Prescribing Errors With Low-Molecular-Weight Heparins

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Background: Low–molecular-weight heparins (LMWHs) are used in the prevention and treatment of venous thromboembolism (VTE). Bleeding is the primary major complication of LMWH therapy, which is associated with dose. The administration of appropriate dosages of LMWHs depends on the patient's risk of VTE, risk of bleeding, bodyweight, and renal function. Therefore, LMWH prescribing is prone to errors. However, no earlier study has explored the frequency of prescribing errors with LMWH.

Purpose: The aim of the study was to determine the frequency and determinants of in-hospital LMWH-prescribing errors.

Methods: A cross-sectional study was conducted to examine the frequency and determinants of LMWH prescribing errors between April and August 2014. We randomly selected 500 patients 18 years and older with at least one LMWH prescription during inpatient hospitalization. A prescribing error was a deviation from the internal hospital guidelines. Logistic regression estimated determinants of prescribing error.

Results: A prescribing error was present with 34% of all LMWH users. The most frequently recorded error was a dose that was not adjusted to body weight and/or renal function (85%). Prophylactic LMWH prescribing in medical wards was associated with a higher risk of prescribing error as compared with surgical wards.

Conclusions: The frequency of prescribing errors was 34% in a tertiary care hospital. Being a patient with prophylactic LMWH use on a medical ward is a determinant for LMWH prescribing error. Interventions that will lead to better electronic recording of body weight and more awareness among medical doctors may reduce the total number of prescribing errors.

Key Words: anticoagulants, heparin, low molecular weight, medication errors, prescriptions, safety

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Venous thromboembolism (VTE) is a common but preventable complication of hospitalization and a potentially lethal disease.[1] Compared with the general population, patients who are hospitalized have a greater than 100-fold increased risk of acute VTE.[2] Risk factors for VTE are common among hospitalized patients and include age, major surgery, immobilization, cancer, and trauma.[3–6] Venous thromboembolism is the third leading cause of cardiovascular mortality in Europe.[1] Deaths that occur as a consequence of hospital-acquired VTE comprise 71% of the total number of VTE-related deaths in six European countries.[1] Pulmonary embolism patients are especially at high risk for death. Untreated acute pulmonary embolism is associated with a mortality rate of up to 25%.[7]

Despite direct oral anticoagulants are increasingly used for VTE prophylaxis in patients after knee and hip surgery, fondaparinux and low–molecular-weight heparins (LMWHs) are still the cornerstone of VTE prophylaxis in hospitalized patients.[8,9] Besides thrombosis prophylaxis, LMWHs are also used in therapeutic dosages for treatment of VTE or as so-called "bridging therapy" in patients on vitamin K antagonists who have to interrupt this therapy because of planned invasive procedures.[8–10] Administration of inappropriate dosages of LMWHs can lead to serious complications: overdosage may cause major bleeding, but on the contrary, underdosage of LMWHs may lead to inadequate prevention of VTE events.[11] When prescribing the appropriate dosage of LWMHs, the treating physician should not only decide whether a prophylactic or therapeutic dosage is needed but also should take into account patient-related factors such as bleeding risk, body weight, and renal function.[12] Reduced renal clearance of LMWHs in patients with renal insufficiency may lead to accumulation of the LMWH and stronger anticoagulation effects as a result, which can lead to serious adverse events such as bleeding.[13] Patients using enoxaparin had a 2- to 3-fold increased risk of major bleeding when they experienced severe renal insufficiency (creatinine clearance ≤ 30 mL/min), as compared with patients with normal renal function.[14] This is important to note, because moderate renal insufficiency has been reported in a quarter of medical inpatients in tertiary care hospitals, and approximately 10% experience severe renal insufficiency.[15]

Therefore, prescribing LMWHs may be complex and prone to errors. However, no earlier study has explored the frequency of prescribing errors with LMWHs. Insight into potential risk factors of these prescribing errors is necessary to prevent prescribing errors. Several potential risk factors were identified in studies on prescribing errors in general. Type of hospital ward[16,17] and age[18,19] were examples of identified potential risk factors. Nevertheless, it is unknown whether these also apply to prescribing errors with LMWHs. Therefore, the aim of this study was to determine the frequency and determinants of in-hospital LMWH prescribing errors.

