoxaparin indications population also occurred quite often (22.4%). Orthopedic surgical patients who received enoxaparin for VTE prophylaxis and those with Hb $<10\text{g/dL}$ were more prone to bleeding.

There have been reports of 15% and 29.2%, respectively, of enoxaparin underdosing in NSTEMI/UA patients, according to

studies by Macie C, et al.¹³ and LaPointe NM, et al.¹¹ In our study, the overall underdosing prevalence was approximately 15%, but when only NSTEMI/UA indication was considered, the underdosing prevalence was 22.4%, which was also uniform with the two studies. The average age of the participants in previous studies was 66 and 68 years, which are younger than the 74 years in our study. Therefore, considering the age range in 3 studies, underdosing is the problem that affects all elderly subgroups, including the younger-old, middle-old, and oldest-old groups.

Furthermore, our study also demonstrated that underdosing occurred quite often in VTE treatment. Enoxaparin underdosing may increase the risk of recurrent thromboembolism, yet in the NSTEMI/UA and VTE therapy groups, we only had one recurrent episode. Our finding should not be interpreted that underdosing in elderly population is acceptable. Because we monitored solely in-hospital event, the long-term risk from underdosing of enoxaparin for thromboembolic cannot be determined or extrapolated. However, some evidence suggested that underdosing of enoxaparin in the elderly may not be harmful. A study by Levin A, et al.¹² in which the average age of the studied population was comparable to ours, discovered that a comparable percentage of patients (85.3% vs. 82.6%) who received an enoxaparin dose of 0.61-0.8 mg/kg/12 hours and a dose of 0.81-1.1 mg/kg/12 hours experienced therapeutic anti-Xa activity. Considering this data and our findings, it may be prudent and necessary to monitor anti-Xa activity in elderly patients receiving therapeutic doses of enoxaparin, especially in individuals with BMI $\geq 25\text{kg/m}^2$, aged over 70 or 80 years, in addition to patients who are underweight, or renally impaired.¹⁸ This is because the clinical consequence of underdosing in the elderly population is uncertain. It is crucial that controlled trials are conducted to determine appropriate enoxaparin dose for the elderly population.

Undocumented body weight was the second common problem among our studied population. The proportion of patients

