

RESEARCH ARTICLE

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# Dosing practice of low molecular weight heparins and its efficacy and safety in cardiovascular inpatients: a retrospective study in a Chinese teaching hospital

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## Abstract

**Background:** Low-molecular-weight heparins (LMWHs) are safe and effective anticoagulant options for cardiovascular patients when applied as body weight-adjusted doses. However, there are some barriers that make it difficult to implement weight-adjusted doses in clinical practice. Therefore, it is vital to learn the dosing practices of LMWH and its efficacy and safety in clinical practice.

**Methods:** A retrospective study was conducted in cardiovascular inpatients who had received at least one dose of LMWH during a 6-month period. Appropriateness of LMWH dosing was determined and major clinical outcomes (major adverse vascular events and major bleeding) during hospitalization were evaluated.

**Results:** A total of 376 admissions representing 364 patients received LMWH treatment. Of these, 17.0% (64/376) of admissions did not have body weight records. Of the 312 admissions included for the outcome study, only 34 cases (10.9%) received the recommended doses of LMWH, while 51 cases (16.3%) received mild underdoses, 223 cases (71.5%) received major underdoses and 4 (1.3%) received excess doses. There were 10 major adverse vascular events, which occurred more often in patients receiving excess doses of LMWH than in patients receiving recommended, mild or major underdoses (50%, 2.9%, 2.0% and 2.7%, respectively,  $P < 0.001$ ). After multivariable analysis, severe renal insufficiency was an independent risk factor for major adverse vascular events [odds ratio (OR), 31.93; 95% confidence interval (CI), 5.99-170.30;  $P < 0.001$ ]. No major bleeding was recorded.

**Conclusions:** Underdose of LMWH is commonly used in cardiovascular inpatients, which was suboptimal according to guidelines. Using LMWH at a fixed, low dose for treatment purposes in patients without severe renal insufficiency was not associated with a higher risk of adverse vascular events in the current study, though larger studies with extended follow-ups are required to fully assess the long-term consequences of LMWH underdosing.

**Keywords:** Low molecular weight heparin, Dosing practice, Cardiovascular inpatients, Efficacy, Safety

## Background

Cardiovascular diseases are the leading cause of morbidity and mortality in the world. Thrombosis is the final biological evolution of the atherosclerotic process, which promotes the development and progression of cardiovascular diseases [1]. In recent years several clinical trials have established, that low molecular weight heparins

(LMWHs) are safe and effective anticoagulant options for patients with venous thromboembolism (VTE), acute coronary syndrome (ACS), pulmonary embolism, unstable angina and non-ST-segment elevation myocardial infarction [2-5]. This is partly due to the fact that LMWHs have superior pharmacokinetic properties as compared to unfractionated heparin (UFH) and without the need for routine coagulation tests [6]. Therefore, LMWHs have replaced UFH in most situations [7]. However, LMWHs have a longer half-life than UFH, with no potential for full reversal. Thus, if an excess dose of

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LMWH is given, it may result in equal or more devastating outcome than UFH. LMWHs are typically administered for embolism therapy, based on body weight, creatinine clearance and age ( $\geq 75$  years) [6]. Appropriate dosing of LMWH is vital for its efficacy and safety. Previous data have shown a relationship between LMWH dose, the intensity of anticoagulation and incidence of major hemorrhage, including intracranial bleeding [8].

However, there are some barriers existing in “real world” clinical practice that make adherence to weight-adjusted doses, according to the dose-finding trials difficult [9-11]. First, accurate weight assessment is a challenge for seriously ill patients. Second, due to the high concentration of pre-filled doses of LMWH, precise measurement of a weight-based dose is difficult; this could lead to an increase in medical errors and drug waste [12]. Third, patients in real-world cardiovascular units tend to be older, have more comorbidity and are taking more prescribed drugs compared with those in clinical trials [13]. Therefore, in China, some cardiologists tend to use a lower, fixed dose of LMWH relative to the dose suggested by Chinese guidelines and recommended from the clinical trials, to reduce the perceived risk of hemorrhage and to simplify the dosing regimen. However, to our knowledge, the efficacy and safety of this “real word” clinical practice has not yet been studied.