METHODS

Source Population

This cross-sectional study was conducted at the department of clinical pharmacy of a tertiary care hospital in Maastricht, the Netherlands, between April and August 2014. All wards (except the intensive care units) used a computerized physician order entry system (CPOE), which includes real-time checks on prescribing errors such as underdosages and overdosages and drug interactions (VCD Pharma, the Netherlands). It could also track and trace every prescription from the time of prescribing up to administration, which is electronically confirmed by nursing staff. Furthermore, the hospital kept electronic medical records (EMRs) for every patient.

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M.S., P.B., and F.V. had substantial contributions to the conception or design of the work, F.V. had substantial contributions to the acquisition, J.D. and R.W. had substantial contributions to analysis, and M.S., A.P., J.D., R.W., F.V., R.O., N.M., and P.B. had substantial contributions to the data for the work. M.S., A.P., J.D., R.W., F.V., R.O., N.M., and P.B. drafted the work or revising it critically for important intellectual content. M.S., A.P., J.D., R.W., F.V., R.O., N.M., and P.B. had the final approval of the version to be published.

TABLE 1. Recommended Tinzaparin Dosages for Therapeutic Use According to Body Weight and Renal Function

Body Weight, kg	Frequency	eGFR ≥ 60*	eGFR 30–60*†	eGFR ≤ 30*‡
≤60	Once daily	10,000 IU	7000 IU	5000 IU
60–80	Once daily	14,000 IU	10,000 IU	7000 IU
80–100	Once daily	18,000 IU	14,000 IU	10,000 IU
100–120	Once daily	20,000 IU	14,000 IU	10,000 IU
120–140	Once daily	24,000 IU	18,000 IU	10,000 or 14,000 IU
140–160	Once daily	28,000 IU	20,000 IU	14,000 IU

*Units: mL/min/1.73 m2.

†Based on a 25% dosage reduction of tinzaparin, with dosages round up to commercially available preparations, if possible.

‡Based on a 50% dosage reduction of tinzaparin, with dosages round up to commercially available preparations, if possible.

Physicians prescribed electronically by selecting the drug's substance name, its daily dose, administration route, and administration frequency in the CPOE. A patient's body weight could be registered by nurses in the structured "vital signs section" of the EMR, or it could be written as free text in the medical notes by physicians. In addition, physicians, pharmacists, or other authorized staff could record body weight in the CPOE, but this was not obligatory. Renal function was registered in the laboratory test section of the EMR.

Study Population

From April 2014 through August 2014, 500 patients 18 years and older who had been prescribed LMWH either in prophylactic or therapeutic dosage during their hospitalization were randomly selected. In our hospital guideline, once-daily nadroparin is the LMWH of choice for prophylactic indications, whereas for therapeutic indications, the physician can either choose once-daily tinzaparin or twice-daily nadroparin. Other LMWHs were not available in the hospital. When a patient was hospitalized more than once, we randomly selected one hospitalization episode. During each hospitalization, every patient was followed from the date of his first LMWH prescription until the date of discharge, death, or occurrence of outcome, whichever came first. For nadroparin, the time until the subsequent administration was determined to define whether nadroparin was prescribed in a twice-daily therapeutic regimen (i.e., the time between two administrations was < 18 hours) or in a prophylactic once-daily regimen (i.e., the time between two administrations was ≥18 hours). Patients whose LMWH prescription was discontinued before the LMWH was administered or in whom we could not determine whether a therapeutic or prophylactic dosage was prescribed were excluded. In addition, we excluded patients on intensive care units, because they did not use the CPOE system.

Other Variables

Baseline characteristics were determined at the first LMWH prescription. The most recently recorded body weight was extracted from the vital signs section of the EMR. Only in case of a missing body weight, the medical notes and CPOE were reviewed for the most recently recorded body weight. When two or more different values for body weight were recorded on the same day, the highest value was used. All renal functions were extracted from the electronic laboratory test results. The estimated glomerular filtration rate (eGFR) was estimated from serum creatinine levels using the Modification of Diet in Renal Disease formula (MDRD).

Patients were hospitalized in different nursing wards. For this study, we decided to divide these wards into two main categories: medical wards and surgical wards. Medical wards included internal medicine, gastroenterology, rheumatology, pulmonology, endocrinology, cardiology, and neurology. Surgical wards included general surgery, orthopedics, ophthalmology, oral and maxillofacial surgery, dermatology, plastic surgery, urology, cardiothoracic surgery, as well as gynecology and obstetrics. Oncology patients were hospitalized in the ward depending on their type of malignancy and could be treated on either surgical or medical wards.

