Influence of Coadministration of Antithrombotic Medicines, Warfarin, and NSAIDs on Heparin Safety: Data from a Prospective Observational Study

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ABSTRACT

BACKGROUND: Utilization of heparins has been increasing in the last decade, thus, in-depth analysis is needed to assess heparins safety monitoring patterns, incidence rates of adverse drug reactions (ADR), and frequency of coadministration with other medicines.

OBJECTIVE: To investigate the safety monitoring of heparin in hospitals and the influence of coadministration of nonsteroidal anti-inflammatory drugs (NSAIDs), antithrombotic medicines, and warfarin on heparin safety.

METHODS: We reviewed hospital records of 339 patients who had orders for heparin or low molecular weight heparin from May 2009 to May 2010. IBM SPSS Statistics version 18.0 was used to perform statistical analysis.

RESULTS: Dalteparin ($n=238$, 70.21%) was the most frequently prescribed heparin. The most frequent indications given were for prophylaxis of venous thrombosis ($n=135$, 39.82%) and treatment of unstable coronary artery disease and myocardial infarction ($n=166$, 48.97%). ADRs were reported for 75 patients (22.12%), including coagulation abnormalities in 25 patients (7.37%), renal dysfunctions in 24 patients (7.08%), and thrombocytopenia in 10 patients (2.95%). 256 patients (75.52%) had relative contraindications. ADRs were associated with the previously reported relative contraindications (Spearman's rank correlation coefficient [r_s] = 0.261, Pearson's chi-squared test [χ^2] = 45.5, $P<0.0005$) and with prolonged treatment with heparins ($r_s=0.279$ and $\chi^2=74.7$, $P<0.0005$). ADRs were not related to heparin use but indicated increased risk for negative treatment outcomes. Coadministration of heparin with warfarin, acetylsalicylic acid, clopidogrel, ketorolac, and NSAIDs was associated with the increased risk of adverse drug reactions. The relationship was low but statistically significant. The strongest relationship was with coadministration of aspirin ($r_s=0.283$, $\chi^2=21.42$, $P<0.0005$), while the coadministration of NSAIDs showed only a very weak relationship to the development of ADRs ($r_s=0.133$, $\chi^2=21.01$, $P<0.0005$). For the development of thrombocytopenia, the strongest risk was calculated for coadministration of warfarin ($r_s=0.248$, $\chi^2=28.14$, $P<0.0005$), while coadministration of medicines from the list did not have a relationship with the risk of thrombocytosis.

CONCLUSIONS: Safety monitoring of heparin orders is essential, especially for patients with relative contraindications during long-term treatment and in case of coadministration of oral anticoagulants, platelet inhibitors, and NSAIDs.

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What is already known about this subject

- Monitoring of drug treatment can have several benefits: better selection of the appropriate drug therapy, improved adherence to clinical guidelines, and, as a result, improved treatment outcomes. Moreover, monitoring can also help in the identification of potential adverse drug reactions.
- Despite the fact that the value of monitoring is confirmed, a number of published studies report very low compliance in the monitoring of heparin usage in different countries.

What this study adds

- Descriptive analyses were performed and published that characterize heparin use, patient safety, and compliance with national prescribing guidelines at particular hospitals in several countries, although there were no such data available for Lithuania.
- The study results highlighted the fact that there were some gaps in the orders and documentation of information regarding the use of low-molecular-weight heparin (LMWH). Thus, we concluded that implementation of national guidelines on the use of LMWH should be prioritized.
- The results of our study confirmed the very low adherence of LMWH effectiveness and safety monitoring in local hospitals in comparison with international standards. The periodic evaluation of real-life practices may improve adherence to guidelines and potentially improve clinical outcomes.

Monitoring of drug treatment can ensure better selection of the appropriate drug therapy, improved adherence to clinical guidelines, and, as a result, improved treatment outcomes. Moreover, monitoring can also help in the identification of potential adverse drug reactions (ADRs).^{1-2,4}

Monitoring might be defined as the prospective supervision, observation, and testing of an ongoing process.³ Monitoring provides reassurance that the goal has been or will be achieved or suggests changes that will allow it to be achieved.^{3,4} Therapeutic drug monitoring has typically concentrated on the efficacy and safety of drugs and their concentrations to achieve benefit, avoid harm, or both. Patients and their clinicians can also monitor the progress of a disease and adjust treatment

accordingly. However, very little consideration has been given to developing effective schemes for monitoring the occurrence of ADRs, such as biochemical or hematological disturbances.⁵ Yet monitoring treatment to anticipate or detect adverse reactions to drugs before they become inevitable or irreversible is clearly important.^{6,7}

