

Enoxaparin Dosing and Associated Risk of In-Hospital Bleeding and Death in Patients With Non-ST-Segment Elevation Acute Coronary Syndromes

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Background: The efficacy of enoxaparin sodium in non-ST-segment elevation acute coronary syndromes is well established; however, concerns remain regarding bleeding risk. The extent to which bleeding risk is attributable to excess dosing of enoxaparin is unclear.

Methods: Using data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative, we determined the frequency of administration of excess (>10 mg above the recommended dose), lower-than-recommended (>10 mg below the recommended dose), and recommended doses of enoxaparin. We also determined unadjusted and adjusted risks of in-hospital major bleeding and death associated with excess and lower-than-recommended doses of enoxaparin.

Results: Of 10 687 patients, 2002 (18.7%) received an excess dose and 3116 (29.2%) received a lower-than-recommended dose of enoxaparin. Patients receiving ex-

cess doses were older (median age, 78 vs 66 years), smaller (median body mass index [calculated as weight in kilograms divided by height in meters squared], 26.2 vs 27.8), and more likely to be female (59.5% vs 38.2%) than patients receiving recommended doses ($P < .001$ for all). After adjustment for baseline characteristics, an excess dose was significantly associated with major bleeding (odds ratio, 1.43; 95% confidence interval [CI], 1.18-1.75) and death (odds ratio, 1.35; 95% CI, 1.03-1.77) compared with a recommended dose. A lower-than-recommended dose was not associated with major bleeding (odds ratio, 1.01; 95% CI, 0.84-1.21), but there was a trend toward higher mortality (odds ratio, 1.25; 95% CI, 0.93-1.68).

Conclusions: Almost half the patients treated with enoxaparin did not receive a recommended dose and had worse outcomes, especially those receiving an excess dose. Improved adherence to the recommended dose could substantially improve the safety profile of enoxaparin.

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ENOXAPARIN SODIUM, A LOW-molecular-weight heparin, has been shown to be effective in reducing death or myocardial infarction in non-ST-segment elevation acute coronary syndromes (NSTEMI ACS).¹⁻⁴ The 2002 American College of Cardiology/American Heart Association guidelines for the management of NSTEMI ACS recommend not only the use of either subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin with aspirin as a class I recommendation but also the use of enoxaparin as a class IIa recommendation in lieu of unfractionated heparin if coronary artery bypass graft surgery is not planned within 24 hours.⁵

Despite these advantages, the bleeding risk with enoxaparin has been found to be equal to or greater than that with either unfractionated heparin³ or the newer selective Xa inhibitor fondaparinux.^{4,6} Major

bleeding rates with enoxaparin in clinical trials for NSTEMI ACS have ranged from approximately 1% to 6.5%, depending on the definition of major bleeding, the time of the observation, and the use of concomitant therapies.^{1-4,7,8} These clinical trials also excluded or minimally enrolled patients with renal insufficiency, multiple comorbidities, obesity, and advanced age,⁹ patients who are frequently encountered in clinical practice. Therefore, the bleeding rates reported in these clinical trials may actually underestimate bleeding rates in clinical practice.

Enoxaparin clearance is decreased in renal insufficiency, making empirical dose reductions necessary to minimize bleeding risk.⁹⁻¹² Current recommendations suggest that the enoxaparin dosing interval should be extended from every 12 to 24 hours in patients with a creatinine clearance less than 30 mL/min (to convert to milliliters per second, multiply by 0.0167).^{13,14} Guidance on dosing in pa-

tients with moderate renal insufficiency, obesity, or advanced age is less specific.^{15,16}

The purpose of this study was to determine the extent to which enoxaparin was dosed in accordance with the current recommendations in a large, contemporary, community-based NSTEMI ACS population. We identified patients at highest risk for receiving an excess dose and a lower-than-recommended dose and investigated the unadjusted and adjusted risks of in-hospital major bleeding and death associated with enoxaparin dose.