The LMWH Dosing Scheme

Therapeutic and prophylactic weight-based standard doses for tinzaparin and nadroparin were derived from the internal hospital prescribing guidelines, as shown in Tables 1 to 3. In our hospital, reduced dosages for all therapeutic LMWH in patients with moderate (MDRD 30–60 mL/min/1.73 m^2) to severe (MDRD-eGFR < 30 mL/min/1.73 m^2) renal insufficiency are prescribed empirically. According to the current guidelines of the Dutch Nephrology Federation, this dosage reduction comprises 25% and 50% for moderate and severe renal insufficiency, respectively.[20] Prophylactic dosages were not adjusted in case of renal insufficiency. For patients on prophylactic

TABLE 2. Recommended Nadroparin Dosages for Therapeutic Use According to Body Weight and Renal Function

Body Weight, kg	Frequency	eGFR ≥ 60*	eGFR 30–60*†	eGFR ≤ 30*‡
≤50	Twice daily	3800 IU	2850 IU	2850 IU
50–70	Twice daily	5700 IU	3800 IU	2850 IU
70–110	Twice daily	7600 IU	5700 IU	3800 IU
≥110	Twice daily	9500 IU	7600 IU	3800 or 5700 IU

*Units: mL/min/1.73 m^2.

†Based on a 25% dosage reduction of nadroparin, with dosages round up to commercially available preparations, if possible.

‡Based on a 50% dosage reduction of nadroparin, with dosages round up to commercially available preparations, if possible.

TABLE 3. Recommended Nadroparin Dosages for Prophylactic Use According to Body Weight

Body Weight, kg	Frequency	Regular Dose	Intermediate Dose*
≤70	Once daily	2850 IU	5700 IU
70–90	Once daily	3800 IU	7600 IU
≥90	Once daily	5700 IU	7600 IU

*Intermediate dose for patients with estimated high VTE risk.

dosages, the prescribing physician can choose, based on the patient-related VTE risk, between the regular prophylactic dosage and an intermediate dosage.

Outcome

The primary outcome was the first prescribing error with LMWH during follow-up. A prescribing error was defined as a deviation from the internal hospital guidelines regarding one of the following aspects.

For therapeutic LMWH users, (1) the prescribed dosage was not adjusted to body weight and/or renal function according to the internal hospital guidelines (Tables 1 or 2), or (2) body weight was not electronically recorded in the past 365 days before LMWH prescribing, or (3) the eGFR was unknown or it was considered unreliable (i.e., when a value > 60 mL/min/1.73 m^2 was recorded >1 year ago or when a value < 60 mL/min/1.73 m^2 was recorded >2 weeks ago). For prophylactic LMWH users, a prescription error was counted either when the dosage was not adjusted to body weight according to the hospital's internal guidelines (Table 3) or when body weight was not electronically recorded in the past 365 days before LMWH prescription.

Statistical Analyses

Descriptive statistics was used to determine the frequency of prescribing errors.

In a subsequent analysis, the association of several potential risk factors (age, sex, ward type, prophylactic versus therapeutic LMWH use) with the outcome was determined. In addition, results were stratified for prophylactic or therapeutic use.

Logistic regression was used to investigate whether ward type, age, sex, and prophylactic/therapeutic dosage of LMWH were associated with a prescribing error, using SAS 9.2 software (SAS Institute, Carey, NC).

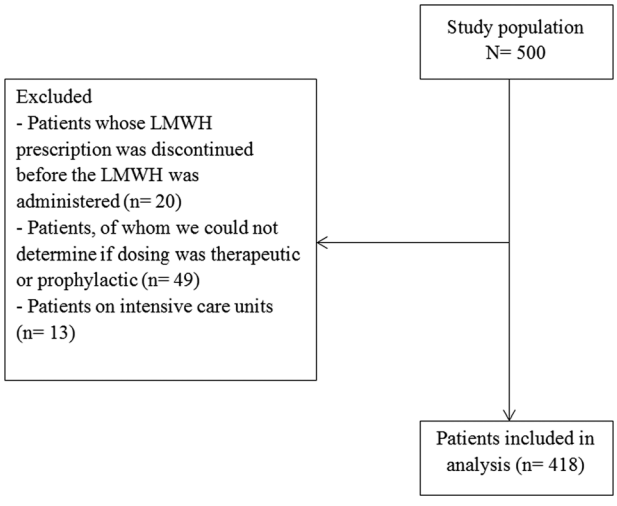

FIGURE 1. Study population flow chart.

