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Utilisation and Safety of Low Molecular Weight Heparins

Prospective Observational Study in Medical Inpatients

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Abstract

Aims: Low molecular weight heparins (LMWHs) are widely used as curative or preventive treatments of thromboembolic diseases. The aim of our study was to: (i) investigate the pattern of prescription of LMWHs in different departments of French teaching hospitals; and (ii) estimate the incidence of adverse drug reactions (ADRs) induced by LMWHs and associated risk factors for the occurrence of bleeding events.

Methods: This prospective study was performed in two teaching hospitals in Toulouse (south-western France) in March 1999 in different medical wards. All patients receiving a prescription for a LMWH were included in the survey. All data were prospectively recorded in each ward.

Results: A total of 334 patients were included. Sex ratio (male/female) was 1.25 and mean age was 72.5 ± 16.3 years (extremes:18–101). 450 prescriptions for LMWHs were collected (1.34 prescription per patient) and involved mainly enoxaparin (61%), which was more frequently used than tinzaparin in patients over 75 years old (71.7 vs 28.3%; $p < 0.0001$). Ninety-nine patients received a LMWH for curative treatment (corresponding to 127 prescriptions of which 99 were for enoxaparin and 28 were for tinzaparin [$p < 0.0001$]). Indications included therapy for deep venous thrombosis, pulmonary embolism, acute coronary syndrome, unstable angina pectoris, non-Q-wave myocardial infarction. Serious renal insufficiency was significantly more frequent in patients from the geriatrics department ($p < 0.00001$). Enoxaparin was prescribed more frequently in patients with serious or moderate renal insufficiency than tinzaparin (72 vs 61%, $p < 0.05$). The incidence of LMWHs-induced ADRs was 10.5% occurring in 22 cases during preventive treatment of deep venous thrombosis and in 13 cases during curative

therapy. ADRs were classified as 'serious' in 11 cases (31.4%). Reported ADRs were bleeding events (n = 15), thrombocytosis (n = 13), thrombopenia (n = 4) and hepatic cytolysis (n = 1). The mean delay for the occurrence of bleeding effects was 8.0 ± 9.1 days (range 1–40). Multivariate analysis of the influence of several criteria on the occurrence of haemorrhagic effects showed that the decrease of creatinine clearance (10 ml/min) was associated with an increased haemorrhagic risk (relative risk [RR] = 1.34, 95% CI 1.12–1.65; $p < 0.05$). Moreover, the risk of adverse bleeding effects increased for patients with a creatinine clearance <20 ml/min (RR = 2.8; 95% CI 1.00–7.8).

Conclusion: Our data firstly show a different pattern of LMWHs prescription in different clinical wards. Secondly, the risk of bleeding ADRs in patients treated by LMWHs increases significantly with renal function impairment for the two LMWH preparations studied. More pharmacoepidemiological studies are necessary in patients with several risk factors, particularly in elderly people who often have renal impairment, in order to determine the optimal pattern use of each LMWH.

Background

Deep venous thrombosis (DVT) and pulmonary embolism (PE) have a high prevalence among inpatients and are significant causes of morbidity and mortality leading to death in 10% of cases.[1,2] Low molecular weight heparins (LMWHs) are widely used in the curative or preventive treatment of thromboembolic diseases: several meta-analyses have concluded that LMWHs are as least as efficient than unfractionated heparin (UFH) for preventive[3,4] and curative treatment of DVT.[5-7] Recent data suggest that LMWHs could be used for PE,[8] unstable angina pectoris or non-Q-wave myocardial infarction as an adjunct therapy.[9,10] Recently, enoxaparin was approved in Europe for medical preventive treatment of DVT.[11] Compared to UFH, LMWHs are more convenient for nurses and patients due to their twice daily or even once daily (tinzaparin, nadroparin) administration schedule allowing ambulatory care of DVT. However, as they are mainly eliminated by kidney, caution must be taken in patients with renal insufficiency. Despite some different properties (mean molecular weight, anti-Xa and anti-IIa activities, etc.), the pharmacodynamic parameters of LMWHs are considered closely equivalent.