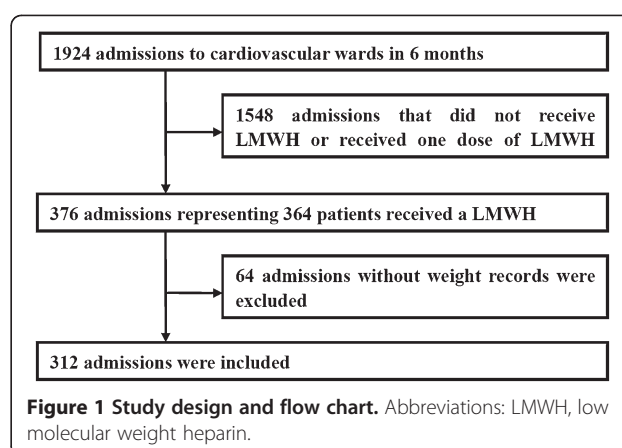
In this retrospective study from a Chinese teaching hospital, we examined the dosing practice of LMWHs, and then determined the efficacy and safety of this practice in cardiovascular inpatients discharged from Jan 1 to Jun 30, 2010.

## Methods

### Study subjects

This study was conducted in a general, university-affiliated, teaching hospital with 2,200 licensed inpatient beds, and approximately 77,000 admissions per year. Using an electronic medical records database, the patients that were  $> 18$  years of age and who were discharged from cardiovascular wards between Jan 1 to Jun 30, 2010 were selected. Multiple admissions of a single patient were counted as separate events. An admission was excluded if the patient did not receive any LMWH agents, received a single dose of LMWH, or had no weight record (Figure 1). The study protocol was approved by the medical ethics committee of the Second Affiliated Hospital, Zhejiang University School of Medicine, China (No. 2012–37).

Three types of LMWHs were used in this hospital: Clexane<sup>®</sup> (Enoxaparin Sodium Injection, Aventis Intercontinental, 0.4ml: 4000AxaIU), Fraxiparine<sup>®</sup> (Nadroparin Calcium Injection, GlaxoSmithKline Inc, 0.4ml: 4100AxaIU), and Fragmin<sup>®</sup> (Dalteparin Sodium Injection,



Pfizer Inc, 0.2ml: 5000AxaIU) (Table 1). All LMWHs were administered by nurses during the hospitalization.

### Data collection and definition

A chart review was conducted for each patient included in the study. Data included basic patient demographics (gender, age, weight, and height), clinical parameters (blood creatinine, diagnosis and treatment), dosage of LMWH, and clinical outcomes (major adverse vascular events and major bleeding) during the hospitalization. The body-mass index (BMI) was calculated by dividing the individual’s weight (in kg) by the square of his or her height (in meters). Hypertension was determined by blood pressure  $> 140/90$  mmHg or current use of anti-hypertensive medication. Severe renal insufficiency (RI) was determined by creatinine clearance  $< 30$  ml/min. Creatinine clearance was estimated by the Cockcroft-Gault equation  $[140 - \text{age (years)}] \times \text{weight (kg)} \times (0.85 \text{ if female}) / [72 \times \text{serum creatinine (mg/dl)}]$ . Medication orders were evaluated with the initial dose prescribed. Dosing errors were determined strictly on the initial mg/kg/dose. Interval frequency for LMWH was also collected, which was adjusted by creatinine clearance. The recommended LMWH dosage was defined in accordance with product package inserts (Table 1). Because clinical evidence of dosing strategies for nadroparin and dalteparin in patients with RI and elderly patients ( $\geq 75$  years) are limited, we used the dosing strategies recommended from the data on the use of enoxaparin [14].