METHODS

The study cohort was obtained from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative. The CRUSADE initiative contains clinical data from patients hospitalized for NSTEMI ACS at participating US hospitals. For inclusion in the CRUSADE initiative patients must have symptoms consistent with cardiac ischemia for more than 10 minutes and have either positive cardiac markers (troponin or creatine kinase-MB fraction), ST-segment depression greater than 0.5 mm, or transient ST-segment elevation of 0.6 to 1.0 mm for more than 10 minutes. Between January 1, 2001, and December 31, 2005, a total of 550 hospitals participated in the CRUSADE initiative. Collected data elements and registry processes have been previously presented.¹⁷

In 2004 the enoxaparin dosing interval was added as a new data element on the CRUSADE data collection form. For this study, patients were identified who received enoxaparin and were enrolled in 2005 using the data collection form that included the enoxaparin dosing interval. The institutional review board of each hospital approved their organization's participation in the CRUSADE initiative.

ENOXAPARIN DOSE

For each identified patient the recorded initial enoxaparin dose and dosing interval were used to determine the total amount of enoxaparin administered in 1 day (administered daily dose). The recommended daily dose of enoxaparin was then calculated for each patient. On the basis of product labeling, the recommended enoxaparin sodium dose is 1 mg/kg every 12 hours for patients with a creatinine clearance of 30 mL/min or greater and 1 mg/kg every 24 hours for patients with a creatinine clearance less than 30 mL/min. Thus, the recommended daily dose of enoxaparin sodium was 2 mg/kg for patients with a creatinine clearance of 30 mL/min or greater and 1 mg/kg for patients with a creatinine clearance less than 30 mL/min. The patient's recorded body weight was used for this calculation. Creatinine clearance was estimated using the Cockcroft-Gault equation using the patient's baseline serum creatinine level and lean body weight, as determined by height and sex.^{18,19}

For each patient the administered daily dose of enoxaparin was then compared with the recommended daily dose. If the administered daily dose exceeded the recommended daily dose by more than 10 mg, the patient was categorized as having received an "excess" dose of enoxaparin. If the administered daily dose was more than 10 mg below the recommended daily dose, the patient was categorized as having received a "lower-than-recommended" dose of enoxaparin. If the administered daily dose and recommended daily dose did not vary by more than 10 mg, the patient was categorized as having received the "recommended" dose of enoxaparin. These definitions were determined a priori and were

established to allow for a small variation for rounding in the recommended dose.

Secondary analyses were conducted by splitting the group of patients with excess doses into 2 groups. The first group contained those who had a "low" excess dose, defined as having an administered daily dose of enoxaparin that was more than 10 mg above the recommended dose but not more than 30 mg above the recommended dose. The second group contained those who had received a "high" excess dose, defined as an administered daily dose that was more than 30 mg above the recommended dose.

OUTCOME MEASURES

The clinical outcome measures for this study were in-hospital major bleeding and death. Patients who were transferred to another hospital were excluded from all analyses, and patients who had coronary artery bypass graft surgery during hospitalization were also excluded from the analyses for major bleeding. Major bleeding was defined as (1) an absolute decrease in hematocrit concentration of at least 12% from baseline, (2) intracranial hemorrhage, (3) retroperitoneal bleeding, (4) a red blood cell transfusion in patients who had a baseline hematocrit level of 28% or greater, or (5) a red blood cell transfusion in patients who had a baseline hematocrit level less than 28% with a documented bleeding event of any kind. In-hospital death included any death regardless of cause.

STATISTICAL ANALYSIS

The focus of the analysis was to describe and compare baseline patient characteristics, clinical presentation, hospital characteristics and care, and clinical outcomes (major bleeding and death during hospitalization) between patients who received an excess dose of enoxaparin and those who received the recommended dose of enoxaparin and between those who received a lower-than-recommended dose and those who received the recommended dose. In addition, comparisons of patient characteristics were made between the study cohort and patients who were excluded. Medians and 25th and 75th percentiles are reported for continuous variables and percentages are reported for categorical variables. To test for the independence of excess enoxaparin dose and characteristics and outcomes, the Mantel-Haenszel χ^2 test was used, controlling for hospital site.