In clinical practice, as optimal use of oral anticoagulants is difficult in some patients, particularly elderly people, LMWHs are frequently used outside the approved Summary Characteristics of Product (SPC), i.e. for a duration of more than 10 days during curative treatment of DVT, in patients with severe renal impairment or in association with multiple drugs causing haemorrhagic events. However, as far as we know, few pharmacoepidemiological studies have investigated the effects of the different LMWHs used in daily practice, even in patients with a likely risk factor for haemorrhagic events.

In 1999, the geriatrics departments of Toulouse University Hospital reported several cases of serious bleeding adverse drug reactions (ADRs) in patients exposed to LMWHs, to the Midi-Pyrénées Center of Pharmacovigilance. Therefore, we attempted a prospective observational drug utilisation study in order to: (i) to investigate the pattern of prescription of LMWHs in several wards in French university hospitals; and (ii) to assess the incidence of LMWHs-induced ADRs and the associated risk factors for bleeding events.

Material and Methods

This prospective observational study was performed in two university hospitals in Toulouse (south-west France), during a period of 1 month

(1–31 March 1999) in five medical wards with relatively different patterns of LMWHs prescription:

- two departments of cardiology where LMWHs are mainly prescribed in unstable angina and non-Q-wave myocardial infarction;
- one department of geriatrics including three clinical wards (cardiology, internal medicine and functional rehabilitation) where LMWHs are mainly prescribed in preventive or curative DVT in elderly patients;
- one department of angiology using LMWHs mainly for DVT or PE; and
- one department of infectious diseases where LMWHs are principally prescribed in medical preventive treatment of DVT.

The feasibility of conducting this survey was previously tested in a pilot study performed for a duration of 2 weeks in the angiology and geriatric departments the month before the beginning of the study.

Inclusion of Patients

During the study period, all patients admitted in the five departments and for whom at least one LMWH was prescribed were included and followed up until their discharge from the hospital (8 July 1999 for the last patient). For each patient, the following data were recorded.

- *Demographic characteristics*: gender, age, weight, WHO scale indicating the degree of autonomy of the patient[12] (0 = normal, able to carry on normal activities; 1 = able to live at home, ambulatory, somewhat impaired activity; 2 = less than 50% of time in bed, work impairment medical and surgical history; 3 = severely disabled and more than 50% of time in bed; 4 = totally bedridden), and duration of hospitalisation. Furthermore, the total number of inpatients during the study period in the five departments was obtained from the Medical Information Department of Toulouse Teaching Hospital in order to estimate the prevalence of exposure to LMWHs.
- *Data relative to the prescription of LMWHs*: duration, dose, reason for prescription and the concordance with the French labelling,[13] oral anticoagulant overlap and concomitant drug treatment. All changes in the dose of LMWH or type of LMWH were considered as a new prescription of a LMWH.
- *ADRs*: assessment of causal relationship of LMWH-related ADRs, by both a member of pharmacovigilance centre and a practitioner, according to the French method[14] and the seriousness according to the WHO definition.[15] An increase in platelet count (thrombocytosis) was defined as a platelet count >400 000/mm^3 and thrombopenia as platelet count <150 000/mm^3.
- *Renal function*: biological data relative to plasma creatinine level in order to calculate renal function according to Cockcroft's formula[16] by creatinine clearance (Cl_{cr}) value (ml/min), anti-Xa activity (during curative treatment) and platelet count. We defined three groups of renal insufficiency: group 1: $Cl_{cr} \leq 30$ ml/min; group 2: $31 < Cl_{cr} \leq 50$ ml/min; and group 3: $51 < Cl_{cr} \leq 80$ ml/min. All values of $Cl_{cr} > 80$ ml/min were considered to correspond to normal renal function. We did not find a unique consensus for the severity of renal insufficiency and the threshold of Cl_{cr} value but our choice was based on French National Formulary[17] which suggest these three borders to define severe, moderate and low renal insufficiency, respectively.

If necessary, data missing from the medical record were completed subsequently with the patient's general practitioner. All informations were reviewed openly by a staff committee including a cardiologist and a member of the regional Pharmacovigilance Centre in order to validate medical data and the assessment of causal relationship of ADRs.