**Table 1 Three types of low-molecular-weight heparins used**

Drug	Recommended usage	Individual adjustment
Enoxaparin	100 IU/kg, every 12 h	1. 75% of the recommended dose, every 12 hours (age $\geq 75$ years);
Nadroparin	86 IU/kg, every 12 h	2. 50% of the recommended dose, every 24 hours (creatinine clearance $< 30$ ml/min).
Dalteparin	120 IU/kg, every 12 h	

The following dosing categories were defined: underdose, recommended dose, and excess dose. An underdose or excess dose was defined as  $\leq 90\%$  or  $\geq 110\%$  of the recommended dose (in mg/kg/day), respectively. The underdose was further divided into mild underdose ( $\leq 90\%$  but  $> 80\%$  of the recommended dose, in mg/kg/day) and major underdose ( $\leq 80\%$  of the recommended dose, in mg/kg/day).

The efficacy and safety of clinical outcomes were evaluated by major adverse vascular events and major bleeding, respectively. Major adverse vascular events were defined as any of the following complications during in-hospital: death, myocardial re-infarction, recurrent angina, revascularization procedures, ischemic stroke, peripheral or visceral embolism, recurrent deep vein thrombosis or pulmonary embolism. Major bleeding was defined as any intracranial hemorrhage, transfusion of at least 2 units of packed red blood cells, or absolute drop in hematocrit of at least 12%; these parameters were similar to definitions used in other trials and registries [15].

### Statistical analyses

Continuous variables are reported as mean  $\pm$  SD, and categorical variables are reported as numbers (percentage). Significance was determined using  $\chi^2$  tests for categorical variables and Student's t-tests or one way analysis of variance (ANOVA) for continuous data variables.

Independent predictors of major adverse vascular events were identified by use of univariable and multivariable logistic regression analysis. Important baseline characteristics such as age, gender, weight, creatinine clearance, hypertension, diabetes mellitus and dosage subgroup of LMWH were entered into the model. The odds ratio (OR) and corresponding 95% confidence interval (CI) were reported for each variable in the model. Variables were retained in the final multivariable model if their level of significance was  $\leq 0.05$ .

## Results

### Patient characteristics

A total of 19.5% (376/1,924) of admissions representing 364 patients in the cardiovascular units received LMWH during this period. Of these, 17.0% (64/376) were lacking body weight records. Thus 312 admissions were analyzed for outcome analysis. Of these, 4.8% (15/312) were treated with dalteparin, 24.4% (76/312) were treated with enoxaparin, and 70.8% (221/312) were treated with nadroparin. As shown in Table 2, the mean age of patients was  $64 \pm 11$  years, (75.3% were men). More than half of the patients (58.6%) received LMWHs for the treatment of unstable angina and non ST-segment elevation myocardial infarction. Of the 67 atrial fibrillation patients, 7 (10.4%) had valvular heart disease (mitral

**Table 2 Patient and treatment characteristics**

Patient characteristics	Data
Age, y	63.8 $\pm$ 11.4
$\geq 75$ years, n (%)	65 (20.8)
Female, n (%)	77 (24.7)
Body mass index	23.8 $\pm$ 3.2
Weight, kg	66.8 $\pm$ 10.9
Diagnosis, n (%)	
ST-segment elevation myocardial infarction	53 (17.0)
Unstable angina/Non ST-segment elevation Myocardial infarction	183 (58.6)
Atrial fibrillation	67 (21.5)
Deep vein thrombosis	9 (2.9)
Concurrent medical conditions, n (%)	
Hypertension	194 (62.2)
Diabetes mellitus	69 (22.1)
Severe renal insufficient, n (%)	7 (2.2)
Creatinine clearance, ml/min	83.1 $\pm$ 27.8
Treatment variables, n (%)	
Cardiac catheterization	26 (8.3)
Percutaneous coronary intervention	195 (62.5)
Radiofrequency catheter ablation	44 (14.1)
Length of hospital stay, d	8.9 $\pm$ 5.8

stenosis or prosthetic heart valves) and had used warfarin prior to hospitalization. Of the other 60 atrial fibrillation patients, only 2 had used warfarin prior to hospitalization although there were 30 cases identified as at "high risk" of stroke (defined as CHA2DS2-VASc score  $\geq 2$ ) [16]. Seven patients (2.2%) with stage 4 chronic kidney disease (CKD) received LMWH treatment.