This is an observational study and according to Dutch national legislation (Wet Medisch Wetenschappelijk Onderzoek met Mensen [legislation for medical scientific research, involving humans]) not subject to ethical approval.

RESULTS

A total of 500 patients were randomly selected between April 2014 and August 2014. Of these 500 patients, 82 were excluded from analysis with the following reasons: LMWH was discontinued before first dose was administered (n = 20), no information on therapeutic or prophylactic dosing scheme (n = 49), and patients admitted on intensive care units (n = 13) (Fig. 1). Thus, for our analysis, we included 418 patients.

TABLE 4. Baseline Characteristics of LMWH Users*

Characteristics	LMWH Users
No. patients	418
No. women	211 (50.5)
Age, mean (SD), y	62.0(17.0)
Age, y	
<50	79 (18.9)
50–69	190 (45.5)
≥70	149 (35.6)
Body weight, mean (SD), kg	77.0(17.5)
Body weight, kg	
<50	11 (2.6)
50–69	122 (29.2)
70–89	178 (42.6)
90–109	71 (17.0)
≥110	17 (4.1)
Not recorded	19 (4.5)
Duration of admission, mean (SD), d	9.9(7.9)
Regime	
Prophylactic	358 (85.6)
Therapeutic	60 (14.4)
Drug	
Tinzaparin	42 (10.0)
Nadroparin	376 (90.0)
Ward type	
Medical†	146 (34.9)
Surgical‡	272 (65.1)
Most recently recorded eGFR	
By time interval	
<14 d ago	314 (75.1)
15–365 d ago	66 (15.8)
>365 d ago	0 (0.0)
Not recorded	38 (9.1)
By value	
eGFR ≥ 60 mL/min/1.73 m^2	286 (68.4)
eGFR 30–60 mL/min/1.73 m^2	76 (18.2)
eGFR ≤ 30 mL/min/1.73 m^2	18 (4.3)
Not recorded	38 (9.1)

*Data are presented as n (%), unless stated otherwise.

†Medical wards included internal medicine, cardiology, gastroenterology, neurology, psychiatry, endocrinology, pulmonology, and rheumatology.

‡Surgical wards included orthopedic, urology, ophthalmology, plastic surgery, and gynecology.

TABLE 5. Clinical Prescribing Errors by Sex, Substance, Ward, and Renal Function*

Type	All Errors (N = 142)	Error With Prophylactic LMWH (n = 117)	Error With Therapeutic LMWH (n = 25)
Sex			
Female	67 (47.2)	52 (44.4)	15 (60.0)
Male	75 (52.8)	65 (55.6)	10 (40.0)
Drug			
Nadroparin	125 (88.0)	117 (100.0)	8 (32.0)
Tinzaparin	17 (12.0)	0 (0.0)	17 (68.0)
Ward type			
Medical	57 (40.1)	48 (41.0)	9 (36.0)
Surgical	85 (59.9)	69 (59.0)	16 (64.0)
Renal function by eGFR			
eGFR ≥ 60 mL/min/1.73 m^2	NA	NA	6 (24.0)
eGFR 30–60 mL/min/1.73 m^2	NA	NA	15 (60.0)
eGFR ≤ 30 mL/min/1.73 m^2	NA	NA	1 (4.0)
Not recorded	NA	NA	3 (12.0)

*Data are presented as n (%).

NA, not applicable.

Patient characteristics are shown in Table 4. The mean age of the LMWH users was 62.0 years, and the proportions of men and women were comparable. The LMWH users had a mean body weight of 77.0 kg and the mean duration of the admission was 9.9 days. A total of 65.1% of the patients were admitted to a surgical ward. Low–molecular-weight heparins were mainly prescribed in a prophylactic dosage (85.6%), and nadroparin was the most prescribed LMWH (90%). Of the 60 patients (14.4%) with a therapeutic regime, 42 patients used tinzaparin and 18 patients used nadroparin. Estimated glomerular filtration rate was not recorded in 38 patients, and more than 75.1% of the patients had their renal function recorded in 2 weeks before baseline. Renal insufficiency was reported in 22.5% of LMWH users.