Statistical Analysis

Data were analysed with EPI-INFO 6.04 and SPSS-10 software. Quantitative data were compared using student's t-test. Qualitative data were compared with the χ^2 test with continuity correction or the exact Fisher test. The risk of haemor-

rhagic effects was evaluated by the odds ratio (OR) as an estimate of the relative risk (RR) presented with its 95% CI. Association of haemorrhagic effects with suspected risk factors was investigated in a univariate approach with a logistic regression model. Risk factors were: age; gender; Cl_{cr}; WHO score; total duration of exposure to LMWHs; curative use of type of LMWH; and association with a drug known to increase the bleeding risk (aspirin [acetylsalicylic acid], nonsteroidal anti-inflammatory drugs [NSAID], steroidal anti-inflammatory drug [SAID], anti-platelet agents, oral anticoagulant and selective serotonin reuptake inhibitors [SSRIs]).

In a second step, we performed several models of backward stepwise logistic regression. Haemorrhagic effects were dependent variables. A first model was fitted using Cl_{cr} as a continuous independent variable. Exposure to individual drugs increasing the risk of bleeding also represented dependent variables in this model. In a second model, Cl_{cr} was the continuous variable and exposure to drugs increasing the risk of bleeding was taken into account as at least one exposure to one of these drugs. In the third, fourth and fifth models, Cl_{cr} was used as a categorical variable and the analyses were done for serious renal insufficiency in the following classes: Cl_{cr} <30 ml/min (group 1 of renal insufficiency) and also, for Cl_{cr} <25 ml/min and Cl_{cr} <20 ml/min. Potentially confounding variables such as age (increasing by 10 years), gender, WHO score (categorical variable using WHO score = 0 as reference), duration of treatment and LMWH treatment were included in all models. The level of statistical significance was $p < 0.05$.

Results

During the survey, data for 334 patients including 186 males (55.7%) and 148 females were recorded. The mean age of patients was 72.5 ± 16.3 (± SD) years (extremes:18–101). Table I summarises the characteristics of the patients in the different medical departments.

Cardiological antecedents were ischaemic cardiopathy, e.g. angina pectoris (45.3%), arterial hypertension (40.4%) and thromboembolic events such as stroke, DVT and PE (26.1%). Neoplastic diseases were found in 12.7% and digestive ulcers in 8.4% of patients.

The mean value of baseline Cl_{cr} was 60.5 ± 31.0 ml/min (extremes: 5–195); values were missing for four patients. Compared with other departments, renal insufficiency was significantly more frequently observed in the geriatric department (61.1% of patients, of whom 30.6% had a Cl_{cr} <30 ml/min; $p < 0.01$).

Renal insufficiency was experienced more frequently by patients over 75 years (26.4% with Cl_{cr} <30 ml/min and 73.6% with 31 < Cl_{cr} <50 ml/min; $p < 0.001$). Women also were affected more frequently by renal insufficiency (62.5%; $p < 0.00001$). Three patients (two from cardiology and one from geriatrics) were at final stage of renal insufficiency (Cl_{cr} ≤10 ml/min). Table I shows the mean value of baseline Cl_{cr} and the percentage of different stages of renal insufficiency in each department.

Duration of Hospitalisation and Low Molecular Weight Heparin (LMWH) Prescriptions

Table I shows data relative to the duration of hospitalisation of patients and the percentage of inpatients receiving at least one LMWH in each department. According to the decision of the Pharmacy and Therapeutic Committee, two LMWHs, (enoxaparin and tinzaparin), were available inside the hospital in 1999. The choice was based, firstly on economic factors since the Committee judged that the available LMWHs had the same clinical equivalence and safety profiles and secondly, the wish of for availability of the first once daily LMWH for curative treatment (tinzaparin).

During this study, a total of 450 prescriptions were collected (1.34 prescription per patient): 73.6% of patients received one prescription of LMWH (dosage, type of LMWH) and two patients had five different prescriptions of LMWHs. Enoxaparin was most frequently prescribed (61%) on the whole, and 2.5 times more than tinzaparin in patients over 75 years old (71.7 vs 28.3%; $p < 0.0001$). The mean number of LMWH prescrip-

Table I. Demographic data, duration of hospitalisation, mean value of creatinine clearance (Cl_{cr}) and the percentage of different stages of renal insufficiency (RI) in each medical department. Difference was statistically significant ($p < 0.001$) for all parameters for the geriatric department compared with others, e.g. duration of hospitalisation, number of female, mean age, patients with WHO score >2, mean value of Cl_{cr} and the number of patients included in group 1, 2 or 3 of RI