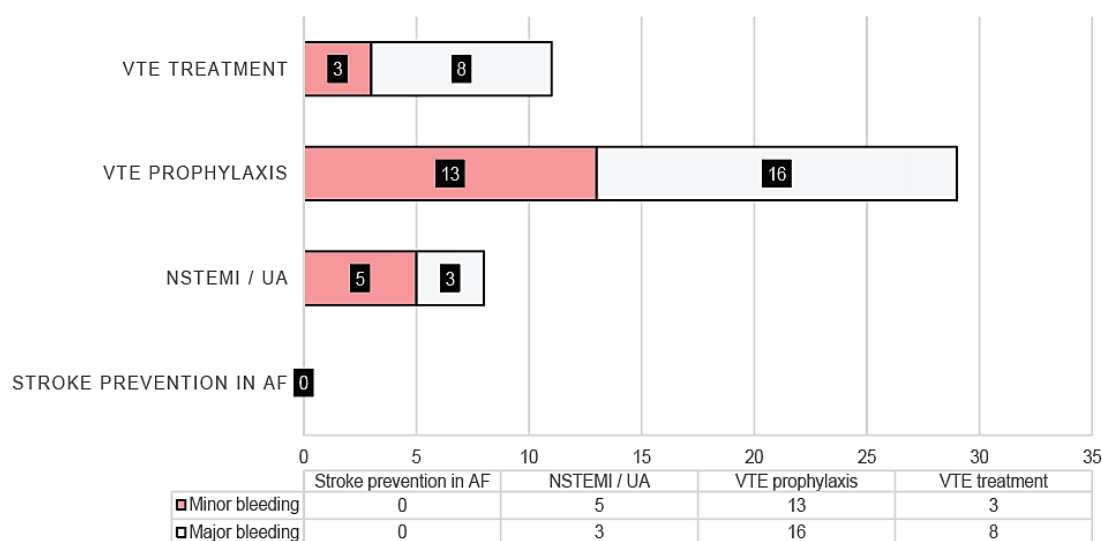


Figure 2. Frequency of bleeding events by indication of enoxaparin

Table 4. Risk factors associated with any bleeding event				
Independent variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	OR (95% CI)	p-value
Sex (male / female)	0.69 (0.34- 1.41)	0.31		
Age (years)	1.01 (0.98 -1.04)	0.45		
Body weight (kg)	1.00 (0.98 – 1.03)	0.77		
NSTEMI/UA indication	0.29 (0.13-0.65)	<0.01	0.55 (0.16-1.90)	0.34
VTE treatment indication	0.85 (0.40 – 1.81)	0.68		
VTE prophylaxis indication	3.75 (1.92-7.32)	<0.01	2.75 (1.17-6.49)	0.02
Creatinine clearance				
CrCl < 15 ml/min	2.74 (0.59-12.79)	0.20		
CrCl 15-29 ml/min	1.10 (0.41-2.93)	0.85		
CrCl ≥30 ml/min	Ref.	Ref.		
Hemoglobin < 10g/dL	3.71 (1.87-7.34)	<0.01	4.25 (2.03-8.91)	<0.01
Platelet count	1.00 (0.99-1.00)	0.71		
Aspirin	0.58 (0.29-1.16)	0.12		
Clopidogrel	0.32 (0.14-0.72)	<0.01		
DAPT	0.35 (0.15-0.82)	0.02	0.85 (0.24-3.01)	0.81
Ticagrelor	1.40 (0.26-7.45)	0.69		
Warfarin	0.54 (0.18-1.63)	0.27		
Dabigatran	3.51 (0.22-57.20)	0.38		
NSAIDs use	0.56 (0.07-4.50)	0.59		
PPI use	1.02 (0.36-2.89)	0.97		
Inappropriate use of enoxaparin	0.53 (0.26-1.10)	0.09	0.55 (0.25-1.21)	0.14
CI: confidence interval; CrCl: creatinine clearance; DAPT: dual antiplatelet therapy; dL: deciliter; g:gram; kg: kilogram; m: meter; min: minute; ml: milliliter; NSAIDs: non-steroidal anti-inflammatory drugs; NSTEMI: non-ST elevation myocardial infarction; PPI: proton pump inhibitor; OR: odds ratio; Ref: reference; UA: unstable angina; VTE: venous thromboembolism				

without body weight to guide enoxaparin dosing in our study was comparable to the study by Macie C, et al. (8.9% versus 9%).¹³ For the indication requiring weight-based dosing such NSTEMI/UA and VTE treatment, body weight is an information necessary to ensure effectiveness and safety of enoxaparin. For VTE prophylaxis indication, body weight might not be used often for determining enoxaparin dose, but in patients with BMI ≥30kg/m², orthopedic patients, higher than usual dose or weight-based dosing has been recommended by some experts.^{10,21-23}

VTE is a serious complication for medical and surgical patients, especially orthopedic patients.^{24,25} The pattern of enoxaparin use for VTE prophylaxis in our study represented solely orthopedic surgical patients; and inconsistent dose per hospital guidance accounted for 17.5% of the total problems. Most inappropriate doses in our study were prescribed as therapeutic doses (1 mg/kg) with dosing frequency of once or twice daily; this put the patients at an increased risk of bleeding, we observed 6 patients (35.3%) who experienced bleedings (2 minor and 4 major) after receiving the inappropriate prophylactic doses. These findings emphasize the significance of adequate enoxaparin dose in elderly orthopedic surgical patients. Basic intervention, such as placing reminder posters in key

prescribing areas of all orthopedic wards, had demonstrated improvement of VTE prophylaxis prescribing in patients with neck of femur fracture;²⁶ this strategy may also be used to optimize enoxaparin dosing along with other problems such as undocumented body weight and unmeasured renal function as observed in our study.

Choosing appropriate enoxaparin dosing frequency is another important practice to prevent drug accumulation and bleeding.²⁷ In our investigation, as expected, we discovered that 4 patients with CrCl <30 ml/min received enoxaparin on a twice daily schedule; however, intriguingly, the remaining patients with inappropriate dosing frequency were those with CrCl >30ml/min receiving once daily regimen for NSTEMI/UA (2 patients), VTE treatment (2 patients), and stroke prevention in atrial fibrillation (1 patient). The inappropriate dosing frequency of those five individuals can be classified as underdosing, and fortunately, no thromboembolic event occurred in this group. We were unable to ascertain whether this was purposeful because of the nature of the retrospective investigation; nonetheless, health professionals, particularly physicians and pharmacists, who oversee drug use and screening, should be made aware of this concern.