To explore the relationships between in-hospital clinical outcomes and use of an excess enoxaparin dose vs the recommended dose and a lower-than-recommended dose vs the recommended dose, a logistic generalized estimating equations method was used. The method accounts for within-hospital clustering of responses, as patients at the same hospital are more likely to be similar to each other than to those at other hospitals.²⁰ Two models were performed with different adjustments. The primary model included baseline patient characteristics only, and the second model included baseline patient characteristics, the use of clopidogrel bisulfate or glycoprotein IIb/IIIa inhibitors within 24 hours of hospital admission, and the use of percutaneous coronary intervention within 24 hours of admission. Baseline patient characteristics included in the models were age; sex; race; body mass index (calculated as weight in kilograms divided by height in meters squared); family history of coronary artery disease; renal impairment (creatinine clearance <60 mL/min on admission); history of hypertension, diabetes mellitus, and hypercholesterolemia; previous myocardial infarction, stroke, coronary artery bypass graft, percutaneous coronary intervention, and heart failure; current or recent smoker; ST-segment depression; transient ST-segment elevation; clinical signs of heart failure on admission; positive cardiac markers on admission; admission heart rate; and admission systolic blood pressure. In the second model, use of clopidogrel, glycoprotein IIb/IIIa inhibitors, and percuta-

neous coronary intervention within 24 hours and contraindications to clopidogrel, glycoprotein IIb/IIIa inhibitors, and percutaneous coronary intervention were included as additional variables. Interactions between age and excess dose, sex and excess dose, and in-hospital renal impairment and excess dose were explored for each clinical outcome in the primary model. Secondary analyses were conducted comparing low excess dose vs recommended dose, high excess dose vs recommended dose, and lower-than-recommended dose vs recommended dose. $P < .05$ was considered statistically significant for all tests. All analyses were performed using a software program (SAS version 8.2; SAS Institute Inc, Cary, North Carolina).

RESULTS

In 2005, of 33 094 patients with NSTEMI ACS, 13 225 (40.0%) received enoxaparin as part of their treatment. Of these, 2094 (15.8%) were excluded owing to missing the initial enoxaparin dose or dosing interval, and another 444 (3.4%) were excluded owing to missing serum creatinine or weight values. The resulting study cohort consisted of 10 687 patients from 332 hospitals. There were no clinically significant differences in baseline patient characteristics between the study cohort and patients who were excluded. There was no significant difference between the study cohort and those who were excluded in the proportion of patients with major bleeding (8.8% for each) or the proportion who died during hospitalization (3.3% vs 4.2%; $P = .07$).

ENOXAPARIN DOSING

The distribution of differences between the administered dose and the recommended dose is presented in **Figure 1**. In the study cohort, 2002 patients (18.7%) received an excess dose of enoxaparin, 3116 (29.2%) received a lower-than-recommended dose, and 5569 (52.1%) received the recommended dose. Of patients who received an excess dose, 1157 (57.8%) had a creatinine clearance less than 30 mL/min, the point at which extension of the dosing interval is recommended. Patient characteristics and comparisons by dosing group are given in **Table 1**.

IN-HOSPITAL MAJOR BLEEDING

Of the 7920 patients in the study cohort, 699 (8.8%) had major bleeding during hospitalization. The proportion of patients with major bleeding was significantly higher in patients who received an excess enoxaparin dose than in those who received the recommended dose (14.2% vs 7.3%; $P < .001$) (**Figure 2**). There was no significant difference in the proportion with major bleeding among those who received a lower-than-recommended dose compared with those who received the recommended dose (7.9% vs 7.3%; $P = .50$).

The unadjusted and adjusted risks of major bleeding are given in **Table 2**. Excess dose compared with recommended dose was independently and significantly associated with an increased risk of major bleeding after adjustment for baseline patient characteristics (odds ratio [OR], 1.43; 95% confidence interval [CI], 1.18-1.75). Using the second model, there continued to be a significant association between excess dose and major bleeding (OR, 1.47; 95% CI, 1.21-1.80) (Table 2). There

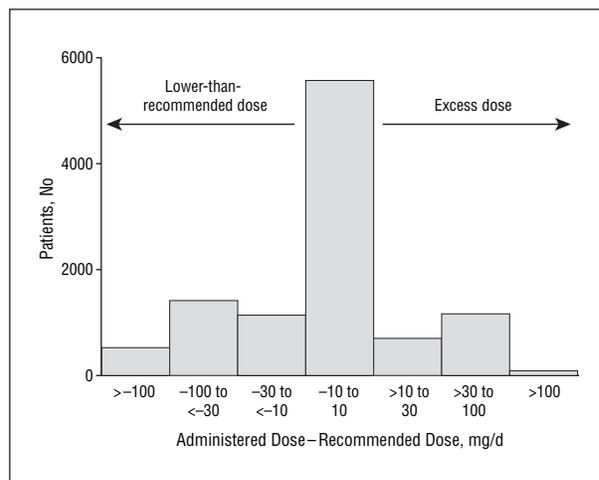


Figure 1. Distribution of differences between the administered daily dose and the recommended daily dose of enoxaparin sodium. Excess was defined as an administered daily dose that exceeded the recommended dose by more than 10 mg/d; recommended; an administered daily dose that did not vary from the recommended dose by more than 10 mg/d; and lower-than-recommended, an administered daily dose that was more than 10 mg/d less than the recommended dose.

was no statistically significant unadjusted or adjusted association with risk of major bleeding between use of a lower-than-recommended dose compared with the recommended dose in these models.