	Medical department				Total	p-Value
	cardiology	geriatrics	angiology	infectious diseases		
Total number of inpatients	397	193	119	142	851	
Number of patients included (%)	147 (37)	125 (64.8)	34 (28.6)	28 (19.7)	334	
Mean duration of hospitalisation in days ± SD (extremes)	5.7 ± 3.3 (1–21)	25.1 ± 14.9 (2–141)	13.2 ± 9.1 (2–56)	19.3 ± 13.6 (4–81)		p < 0.001
Sex ratio (male : female)	3.3	0.45	1.8	0.75	1.25	p < 0.001
Mean weight in kg ± SD	73.0 ± 13.5	60.6 ± 13.8	73.0 ± 12.9	63.6 ± 15.8	67.7 ±15.2	p < 0.001
Mean age in years ± SD	64.3 ± 14.5	85.5 ± 7.0	66.2 ± 14.8	64.4 ± 18.5	72.5 ± 16.3	p < 0.001
Number of patients with WHO score >2 (%)	13 (8.9)	94 (75.2)	8 (23.5)	8 (28.5)		p < 0.001
Mean creatinine clearance value in ml/min ± SD (minimum value)	71 ± 29 (5)	42 ± 20 (10)	77 ± 32 (37)	64 ± 34 (29)	60.5 ± 31	p < 0.001
Group 1 of RI – Cl_{cr} ≤30 ml/min (%)	9 (6.2)	38 (30.6)	0	3 (10.7)	50 (14.9)	p < 0.001
Group 2 of RI – 30 <Cl_{cr} ≤50 ml/min (%)	25 (17.2)	59 (47.5)	8 (23.5)	3 (10.7)	95 (28.4)	p < 0.001
Group 3 of RI – 50 <Cl_{cr} ≤80 ml/min (%)	61 (42)	21 (16.9)	13 (38.2)	12 (42.8)	104 (32)	p < 0.001

tions was 1.22 for cardiology, 1.32 for angiology, 1.36 for infectious diseases and 1.49 for geriatrics. In geriatrics, preventive or curative enoxaparin prescription was more frequent than tinzaparin while the cardiology department prescribed enoxaparin more frequently for preventive treatment of thromboembolic diseases and the two LMWHs in the same proportions for curative treatment. 99 patients received a LMWH as curative treatment (corresponding to a total of 127 prescriptions) involving more frequently enoxaparin (99 prescriptions, i.e. 78%) than tinzaparin ($p < 0.0001$). Medical or surgical prevention of thrombosis or atrial fibrillation involved 235 patients: enoxaparin was used in 52.7% of LMWHs prescriptions (figure 1). During curative treatment, an overdose of LMWHs (>175 IU/kg/day for tinzaparin and 200 IU/kg/day for enoxaparin) was noted for 13 prescriptions for tinzaparin (46%) and seven prescriptions for enoxaparin (7%) [$p < 0.001$].

A LMWH for curative treatment was prescribed for 21.5% (n = 72) of patients with serious renal insufficiency (in six patients, an overdose of LMWH associated with renal insufficiency was noted). Enoxaparin was prescribed more frequently in patients with renal insufficiency (group 1 and 2) than tinzaparin (72 vs 28%; $p < 0.05$).

In 27% of cases the duration of therapy was longer than 10 days: for preventive treatment LMWH therapy was prolonged beyond 100 days in three patients of the geriatric department; for curative treatment the duration exceeded 10 days (from 13–105 days) for 11 prescriptions for tinzaparin and 15 prescriptions for enoxaparin.

A history of LMWH prescription was found in 23.6% of patients at the time of their admission and 36.8% of them left hospital with a LMWH prescription. Finally, an overlap with oral anticoagulant was noted in 3.6% of patients.