We selected unfractionated heparin (UFH) and low-molecular-weight-heparins (LMWH) for our evaluation. The utilization of heparins has been increasing over the past decade. The comprehensive list of indications for this pharmaceutical category illustrates how frequently these drugs are used in daily medical practice.^{8,9} Worldwide heparin utilization trends have shown 10% to 15% yearly growth in the past decade. These medicines were primarily used in the inpatient setting, and heparins consumed up to 10% of the total medication costs in hospitals. For example, in Lithuania, the utilization of heparins increased from 322,000 defined daily doses (DDDs) in 2003 to 2,074,000 DDDs in 2010—greater than a 6-fold increase—while total heparin expenditures increased almost 9-fold during this period, from 1,088,000 Lithuanian litas (LTLs) in 2003 up to 9,395,000 LTLs in 2010.¹⁰ Expenditures demonstrated a tendency to increase markedly faster than could be explained by the increased utilization rate of heparin in the country. Therefore, it was important to identify reasons behind that disproportional growth and to anticipate relevant actions that could be taken to manage costs. Thus, it was very important to investigate if the heparins and LMWHs were rationally used in daily medical practice.

Several descriptive analyses were performed and published by other authors¹¹⁻¹⁴ that characterize heparins' use, patient safety, and compliance with national prescribing guidelines at particular hospitals in many countries to improve safe use of heparins in hospital practice.

■ Methods

Study Objectives

The primary objective of this prospective observational study was to investigate safety monitoring patterns of heparin therapy by assessing the incidence rate of heparin ADRs, the influence of co-orders with nonsteroidal anti-inflammatory drugs (NSAIDs), antithrombotic medicines, and warfarin on ADRs associated with the use of LMWH, the reporting of ADRs to medical records and national pharmacovigilance databases, and adherence to safety monitoring guidelines.

Study Location

This study was conducted at a secondary-level clinical hospital in the second largest city in Lithuania. We anticipated that such a hospital would accurately represent the average secondary-level health care services provider in the country.

Study Population

All patients over 18 years of age who were admitted to the city hospital and received at least 1 order of heparin during the study period of May 1, 2009, through May 1, 2010, were included in the analysis. Subjects excluded included those whose medical records were illegibly written or incomplete (outstanding information on demographic data, current diagnosis, description of treatment, duration of hospitalization and/or treatment, treatment outcome) or those who were pregnant or breast-feeding. All patients were followed up until their discharge from the hospital to ensure a full picture of their treatment process and corresponding treatment outcomes.

Study Plan

The following data were collected from inpatient medical records and used for further analysis:

- demographic data (age and gender)
- duration of hospitalization at the inpatient setting
- treatment indication
- relative contraindications and their documentation in medical records
- data about UFH or LMWH orders (heparin name, dosage, pharmaceutical form, duration of treatment)
- monitoring of safety parameters
- treatment outcomes (assessed and classified as recovered, not recovered, recovered with sequel, death)
- ADR incidences and their reporting patterns (ADR identification, monitoring, reporting to medical records and national authorities, and follow-up)

Safety Assessments

Safety assessments were defined as the identification and reporting of ADRs. The following ADRs were analyzed in this research: coagulation abnormalities, renal dysfunction, thrombocytopenia, thrombocytosis, hyperkalemia, hematoma, anaphylactic reaction, headache/dizziness. ADR selection was based on the European Medicines Agency (EMA) Guideline on Similar Biological Medicinal Products Containing Low-Molecular-Weight Heparin, issued in April 2008. According to the World Health Organization's Adverse Reaction Terminology, an adverse drug reaction is defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen, or withdrawal of the product.^{1,15} In other words, it is an unexpected or dangerous reaction to a drug or an unwanted effect caused by the administration of a drug.

Adherence to Heparin Use and Monitoring Guidelines

Heparin order records were compared with the monitoring standards/guidelines recommended by the EMA Guideline on Similar Biological Medicinal Products Containing Low-Molecular-Weight Heparin and Clinical Guideline for the Use and Monitoring of Low-Molecular-Weight-Heparins in Community Hospitals and Community Settings.^{14,16-20} The following parameters were evaluated and compared: history of bleeding, acute peptic symptoms or other contraindications, concomitant use of drugs that may prolong bleeding time or affect platelet function, patients' weight, and obligatory laboratory tests before administration and during the therapy.