Among patients who received an excess dose, 1282 (64.0%) received a high excess dose. In secondary analyses, use of a high excess dose was significantly associated with a higher risk of major bleeding compared with those receiving the recommended dose (OR, 1.53; 95% CI, 1.24-1.89), but use of a low excess dose was not (OR, 1.21; 95% CI, 0.85-1.70).

We also tested for interactions between enoxaparin dose and patient age, renal insufficiency, and sex. Although the effect of excess dosing did not vary by patient age and renal function, there was a greater risk of major bleeding associated with receiving an excess enoxaparin dose compared with receiving the recommended dose in women (OR, 1.68; 95% CI, 1.33-2.11) but not in men (OR, 1.16; 95% CI, 0.83-1.62); $P = .03$ for interaction.

IN-HOSPITAL DEATH

Of the 8960 patients in the study cohort, 292 (3.3%) died during hospitalization. A significantly greater proportion of patients who received an excess dose of enoxaparin died compared with those who received the recommended dose (5.6% vs 2.4%; $P < .001$) (Figure 2). There was no significant difference in the proportion of patients who received a lower-than-recommended dose of enoxaparin who died during hospitalization compared with those who received the recommended dose (3.3% vs 2.4%; $P = .11$).

The unadjusted and adjusted risks of in-hospital death are given in Table 2. There was a significantly higher risk of in-hospital death in patients who received an excess dose compared with those who received the recommended dose when adjusting for baseline characteristics (OR, 1.35; 95% CI, 1.03-1.77), but the association between death and use of a lower-than-recommended dose

Table 1. Characteristics of Patients With Excess, Lower-Than-Recommended, and Recommended Enoxaparin Sodium Doses^a

Characteristic	Patient Receiving				
	Recommended Dose (n = 5569)	Excess Dose (n = 2002)	P Value ^b	Lower-Than-Recommended Dose (n = 3116)	P Value ^c
Age, y ^d	66 (56-77)	78 (65-85)	<.001	66 (55-76)	.08
BMI ^d	27.8 (24.6-31.5)	26.2 (22.7-30.3)	<.001	30.3 (26.2-35.3)	<.001
Weight, kg ^d	81.6 (69.4-94.8)	71.7 (60.3-83.0)	<.001	89.0 (75.5-107.0)	<.001
Male sex	61.8	40.5	<.001	65.1	<.001
White race	82.7	80.2	.40	80.2	>.99
History of hypertension	69.4	78.9	<.001	72.3	.01
History of diabetes mellitus	30.1	37.5	<.001	35.5	<.001
Previous myocardial infarction	27.2	32.4	<.001	27.9	.60
Previous PCI	21.4	19.5	.40	22.7	.09
Previous CABG	18.9	20.6	.03	18.2	.30
History of heart failure	12.7	24.9	<.001	16.6	<.001
Previous stroke	8.1	13.9	<.001	9.0	.40
Current smoker	28.9	18.9	<.001	27.6	.40
Baseline hematocrit, % ^d	41.6 (37.9-44.7)	38.7 (34.8-42.3)	<.001	41.3 (37.3-44.7)	.70
Renal insufficiency ^e	51.5	79.6	<.001	52.3	.50
Acute medications (< 24 h)					
Aspirin	97.3	96.8	.40	97.0	.90
β-Blockers	93.1	91.8	.05	91.6	.06
ACE inhibitors	48.2	52.2	.008	49.3	.30
Clopidogrel bisulfate	54.8	53.0	.10	55.6	.80
Glycoprotein IIb/IIIa inhibitors	48.9	38.1	<.001	44.4	.02
Catheterization within 48 h	59.9	45.9	<.001	57.7	.05
PCI within 48 h	37.8	27.7	<.001	36.6	.60
CABG	13.6	10.4	.20	12.2	.50
Cardiogenic shock	1.4	2.3	.04	2.0	.10
Hospital region			.02		<.001
West	10.0	10.3		10.7	
Northeast	14.5	17.3		20.0	
Midwest	35.3	34.4		34.6	
South	40.2	38.1		34.8	
Academic hospital ^f	18.2	22.4	<.001	22.8	<.001

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

^aData are given as percentages except where otherwise specified.