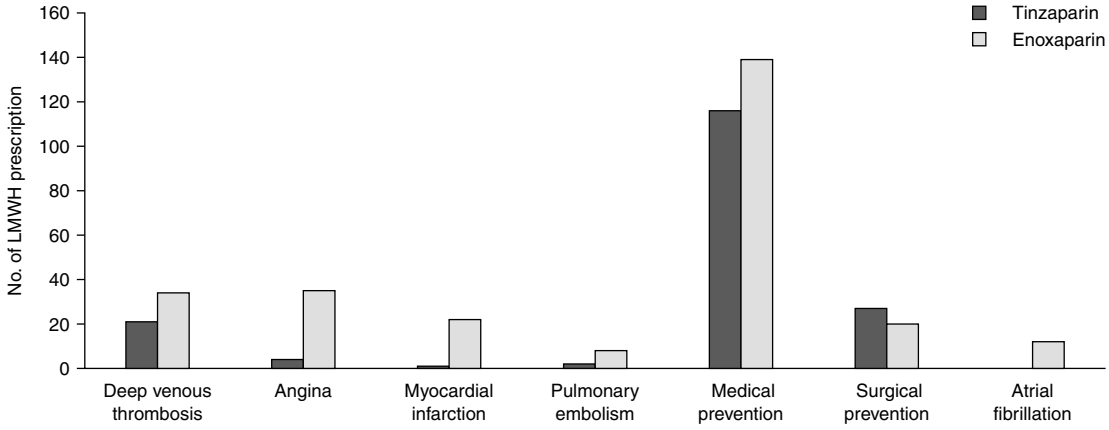

Fig. 1. Pattern of enoxaparin or tinzaparin (low molecular weight heparin [LMWH]) prescription in different preventive or curative indications.

Concomitant Medication

The mean number of drugs co-prescribed with LMWHs was 7.85 ± 3.3 (extremes: 0–21): 41% of the patients received more than nine drugs. Cardiovascular drugs were predominant with aspirin (52.7%) as antiplatelet agent, nitroglycerin (35.3%), furosemide (27.3%), molsidomine (15.3%), amiodarone (11.4%) or digoxin (10.5%). The proton pump inhibitor, omeprazole was used in one-third of patients. The psychoactive agents, meprobamate and bromazepam, were prescribed for 11 and 9% of patients, respectively, (figure 2).

Adverse Drug Reactions

A total of 35 LMWH-related ADRs were reported during the survey, occurring in 34 patients. They were classified as 'serious' in 11 cases (31.4%) since they led to the prolongation of hospitalisation. The incidence of LMWH-induced ADRs was estimated at 10.2% (95% CI 7.9–13.1) of which 14 occurred with tinzaparin for a total of 134 exposures, (9.7% [5.4–15.4]) and 21 with enoxaparin for a total of 201 exposures (10.4% [6.2–14.6]); the difference was not significant.

Reported adverse drug reactions were: 15 cases of bleeding events including haematoma (n = 7), digestive haemorrhage with melena, haematemesis or rectorrhagia (3), epistaxis (1), ecchymosis (2), haematuria (1) and gingival haemorrhage (1), 13 cases of thrombocytosis (maximal platelet count 965 000/mm^3), four cases of thrombopenia (minimal platelet count 72 000/mm^3) and one case of hepatic cytolysis during enoxaparin administration with a doubtful causal relationship owing to liver failure of the patient and association with amoxicillin + clavulanic acid.

Among the 35 cases, 14 patients had renal insufficiency (11 moderate and three serious), 13 were exposed to LMWHs for more than 10 days and 13 had a WHO score >2 (table II). Concerning the bleeding events (n = 15), eight occurred during preventive treatment and seven during curative treatment (incidence of 3.4 and 7%, respectively) and 10 cases were reported in patients with renal insufficiency (nine moderate and one serious) [table II]. In three patients, ADRs occurred during administration of tinzaparin with higher dosage than recommended by the French SPC: one case of haematoma (patient in group 2 renal insufficiency treated for 40 days, 272 IU/kg), one case of rectorrhagia (patient in group 3 renal insufficiency treated for 4 days, 192 IU/kg) and one case of thrombocytosis.

The impact of several factors on the occurrence of bleeding events is presented in table III. The

decrease of 10 ml/min of the Cl_{cr} was associated to an increase in the bleeding risk with an adjusted OR of 1.34 (95% CI 1.12–1.65; $p < 0.05$). After adjustment on other potentially confounding variables, bleeding effects remained associated to increasing age, WHO score, decreasing of Cl_{cr} or SSRI co-medication and exposure to at least 1 drug which could favour bleeding events. Exposure to LMWH for curative treatment whatever the drug was not found as an explicative factor for bleeding effects. In other models using Cl_{cr} as a threshold to define renal insufficiency, we found a significant association only with a threshold of 20 ml/min with an OR of 3.48 (95% CI 1.27–9.54).