We found that 34.0% of LMWH prescriptions contained a prescribing error. The most frequently recorded error was a dose that was not adjusted to body weight and/or renal function (84.5%), followed by lack of electronic recording of body weight (12.7%). Only three patients with a therapeutic regime had missing data for renal function and one patient had an unreliable eGFR. Table 5 shows the prescribing errors by sex, substance, ward, and renal function.

Table 6 shows that age, sex, ward, and therapeutic or prophylactic use were not significantly associated with risk of a prescribing error. Prophylactic LMWH prescribing in medical wards was associated with a higher risk of prescribing error as compared with surgical wards, when stratified for prophylactic or therapeutic LMWH prescription (Table 6). The risk further increased after the addition of the type of LMWH use (prophylactic/therapeutic use) to the multivariate model (Table 7).

DISCUSSION

This study showed that prescribing errors of LMWHs are common in a Dutch tertiary care hospital. In this study, 34.0% of all LMWH prescriptions had a clinical prescribing error. Most prescribing errors with LMWH treatment included overdosages and underdosages that were not adjusted to body weight or renal function, followed by missing data on body weight. Almost every therapeutic LMWH user had a reliably recorded renal function. Overall risk factors of prescribing errors were not identified. When we stratified prescribing errors into prophylactic or therapeutic LMWH use, we found that among prophylactic

TABLE 6. Potential Risk Factors of Prescribing Errors of Tinzaparin or Nadroparin; Stratified for Prophylactic or Therapeutic LMWH Prescription

Exposure	Adjusted OR (95% CI)		
	All Errors	Prophylactic LMWH Errors	Therapeutic LMWH Errors
Age, y			
<50	Reference	Reference	Reference
50–69	1.08 (0.62–1.89)	0.98 (0.54–1.77)	2.42 (0.36–16.40)
≥70	1.20 (0.68–2.13)	0.92 (0.49–1.73)	3.58 (0.54–23.78)
Female sex*	0.79 (0.52–1.18)	0.65 (0.41–1.02)	2.06 (0.74–5.74)
Medical ward†	1.44 (0.95–2.18)	1.65 (1.04–2.63)	0.64 (0.23–1.78)

Adjusted for all other variables in the table.

*Reference: male.

†Reference: surgical ward.

CI, confidence interval; OR, odds ratio.

TABLE 7. Potential Risk Factors of Prescribing Errors of Tinzaparin or Nadroparin, Including Type of LMWH use

	Adjusted OR (95% CI)
Exposure	**All Errors**
Age, y	
<50	Reference
50–70	1.03 (0.59–1.80)
≥70	1.06 (0.59–1.90)
Female sex*	0.77 (0.51–1.16)
Therapeutic prescription†	1.41 (0.93–2.15)
Medical ward‡	2.01 (1.18–3.41)

Adjusted for all other variables in the table.

*Reference: male.

†Reference: prophylactic prescription.

‡Reference: surgical ward.

users, admission on a medical ward was more associated with prescribing errors than on a surgical ward. This was also shown, when the type of LMWH use was added to the multivariate model.

This is probably the first study that specifically evaluated prescribing errors with LMWHs. A previous study that was conducted in a US tertiary care hospital in Boston, Massachusetts, showed a 350-fold lower proportion of all medication errors with LMWH (including prescribing errors) as compared with our study.[21] This substantial difference is probably caused by a difference in the methods of data collection: the previous study obtained medication errors that were self-reported, whereas we retrospectively evaluated routinely collected electronic medical records. On the other hand, our study may have overestimated the true number of clinical prescribing error because we also considered missing electronic data on, for example, body weight or renal function as prescribing errors, whereas this information may have been discussed during the consultation. A cross-sectional study among hospitalized patients in Argentina[22] showed that adherence to VTE prophylaxis guidelines was inadequate for 28% of the patients' prescriptions. This number is in keeping with our finding that 29.1% of patients with a recorded body weight had been prescribed an incorrect prophylactic dose of LMWHs. We do not have information on patients that had an indication for LMWH prophylaxis but in whom mistakenly no LMWH was prescribed. In the previously mentioned study, these patients were also included in the 28% inadequate prescriptions.