Bleeding risk from enoxaparin use has been well documented



in the meta-analyses,^{11,12,14,15,28} 2.1% in VTE treatment, and 4.7% in acute coronary syndrome. Overall bleeding events in our study was considerably high (22.4%), this bleeding rates was likely driven by those in the VTE prophylaxis group (13.5%) which is about 8 times higher than 1.7% in the previous report by Turpie AG, et al;²⁸ the high rate of inappropriate prophylactic dose in our study can explain this observation, along with the average age of our population that is higher (74.4 vs 68.2 years). Bleeding events in VTE treatment in our study were approximately 2.5 times higher than the report by Mismetti P, et al. (5.1% vs 2.1%).¹⁴ The most frequent issue in the VTE therapy group in our study was underdosing, therefore if the dosages were correctly adjusted, the bleeding rate in our study may have been higher. In our investigation, the rate of bleeding for ACS (NSTEMI/UA) indication was somewhat lower than in the study by Petensen JL, et al. (3.7% vs 4.7%), and similar to VTE therapy, underdosing was mostly prevalent in NSTEMI/UA patients.¹⁵ Other than appropriateness of enoxaparin use, the age of our studied population may explain the reason for higher bleeding risk when compared to the previous studies; however, in our regression analyses, age and appropriateness of enoxaparin use, as well as other significant factors previously reported in the literature, were not significantly associated with any bleeding. Only Hb <10g/dL was the significant predictor for any bleeding and major bleedings, regardless of enoxaparin indication; this factor has not been addressed in the previous studies, therefore Hb level should be checked prior to enoxaparin initiation among the elderly, and anemia patients with Hb<10g/dL should be closely monitored. Other significant predictors for bleeding reported in other studies, such as renal function, sex, age, prior use of NSAIDs, clopidogrel use were not associated with bleeding in our study. Inappropriate use of enoxaparin in our study was not associated with bleeding given underdosing was the most common problem found.

Our study provided data on enoxaparin use pattern in a specific elderly subgroup, middle-, and oldest-old predominate population, as well as the factors associated with inappropriate use and bleeding events. However, our data do not represent the use of enoxaparin for VTE prophylaxis in the population other than orthopedic surgery and may not be applicable for tertiary care setting. Interpretation of overall results of inappropriate rate or bleedings in our study should be caution, given the variety of indication with different nature of drug use

and different bleeding prognosis. Certain risk factor such as history of gastrointestinal bleeding was not clearly addressed in our study due to the nature of retrospective chart-review study, but we may partially imply the effect of this risk factor based on the history of prior PPIs use.

CONCLUSIONS

In the predominately middle-, and oldest-old population, inappropriate enoxaparin use, including underdosing, undocumented body weight and renal function, and inconsistent dosing per hospital guidance, are common, but not associated with bleeding; those with BMI>25kg/m² were more likely to experience inappropriate enoxaparin use, particularly underdosing. Hb level <10g/dL was the strong predictor for bleeding in this population.

DECLARATION OF INTEREST: the authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTION: AP: formulating research question, designing study, collecting and analyzing data, drafting manuscript; SK: collecting and analyzing data, drafting manuscript; ML: analyzing and reviewing data, writing and finalizing manuscript; SC: formulating research question, designing study, collecting and analyzing data, drafting and finalizing manuscript.

DATA ACCESS: The authors have complete access to all unidentified study data, additional data analyses can be executed, but additional data collection cannot be performed.

DATA AVAILABILITY STATEMENT: The data underlying this article are available in the article and in its online supplementary material.

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Supplementary Table 1. Risk factors associated with any bleeding event in non-VTE prophylaxis patients				
Independent variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Sex (M/F)	0.72 (0.26-2.04)	0.54		
Age (years)	0.99 (0.95-1.03)	0.58		
Body weight (kg)	0.96 (0.35-2.65)	0.94		
Creatinine clearance				
CrCl < 15 ml/min	5.60 (1.12-27.86)	0.04	3.46 (0.61-19.59)	0.16
CrCl 15-29 ml/min	1.32 (0.34-5.12)	0.69	0.84 (0.20-3.56)	0.81
CrCl ≥30 ml/min	Ref	Ref	Ref	Ref
Hemoglobin <10g/dL	5.39 (1.95-14.86)	<0.01	4.99 (1.73-14.42)	<0.01
Platelet	1.00 (0.99-1.00)	0.42		
Aspirin	0.79 (0.30-2.07)	0.63		
Clopidogrel	0.51 (0.19-1.38)	0.19		
DAPT	0.67 (0.25-1.82)	0.43		
Ticagrelor	2.66 (0.48-14.81)	0.26		
Warfarin	1.23 (0.37-4.09)	0.73		
NSAIDs use	0	1.00		
PPI use	1.04 (0.32-3.44)	0.94		
Inappropriate use of enoxaparin	0.50 (0.17-1.49)	0.21		