Discussion

Different studies have been undertaken to determine the incidence of the bleeding risk with oral anticoagulants or UFH.[18-20] However, few pharmacoepidemiological studies have been performed with LMWHs despite their extensive use. In France, Callaert et al.[21] did a cross-sectional study (1 day) in 334 patients, investigating the concordance of LMWHs prescriptions with hospital guidelines. Another study looked at the recommendations for LMWHs use in 104 patients hospitalised for 4 months.[22] Our study investigated the use of LMWHs in a sample of inpatients (n = 334) in different medical departments without any modification of their daily practice.

Owing the diverse origins of the patients, prescription of LMWHs seemed to differ. Enoxaparin prescription (preventive or curative) was more frequent in geriatrics departments, which is perhaps explained by the occurrence of a few cases of serious bleeding with tinzaparin in 1999. The more frequent use of enoxaparin for prevention of thromboembolic diseases in cardiology could be explained by the data from the MEDical patients with ENOXaparin (MEDENOX) trial.[11] However, this study did not provide data about the risk of overdose in underweight or old patients. In our study, LMWHs were prescribed in 56.6% of cases for medical prevention of DVT. Tinzaparin use in PE was based on the data of the Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire (THESEE) trial[8] and concerned eight

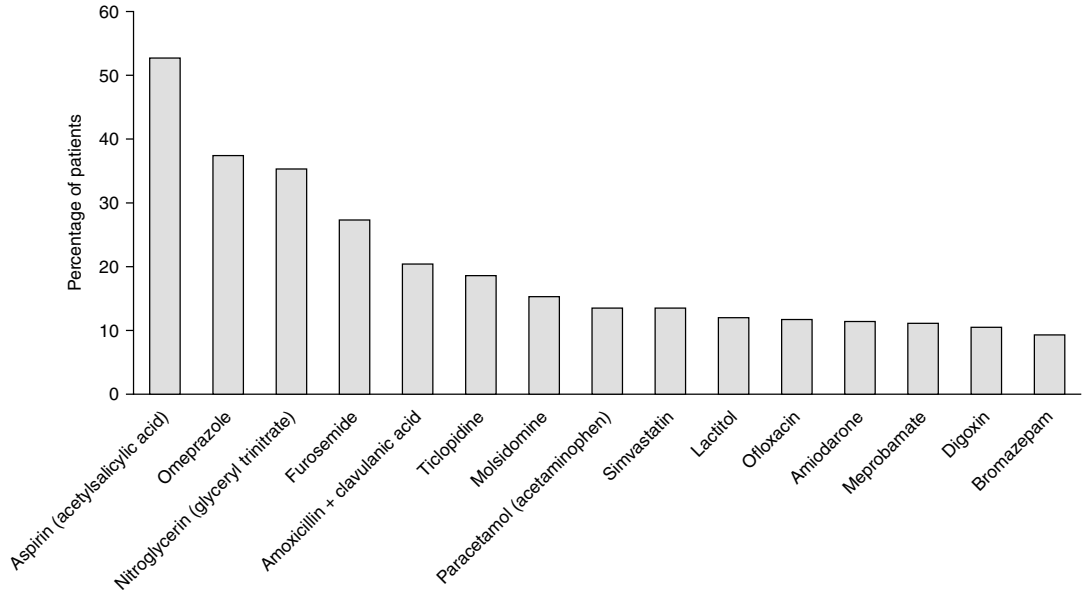

Fig. 2. Pattern of concomitant medication use in patients prescribed a low molecular weight heparin.