Our findings on potential risk factors of clinical prescribing errors with LMWH treatment are in line with those from an epidemiological study that evaluated prescribing errors for all classes of drugs in two Dutch teaching hospitals in the Netherlands.[16] Both studies showed that patient's age and sex were not associated with prescribing or dosing errors. In literature, we found differences in ward type as risk factor for clinical prescribing errors.[23,24] In a study in eight hospitals of Scotland, surgical wards were associated with a higher risk of prescription errors; however, in a three center study in the United Kingdom, medical wards were more associated with errors. Other risk factors such as prescriber characteristics (e.g., experience or age) or drug characteristics could explain these differences.

Comparing the reported incidence of prescribing errors is difficult because it varies and depends on the definition of prescribing error.[25]

Our definition of prescribing errors included mainly dosing errors and was based on deviations from our internal hospital guideline regarding LMWH dosing. For prophylactic LMWH, these hospital guidelines recommend LMWH prescribing based on several patient-related factors, including assessment of the patients individual VTE risk, based on, for example, previous VTE, known thrombophilia, or active malignancy. For these high-risk patients, instead of the regular prophylactic dosage, an intermediate LMWH dosage could be prescribed. Information on this baseline VTE risk is not routinely recorded in the EMR and could therefore not be evaluated. This may have resulted in underestimation of errors with prophylactic LMWH treatment, because we considered nadroparin dosages that could be prescribed prophylactically for both low- or intermediate-risk VTE patients as correct. Our hospital dosing guideline comprises weight-based dosing of LMWH for both therapeutic and prophylactic prescriptions. For prophylactic LMWH, this weight-based dosing is not universally applied in all hospitals. This might have introduced more prescribing errors, because physicians might not be familiar with this weight-based dosing of prophylactic LMWH. For therapeutic LMWH, weight-based dosing is a common practice. We did not validate the electronic recording of body weight; for example, it is unknown whether this had been measured or whether it was based on self-report. When body weight was not recorded, we could not check whether the dose administered was correct or incorrect. Therefore, we had to count this as a prescribing error, while it was possible that the patient had received the right dose, based on verbal information that was not recorded in the EMR. This might have caused an overestimation of the prescribing errors in our study. An EMR should be designed in a way that recording patient data, such as body weight, is obligatory. In our hospital, a dosage reduction of 25% and 50% is implemented for moderate and severe renal insufficiency, respectively, according to the recommendations of the Dutch Federation of Nephrology.[20] Nevertheless, the underlying evidence for these recommendations is weak: treatment with tinzaparin and nadroparin has infrequently been studied in patients with renal insufficiency[10,14] and recommendations regarding dosage reduction and/or anti-Xa monitoring vary.[26]

Our study had several strengths. To our knowledge, it is the first report of prescribing errors with LMWHs. We showed that there is need for improvement based on the high proportion of prescribing errors. We also identified the number of missing patient characteristics such as body weight and renal function of LMWH users as a source of possible prescribing errors. We used a well-defined protocol with a clear definition of prescribing errors. The medical prescriptions were extracted directly from the CPOE retrospectively, without the knowledge of the physicians at moment of prescribing, which has decreased the likelihood of selection bias.

Our study had several limitations as well. We did not compare the incidence of outcomes such as VTE or bleeding with prescribing errors of LMWHs. Other studies showed that 1.5% to 2.7% of all heparin-related medication errors involved patient harm.[27,28] We also did not check whether the anti-Xa concentration was determined and/or correct or whether the prescribing doctor had a specific reason to derogate from the hospital guideline (e.g., bleeding risk of a patient). Although medical doctors in this hospital should be aware of and comply with internal LMWH prescribing guidelines, the results from our study suggest that this may have not been the case.

In conclusion, the frequency of prescribing errors was 34% in a tertiary care hospital. Being a patient with prophylactic LMWH use on a medical ward is a determinant for LMWH prescribing error. Interventions that will lead to better electronic recording of body weight and more awareness among medical doctors, in particular when prescribing therapeutic LMWH treatment, may reduce the total number of prescribing errors. A more effective way to improve the prescribing of LMWHs can be found in more hardwired solutions, such as a Clinical Decision Support System, which contains two or more items of patient data and which generates a patient specific advice to the doctor.

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