### LMWH dosing practices

As shown in Table 3, only 34 cases (10.9%) received the recommended dose of LMWH, 51 cases (16.3%) received mild underdoses, 223 cases (71.5%) received major underdoses, and 4 cases (1.3%) received excess doses. There were no statistically significant differences in gender, diagnosis or comorbid diseases, such as hypertension and diabetes mellitus among these groups. Patients receiving excess doses of LMWH were older, weighed more, had a poorer renal function, longer administration duration and hospital stays than the patients receiving the recommended dose ( $P < 0.05$ ). Patients receiving major underdoses of LMWH were younger and weighed more than the patients receiving the recommended doses ( $P < 0.05$ ). None of the patients in underdoses groups had severe RI. Major adverse vascular events occurred more often in patients receiving excess doses of LMWH than in patients receiving recommended, mild or major

**Table 3 Baseline patient characteristics for different dosages of LMWH**

Variable	Major underdose (n = 223)	Mild underdose (n = 51)	Recommended dose (n = 34)	Excess dose (n = 4)	P Value
Age, y	62.1 ± 10.7	67.0 ± 11.3	68.6 ± 12.8	77.0 ± 17.5	<0.001
≥75 years, n (%)	24 (10.8)	19 (37.3)	19 (55.9)	3 (75)	<0.001
Female, n (%)	60 (26.9)	10 (19.6)	6 (17.6)	1 (25)	0.531
Weight (kg)	70.3 ± 9.2	58.2 ± 9.1	55.8 ± 8.8	71.5 ± 9.1	<0.001
BMI	24.7 ± 2.9	21.6 ± 2.6	21.0 ± 3.1	26.2 ± 3.1	<0.001
Diagnosis, n (%)					0.167
STEMI	37 (16.6)	9 (17.6)	6 (17.6)	1 (25)	
UA/NSTEMI	126 (56.5)	34 (66.7)	21 (61.8)	2 (50)	
Atrial fibrillation	54 (24.2)	6 (11.8)	7 (20.6)	0	
DVT	6 (2.7)	2 (3.9)	0	1 (25)	
Hypertension	134 (60.1)	34 (66.7)	23 (67.6)	3 (75)	0.668
Diabetes mellitus	53 (23.8)	7 (13.7)	9 (26.5)	0	0.267
Severe RI	0	0	3 (8.8)	4 (100)	<0.001
Creatinine, mg/dl	0.8 ± 0.2	0.8 ± 0.2	1.0 ± 0.3	2.5 ± 1.0	<0.001
Creatinine clearance, ml/min	90.6 ± 26.8	69.7 ± 16.4	61.3 ± 22.6	24.9 ± 5.0	<0.001
Administration duration, d	4.1 ± 2.1	3.9 ± 1.8	4.0 ± 1.6	6.5 ± 5.6	0.128
Length of hospital stay, d	8.8 ± 5.7	9.4 ± 5.8	8.2 ± 4.6	14.8 ± 16.8	0.179
Major adverse vascular events, n (%)	6 (2.7)	1 (2.0)	1 (2.9)	2 (50)	<0.001

Abbreviations: *LMWH*, Low molecular weight heparin; *BMI*, body mass index; *STEMI*, ST-segment elevation myocardial infarction; *UA/NSTEMI*, Unstable angina/Non ST-segment elevation myocardial infarction; *DVT*, Deep vein thrombosis; *RI*, renal insufficient.

underdoses (50%, 2.9%, 2.0% and 2.7%, respectively,  $P < 0.001$ ). No major bleeding was recorded in the whole study population.