Table II. Incidence of low molecular weight heparin (LMWH)-induced adverse drug reactions (ADRs) and type of ADR reported during the study with tinzaparin and enoxaparin

LMWH	Incidence of LMWH-induced ADRs (%) [CI 95%]	No. of cases with bleeding adverse effects	No. of cases with decreased platelet count	No. of cases with increased platelet count	Hepatic cytolysis
Tinzaparin	9.7 [5.4–15.4]	4 (haematoma [2], ecchymosis [1], rectorrhagia [1])	1	8 [min: 460 103 max: 965 103 /mm^3]	
Enoxaparin	10.4 [6.2–14.6]	11 (haematoma [5], ecchymosis [1], haematuria [1], epistaxis [1], digestive bleeding [2], gingival haemorrhage [1])	3	6 [min: 450 103 max: 563 103 /mm^3]	1

patients (2.4%) in our study. In 1999 neither enoxaparin nor tinzaparin were approved for use in medical prevention of DVT or PE respectively, explaining the high rate of 'off label' prescription of these two LMWHs (64%).

The high mean age of the patients (72.5 ± 16.3 years) could be explained by the relatively large contribution of the geriatrics department (n = 125) to the study population, with 64.8% of patients exposed to at least one LMWH during their hospitalisation. In fact, age >60 years is considered as one of the risk factors of thromboembolic diseases.[23] The influence of age as risk factor for bleeding during heparin therapy also remains under discussion: Campbell et al.[24] suggested an increase of bleeding events with age during heparin therapy for DVT. Other authors[25,26] did not find this factor during curative treatment of DVT with UFH or LMWHs. However, other criteria such as WHO score were proposed as predictive risk factors of heparin-induced bleeding.[25] In our study, about one-third of the patients had an impaired general status (WHO score >2 with 70% from geriatric departments) and four cases of bleeding events (26%) occurred in patients with a WHO score of 4. Our data found a significant association with age or WHO score and bleeding risk. Moreover, renal insufficiency also remains a controversial risk factor for haemorrhagic events. Several case reports with various LMWHs suggest a role for renal insufficiency in the occurrence of bleeding events.[27-29] However, few trials have investigated the pharmacokinetics of LMWHs in patients with various degrees of renal insufficiency during at least 10 days of treatment. For nadroparin, Goudable et al.[30] found a significantly prolonged half-life in patients with chronic renal failure and Mismetti et al.[31] suggested a reduction of renal

Table III. Adjusted odds ratio and their 95% CI calculated by logistic regression for haemorrhagic adverse events

	Adjusted odds ratio[a] (95% CI)
Age (per bracket of 10 years)	2.01 (1.38–2.94)
Sex (female/male)	0.89 (0.47–1.69)
WHO score	
1 + 2	33.5 (11.20–97.52)
3 + 4	4.96 (2.18–11.28)
Creatinine clearance (per 10 ml/min decrease)[b]	1.34 (1.12–1.65)
Enoxaparin treatment	2.13 (0.6–7.17)
Tinzaparin treatment	1.95 (0.60–6.24)
At least one curative LMWH treatment	0.97 (0.57–1.63)
Antiplatelet agent	1.07 (0.47–2.40)
Aspirin (acetylsalicylic acid)	1.28 (0.43–3.84)
SSRI	3.36 (1.29–8.76)
At least one drug which could favour bleeding events	3.48 (1.27–9.54)

a Variable included in the final model were: age, sex, WHO score (1 + 2; 3 + 4), creatinine clearance (per 10 ml/min decrease), enoxaparin treatment, tinzaparin treatment, total duration of LMWH therapy, oral anticoagulant overlap, concomitant medication with aspirin, antiplatelet agent (ticlopidine), steroidal anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs, SSRI or at least one drug which could favour bleeding events.

b For each decrease of creatinine clearance by 10 ml/min the increase of risk was 1.34.

LMWH = low molecular weight heparin; **SSRI** = selective serotonin reuptake inhibitor.