^bExcess dose vs recommended dose (excess was defined as an administered daily dose that exceeded the recommended dose by more than 10 mg/d; recommended, an administered daily dose that did not vary from the recommended dose by more than 10 mg/d).

^cLower-than-recommended dose vs recommended dose (lower-than-recommended was defined as an administered daily dose that was more than 10 mg/d less than the recommended dose).

^dData are given as median (25th-75th percentile).

^eDefined as calculated creatinine clearance less than 60 mL/min (to convert to milliliters per second, multiply by 0.0167).

^fMember of the Council of Teaching Hospitals in the American Hospital Association database.

compared with the recommended dose was not statistically significant (Table 2).

No significant interactions between enoxaparin dose status and age ($P = .80$) or sex ($P = .70$) were found. An interaction between excess enoxaparin dose and in-hospital renal impairment was of borderline significance only ($P = .05$). Using the second model, there was no significant difference between excess dose and recommended dose on in-hospital death (OR, 1.31; 95% CI, 0.99-1.73). In secondary analyses, there was no significant increase in death (OR, 0.78; 95% CI, 0.44-1.36) from low excess dose compared with the recommended dose. However, for those with a high excess dose, there was a significantly higher risk of in-hospital death compared with those receiving the recommended dose (OR, 1.57; 95% CI, 1.17-2.09).

COMMENT

In this observational study, we found that in US hospitals participating in the CRUSADE initiative, approximately

1 of every 5 patients who received enoxaparin for the treatment of NSTEMI/ACS received a dose that was in excess of current dosing recommendations. Use of an excess enoxaparin dose was associated with increased risk of in-hospital major bleeding and death, especially among women, those with renal impairment, and those who received a high excess dose (>30 mg/d above the recommended dose).

It has long been known that in-hospital major bleeding can lead to additional complications and prolonged hospitalization; however, more recent evidence²¹ suggests that in-hospital major bleeding is also independently associated with an increase in short- and longer-term risk of death after hospital discharge. In the OASIS 5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) study⁴ patients who had major bleeding during hospitalization had a significantly higher rate of death at 30 days than patients without a major or minor bleed (13.2% vs 2.8%) regardless of whether they received enoxaparin or fondaparinux. Therefore, careful attention to the administered dose of enoxaparin, a modi-

fiable risk factor for major bleeding, to minimize the risk of bleeding and death is imperative.

In a recent study by Alexander et al²² in which data from the CRUSADE initiative were also used, 13.8% of patients who received enoxaparin received an excess dose. In that study, only the initial weight-adjusted dose was available, and an excess dose was defined as a dose greater than 1.05 mg/kg. In addition, that study did not investigate interactions of enoxaparin dosing in patient subsets such as age, sex, and renal function. With the addition of data on the dosing interval we can now take into account dosing recommendations in patients with impaired renal function. The fact that 57.8% of patients who received an excess dose had a creatinine clearance less than 30 mL/min and required extension of the dosing interval likely accounts for the higher frequency of excess enoxaparin doses in this study.

In this study it seemed that most of the increased risk was attributed to the use of very high vs moderately high

excess doses of enoxaparin. Numerous other factors were previously shown to be associated with increased risk of bleeding in patients with ACS, including advanced age, female sex, and renal insufficiency.^{23,24} However, although these risk factors are not modifiable, selection of the enoxaparin dose is. Following the current dosing recommendation for enoxaparin, although it may not currently take into account other patient-specific factors that alter the relationship between dose and effect, could potentially lead to reduced bleeding and death and thus improve overall safety. Although additional studies are needed to further fine-tune this dosing recommendation for special populations, such as obese individuals, very old people, and those with moderate renal impairment,^{15,16} implementation in clinical practice of the existing dosing recommendations could go a long way toward improving safety while potentially more complex and patient-specific dosing recommendations are developed. This evidence-based approach to managing ACS has been focused on getting the correct drug to the correct patient. Now, additional attention needs to be focused on getting the correct dose to those patients.