#### Major adverse vascular events and risk factors

There were 10 major adverse vascular events (3.2%) in this study, including four deaths, three myocardial re-infarctions, two revascularization procedures and one ischemic stroke. Major adverse vascular events occurred at  $5.9 \pm 9.0$  days after admission. There was no difference in the major adverse vascular event rate when comparing different diagnoses ( $P > 0.05$ ). Major adverse vascular events occurred in 4 patients with ST-segment elevation myocardial infarction (7.5%), 4 patients with unstable angina/non ST-segment elevation myocardial infarction (2.2%), 1 patient with atrial fibrillation (1.5%), and 1 patient with deep vein thrombosis (11.1%). Univariate analysis of the risk factors of major adverse vascular events is presented in Table 4. Multivariable analysis found that only one risk factor (severe RI) was independently associated with an increased risk for major adverse vascular events (OR, 31.93; 95% CI, 5.99-170.30;  $P < 0.001$ ), while age  $\geq 75$  years, excess doses of LMWH were not independent predictors of major adverse vascular events.

#### Discussion

In the present study we assessed LMWH dosing practices in 364 cardiovascular inpatients (376 admissions) and identified the efficacy and safety of LMWH treatment in 312 cases as measured by major adverse vascular events and major bleeding. There is a considerable disparity in LMWH use when comparing clinical practice to the guideline [6]. Seventeen percent of patients (64/376) without body weight records received LMWH, 10.9% (34/312) of patients received the recommended doses of LMWH and 87.8% (274/312) received underdoses of LMWH. Interestingly, we found that receiving underdoses of LMWH was not a risk factor for major adverse vascular events. The only risk factor for major adverse vascular events was severe RI.

LMWHs are prescribed based on the patient's weight according to dose-finding studies. However, accurate weight assessment is a challenge for seriously ill patients that are due to the limitations of resources, physical space and time [17]. In our study, we found that approximately 1 in 6 patients received LMWHs without having a record of weight. This is similar to a previous study reported that approximately 1 in 10 patients received enoxaparin for treatment of an ACS without weight documentation [13]. Furthermore, it has been reported that estimation of patients' weights by health

**Table 4 Risk factors for major adverse vascular events (univariable analysis)**

Characteristics	N (%)		OR (95% CI) *	P Value
	Without major adverse vascular events (n=302)	Major adverse vascular events (n=10)		
Age, ≥75 y	60 (20)	5 (50)	4.03 (1.13-14.38)	0.036
Female	72 (24)	5 (50)	3.19 (0.90-11.35)	0.071
Weight, >60 kg	235 (78)	10 (100)	–	0.086
STEMI	49 (16)	4 (40)	3.44 (0.94-12.65)	0.071
Hypertension	186 (62)	8 (80)	2.50 (0.52-11.95)	0.201
Diabetes mellitus	69 (23)	0	–	0.079
Severe RI	4 (1.3)	3 (30)	31.93 (5.99-170.30)	0.001
Inappropriate dose	269 (89)	9 (90)	1.104 (0.14-8.99)	0.701
Excess dose	2 (0.7)	2 (20)	37.5 (4.68-300.75)	0.005
Underdose	267 (88)	7 (70)	0.306 (0.08-1.24)	0.109
Major underdose	217 (72)	6 (60)	0.588 (0.162-2.134)	0.310

Abbreviations: STEMI, ST-segment elevation myocardial infarction; RI, renal insufficient; OR, odds ratio; CI, confidence interval.

\*Reference groups include age <75 years, male, weight ≤60 kg, no STEMI, no hypertension, no diabetes mellitus, no severe RI, recommended dose, no excess dose, no underdose, no major underdose.

care providers is inaccurate having a mean error of 9 to 10 kg [18]. Inappropriate dosing of LMWH can easily occur if the weight is estimated incorrectly, which can lead to medication errors in clinical practice. However, studies of the consequences of inappropriate dosing of LMWHs in real world practices are still scarce.