clearance of nadroparin anti-Xa activity in elderly people reflecting age-related impairment of renal function. For enoxaparin, Gerlach et al.[32] showed, during a retrospective study, a significantly higher frequency of overall or major bleeding in 53 patients with renal insufficiency (based only on the plasma creatinine value and then not satisfactory indicators of renal function) compared with 50 patients with normal renal function. Cadroy et al.[33] found a significantly prolonged half-life in patients with chronic renal failure. Recently, Collet et al.[34] have shown that the optimal dose of enoxaparin in unstable angina depends on the renal function and the reduction of 64% of the recommended dose in patients with Cl_{cr} <30 ml/min provides a similar anti-Xa activity to those with Cl_{cr}>60 ml/min. Concerning tinzaparin, a few investigations in elderly people have suggested its lack of accumulation: Siguret et al.[35] studied 175 IU/kg of tinzaparin once daily in an old population of 30 inpatients (aged >70 years) suggested that neither dose adjustment, nor serial anti-Xa activity monitoring seemed to be required in patients with Cl_{cr} >20 ml/min during the first 10 day treatment. However, in this sample, only four patients (26%) had serious renal insufficiency (Cl_{cr} = 20–29 ml/min). Moreover, data was lacking for the durations of treatment exceeding 10 days, a frequent situation in clinical practice. Our data indicated a significant association with the decreasing value of Cl_{cr} (table III). Creatinine clearance was only calculated by Cockroft formula, which could be a limitation for renal function assessment.

The long-treatment of LMWH as a risk factor for bleeding remains an open question: Harenberg et al.[36] investigated the long-term treatment of LMWHs (between 2 months and 2 years) in 120 patients with contraindications to oral anticoagulants and suggested their safety owing to the low frequency of bleeding (0.4% major bleeding and 4.8% minor bleeding). Monreal et al.[37] found a similar risk of bleeding in patients treated by oral anticoagulant or LMWHs (for DVT or PE) for at least 3 months. Our results did not shown a significant association, but data about LMWHs prescription before and after the hospitalisation was lacking and then the global overall duration in our study remains under-estimated. The absence of oral anticoagulant overlap, namely in elderly people due to the difficulties to obtain a satisfactory compliance or the risk of drug interactions could explain the long-term period of LMWH treatment. Several drugs associated to LMWHs such as aspirin, ticlopidine, corticosteroids, SSRIs[38,39] could favour the occurrence of haemorrhagic events. In our population, the exposure to at least one of these drugs or to an SSRI increased the risk of bleeding events.

Among the other ADRs observed in our study, we underline cases of platelet increase (3.9%) without clinical effects as reported by other authors.[40-42] Liautard et al.[43] showed recently a highly significant association of thrombocytosis with LMWHs. The mechanism of LMWH-induced thrombocytosis in human remains unknown: an increase in blood platelet counts and the number of immature megakaryocytes (MK) and colony forming unit-MK in the bone marrow was found in mice given fraxiparin 0.1–25IU intraperitoneally twice daily for 4 days.[44] However, the relevance of this finding to man in unclear and required further investigations. The frequency of this adverse effect is not well evaluated and not labelled in the SPC of LMWHs marketed in France.

Currently, debate about the clinical equivalence of the different LMWHs remains open to question. Controversy exits regarding the interchangeability of LMWHs because of the variety of approved and unapproved indications for which these drugs are marketed and because of the differences in evidence across indications for each agent.[45-47] The conception of 'LMWH's bioequivalence' could be appropriate for short-term treatment and in patients without multiple risk factors, i.e. the population of clinical trials, but more data are necessary for their extensive use in the whole population (pharmacokinetic profiles in elderly people receiving LMWHs long-term, maximal anti-Xa activity for monitoring, etc). Bara et al.[47] investigated the occurrence of thrombosis and haemorrhage and the relationship with different biological parameters (anti-Xa and anti-IIa activities, D-dimer

plasma levels) for tinzaparin and enoxaparin and suggested little similarity between the two LMWHs. In our study, we did not find such a difference for bleeding effects between the two agents. However, the pattern of LMWHs prescription was different according to the departments for the reasons cited above.

A pharmacovigilance study undertaken in France in 1999 showed both high prevalence of misuse of LMWHs and high risk of occurrence of serious haemorrhagic events in old patients (>75 years) and in those with renal insufficiency leading the French authorities to broadcast a warning about the use of LMWHs.[48,49] Then, since 2001, the SPC of all LMWHs marketed in France included the contraindication for curative treatment with LMWHs in severe renal insufficiency (Cl_{cr} <30 ml/min). In order to improve the use of LMWHs, a guideline for the prescription of LMWHs based on their specific pharmacodynamic pattern, clinical efficacy for various indications, safety and behaviour in patients with risk factors and cost should be useful. Further pharmacoepidemiological studies could provide answers to some of these controversial questions.

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