There are several limitations of this study. This was an observational study comparing clinical outcomes in patients who received an excess dose of enoxaparin and those who received the recommended dose. There were many differences in characteristics between these 2 groups, and we attempted to account for these differences in the statistical model. Given that it would be unethical to randomize patients to a treatment arm that included use of a dose of enoxaparin that was above the recommended dose, a randomized clinical trial to evaluate this question is not possible. Another limitation of this study was that only the initial enoxaparin subcutaneous dose and dosing interval were recorded in the registry. Patients may have subsequently had their dose or dosing interval changed, and the duration of enoxaparin treatment is unknown. It should also be recognized that although we found no statistically significant difference between use of a lower-than-recommended dose vs the recommended dose in the primary analyses for bleeding or in-hospital death, this study

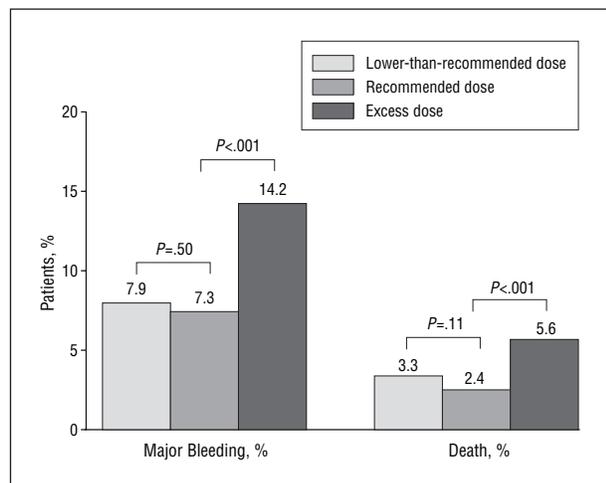


Figure 2. In-hospital major bleeding and death according to the enoxaparin sodium dose received. Excess was defined as an administered daily dose that exceeded the recommended dose by more than 10 mg/d; recommended, an administered daily dose that did not vary from the recommended dose by more than 10 mg/d; and lower-than-recommended, an administered daily dose that was more than 10 mg/d less than the recommended dose.

Table 2. Unadjusted and Adjusted Risks of Major Bleeding and Death by Enoxaparin Sodium Dosing^a

Dosing	Major Bleeding (n = 7920)		Death (n = 8960)	
	OR (95% CI)	P Value ^b	OR (95% CI)	P Value ^b
Unadjusted dosing				
Lower-than-recommended dose	1.07 (0.90-1.28)	.40	1.37 (1.04-1.79)	.02
Excess dose	2.08 (1.73-2.51)	<.001	2.37 (1.84-3.06)	<.001
Adjusted dosing ^c				
Lower-than-recommended dose	1.01 (0.84-1.21)	.90	1.25 (0.93-1.68)	.10
Excess dose	1.43 (1.18-1.75)	<.001	1.35 (1.03-1.77)	.03
Adjusted dosing ^d				
Lower-than-recommended dose	1.01 (0.84-1.22)	.90	1.19 (0.89-1.59)	.20
Excess dose	1.47 (1.21-1.80)	<.001	1.31 (0.99-1.73)	.06

Abbreviations: CI, confidence interval; OR, odds ratio.

^aExcess was defined as an administered daily dose that exceeded the recommended dose by more than 10 mg/d; recommended was defined as an administered daily dose that did not vary from the recommended dose by more than 10 mg/d. Lower-than-recommended was defined as an administered daily dose that was more than 10 mg/d less than the recommended dose).

^bCompared with the recommended dose.

^cAdjusted for baseline patient characteristics.

^dAdjusted for baseline patient characteristics, medications, and procedures.

was not designed to identify other risks associated with use of a lower-than-recommended dose.

In conclusion, enoxaparin is an effective and recommended drug in the treatment of patients with NSTEMI ACS. We found that 18.7% of patients treated with enoxaparin received an excessive dose and that excess dose was independently and statistically significantly associated with an increased risk of major bleeding and death. Although much attention has been focused on the use of evidence-based medications for cardiovascular disease, less attention has been given to the use of appropriate doses of these evidence-based medications. It is expected that increased vigilance in dosing will reduce adverse effects and may improve short- and long-term clinical outcomes.

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