The major complication of anticoagulant and thrombolytic therapy is bleeding. A previous study demonstrated that patients with ACS often received excess doses of LMWH that was accompanied by an increased risk of major bleeding [15]. In order to decrease the risk of bleeding, some clinicians in China often prefer to choose empirical dose strategies when administering LMWHs instead of those reported in the results of clinical trials or suggested by Chinese guidelines. In our hospital, the most commonly adopted dosing strategies are enoxaparin 4,000AxaIU, nadroparin 4,100AxaIU or dalteparin 5,000AxaIU given twice daily when a patient's weight is < 80 kg. For patients that weigh ≥ 80 kg, enoxaparin 6,000AxaIU, nadroparin 6,200AxaIU or dalteparin 7,500AxaIU are given twice daily. These dosing strategies reflected the reason for the high rate of LMWH underdosing in the current study. As a result, there were no major bleeding events in our study; conversely, the rate of major bleeding events has been found to be approximately 1–6.5% in clinical trials of LMWHs [9-11]. Therefore, the practice of underdosing LMWH done in our hospital appears to be safe.

Unlike excess dosing of LMWH, which is related to a risk of bleeding, foremost concern associated with underdose of LMWH is the risk of embolism. Thus, we determined the efficacy of the current dosing practice of LMWHs, as measured by the incidence of embolism.

Surprisingly, in the underdose LMWH group, the incidence of major adverse vascular events was similar to that of the group receiving the recommended dose (2.6% vs. 2.9%). Previous data have demonstrated that patients with low anti-Xa activity increased 30-day mortality [19]. This may be due to the fact that the underdose of LMWH in our study doesn't indicate low anti-Xa activity as LMWH has linear pharmacokinetics but high between-subject variability [20,21]. On the other hand, clinical outcomes are also influenced by patients' characteristics and not only the dosage of LMWH. In the above mentioned study, patients with sub-therapeutic anti-Xa levels were significantly older, and had more impaired renal function and inferior heart function compared with others [19]. However, in our study, patients that received underdoses of LMWH had better baseline characteristics (younger and better renal function) than the recommended and excess dose groups; this may be the primary reason that the underdosing of LMWH was not found to be a risk factor for embolism in our study.

Since there were no severe RI patients receiving underdoses of LMWH, a fixed and weight-independent dosage may be not suitable for severe RI patients. LMWHs are not recommended for use in patients with severe RI due to the risk of accumulation may lead to major bleeding [11,22,23]. According to the results of the ExTRACT-TIMI 25 trial [11], a dose of 1 mg/kg of enoxaparin every 24 h was recommended for patients with an estimated creatinine clearance <30 ml/min. However, in our study, major adverse vascular events occurred more often in severe RI patients than in patients with creatine clearance ≥30 ml/min (30% vs. 1.3%,  $P < 0.001$ ), although 57.1% (4/7) of severe RI patients receiving excess doses

of LMWH. After multivariable analysis, we found that severe RI is the only predictor of major adverse vascular events. In elderly patients ( $\geq 75$  years), STEMI patients, excess doses of LMWH were not independent predictors of major adverse vascular events. Results from the current study are consistent with those from previous studies in which patients with RI have a higher risk for thromboembolic complications [24-26], and support the recommendation for dose adjustments based on anti-Xa activity and not calculated based on a simple dose scheme for LMWH used in RI patients [27]. Our results indicate that using LMWH at a fixed, lower dose in patients without severe RI may be safe and effective.

Nevertheless, there are some limitations to this study. First, our findings are based on the results of a one-center, retrospective study, complementing the prospect and lack of follow-up. Second, unlike randomized trials that have more restrictive inclusion criteria, it must be noted that the patient characteristics in this study were not as well-controlled. Third, due to a lack of anti-Xa assay in our hospital, we could not measure anti-Xa activity in RI patients. Finally, small sample size is a potential limiting factor in this study as well.

## Conclusions

In summary, the current study demonstrated that under-dose of LMWH is commonly used in cardiovascular inpatients. Using LMWH in a fixed, lower dose for treatment purposes in patients without severe RI was not associated with a high risk of adverse vascular events in our study. Larger studies with extended follow-ups are required to fully assess the long-term consequences of LMWH underdosing.

## Competing interests

The authors declare that there are no conflicts of interest regarding this study to be disclosed.

## Authors' contributions

HX, HC and ZQ carried out the medical records database search, statistical analysis, and drafted the manuscript. GX, XY, and HD participated in the design and coordination of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

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