CI: confidence interval; CrCl: creatinine clearance; DAPT: dual antiplatelet therapy; dL: deciliter; g:gram; kg: kilogram; m: meter; min: minute; ml: milliliter; NSAIDs: non-steroidal anti-inflammatory drugs; NSTEMI: non-ST elevation myocardial infarction; PPI: proton pump inhibitor; OR: odds ratio; Ref: reference; UA: unstable angina; VTE: venous thromboembolism

Supplementary Table 2. Risk factors associated with major bleeding event				
Independent variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Sex (Male / Female)	0.829 (0.34-2.00)	0.676		
Age (years)	1.03 (0.99-1.07)	0.14		
Body weight (kg)	0.99 (0.96-1.02)	0.55		
NSTEMI indication	0.20 (0.06-0.67)	0.01	0.26 (0.06-1.07)	0.06
VTE treatment indication	1.29 (0.53-3.15)	0.57		
VTE prophylaxis indication	3.00 (1.32-6.87)	0.01	1.79 (0.68-4.71)	0.24
Creatinine clearance				
CrCl < 15 ml/min	3.14 (0.57-17.27)	0.19		
CrCl 15-29 ml/min	1.87 (0.63-5.51)	0.26		
CrCl ≥30 ml/min	Ref	Ref		
Hemoglobin <10g/dL	4.45 (1.93-10.25)	<0.01	4.71 (1.98-11.20)	<0.01
Platelet	1.00 (0.99-1.00)	0.88		
Aspirin	0.51 (0.21-1.27)	0.15		
Clopidogrel	0.21 (0.06-0.74)	0.01		
DAPT	0.27 (0.08-0.94)	0.04		
Ticagrelor	1.16 (0.13-10.03)	0.89		
Warfarin	0.00	1.00		
Dabigatran	0.00	1.00		
NSAIDs use	0.56 (0.07-4.50)	0.59		

PPI use	1.02 (0.36-2.89)	0.97		
Inappropriate use of enoxaparin	0.74 (0.31-1.77)	0.50		
CI: confidence interval; CrCl: creatinine clearance; DAPT: dual antiplatelet therapy; dL: deciliter; g:gram; kg: kilogram; m: meter; min: minute; ml: milliliter; NSAIDs: non-steroidal anti-inflammatory drugs; NSTEMI: non-ST elevation myocardial infarction; PPI: proton pump inhibitor; OR: odds ratio; Ref: reference; UA: unstable angina; VTE: venous thromboembolism				

Supplementary table 3 Risk factors associated with major bleeding event in non-VTE prophylaxis patients				
Independent variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Sex (Male / Female)	0.93 (0.26-3.34)	0.91		
Age (years)	0.99 (0.94-1.04)	0.70		
Body weight (kg)	1.02 (0.99-1.05)	0.30		
NSTEMI indication	0.27 (0.07-1.08)	0.06		
VTE treatment indication	4.80 (1.21-19.00)	0.03	23.52 (2.06-267.97)	0.01
Creatinine clearance				
CrCl < 15 ml/min	6.93 (1.11-43.43)	0.04	11.93 (0.73-195.53)	0.08
CrCl 15-29 ml/min	3.06 (0.70-13.41)	0.14	8.42 (0.67-101.47)	0.09
CrCl ≥30 ml/min	Ref	Ref	Ref	Ref
Hemoglobin <10g/dL	40.4 (4.94-330.49)	<0.01	70.75 (5.76-869.41)	<0.01
Platelet	1.00 (0.99-1.01)	0.77		
Aspirin	0.49 (0.14-1.75)	0.27		
Clopidogrel	0.33 (0.08-1.30)	0.11		
DAPT	0.43 (0.11-1.68)	0.22		
Ticagrelor	2.00 (0.22-18.23)	0.54		
Warfarin	0	1.00		
NSAIDs use	0	1.00		
PPI use	1.52 (0.38-6.13)	0.56		
Inappropriate use of enoxaparin	0.87 (0.24-3.12)	0.83		
CI = confidence interval, CrCl=creatinine clearance, DAPT = dual antiplatelet therapy, dL = deciliter, g= gram, kg = kilogram, m = meter, min = minute, ml = milliliter, NSAIDs = non-steroidal anti-inflammatory drugs, NSTEMI = non-ST elevation myocardial infarction, PPI = proton pump inhibitor, OR = odds ratio, Ref = reference, UA = unstable angina, VTE venous thromboembolism				

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1-2
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2
Bias	9	Describe any efforts to address potential sources of bias	2
Study size	10	Explain how the study size was arrived at	2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	2
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	2
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) If applicable, explain how loss to follow-up was addressed	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	2
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	2-3
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	3-5
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	3-5
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4-5
Discussion			
Key results	18	Summarise key results with reference to study objectives	5-6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7

Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