Statistical Analysis

Microsoft Office Excel 2007 (www.microsoft.com) was used to arrange data and IBM SPSS Statistics (Statistical Package for the Social Sciences) version 18.0 (www.ibm.com/software/analytics/spss/) was used to perform statistical analyses. We determined the relationships between patient variables and the probability of any monitoring in univariable analyses and then entered the baseline characteristics that were statistically significant at the $P < 0.05$ level. Descriptive statistics involved the estimations of average/mean/median values ($\pm$ standard deviation [SD]) and the 95% confidence interval (CI). Spearman's rank correlation coefficient (r_s) and Pearson's chi-squared test (χ^2) were used to evaluate correlations between the particular groups of variables. The following variables were used to conduct statistical analysis: demographic data (subjects' age and gender), heparin name, treatment indication, dosage, duration of treatment, duration of hospitalization, safety monitoring before heparin administration, safety monitoring during the treatment course, safety monitoring after the treatment course, and treatment outcomes.

Results

Demographic Data and General Administration Trends

Three hundred and thirty-nine patients, including 177 males (52.2%) and 162 females (47.8%) with a mean age of 69.6 years, who were prescribed at least a single dose of LMWH or UFH during their stay in the hospital, were included in the study. The mean duration of hospitalization was 9.6 days ($SD \pm 9.1$), and median duration of hospitalization was 8.0 days. A short-term hospital stay (fewer than 4 days) was the most frequently reported length of hospital stay in our study. The duration of hospitalization for 91 patients (26.9%) exceeded 10 calendar days; the duration of hospitalization for 101 patients (29.8%) was shorter than 6 days; and the duration of 6 to 10 days was applicable for 147 patients (43.4%). There were a few extraordinarily long stays identified. Six patients remained in the hospital for longer than 40 calendar days. Thirty-nine patients (11.5%) had long-term hospitalizations that exceeded 15 days (Table 1).

Data from the patients' medical records showed that the

TABLE 1 General Characteristics of Study Subjects

Characteristic	Value
Number of patients included	339
Female	162 (47.8%)
Male	177 (52.2%)
Age in years (mean, SD)	69.6 (± 13.3)
Duration of hospitalization in days (mean, SD)	9.6 (± 9.1)
Duration of LMWH therapy in days (mean, SD)	4.3 (± 4.4)

LMWH = low-molecular-weight heparin; SD = standard deviation.

most frequent indications were prophylaxis or treatment of unstable coronary artery disease (UCAD) or myocardial infarction (MI; $n = 166$ patients, 49%) and prophylaxis of venous thromboembolism (VT) in surgery ($n = 135$ patients, 39.8%). Other indications were represented by a significantly lower number of patients, including deep venous thromboembolism (DVT) in 14 patients (4.1%) and bedridden patient prophylaxis in 22 patients (6.5%; Table 2).

Safety Assessment

The following variables were analyzed against heparin safety measures: gender and age of subjects, hospital department, duration of exposure to heparin, heparin name used for the treatment, relative contraindications, and coadministration of medicines that must be coprescribed with caution. Safety data review was conducted in the following sequence in order to evaluate heparin safety monitoring patterns at the inpatient setting. Initially, all patients for whom no safety monitoring was conducted during their hospitalization period were separated from the entire sample. Then all subjects for whom safety monitoring had been performed were divided into 2 groups. Safety monitoring was performed for the first group of patients, even though no discrepancies had been identified or reported. For the second group of patients, safety monitoring was performed either as a result of various discrepancies/abnormalities or because ADRs were detected and reported. ADRs developed in 75 patients (22.1%) for whom relative contraindications were not reported at the time of treatment introduction. The most common ADR was coagulation abnormality for 25 patients (7.4%) and renal dysfunction for 24 patients (7.1%; Table 3). ADR development during treatment was associated with the previously reported relative contraindications ($r_s = 0.261$, $\chi^2 = 45.5$, $P < 0.0005$) and with prolonged treatment with heparin ($r_s = 0.279$ and $\chi^2 = 74.7$, $P < 0.0005$). Subjects for whom ADRs developed during the treatment were associated with the increased risk for negative treatment outcomes ($r_s = 0.221$, $\chi^2 = 22.5$, $P < 0.0005$).

Gender and Age of Subjects. Gender and age were not related to the safety monitoring trends. A similar distribution of patients was reported in all gender and age groups. An almost equal number of subjects (both genders) were allocated to the

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TABLE 2 General Overview of Heparin Used, Treatment Indications, and Hospital Departments

		Treatment Indications				
		DVT	Prophylaxis of VT in Surgery	Prophylaxis for Bedridden Patients	Treatment of UCAD or MI	Other
Department	Cardiology	n = 0	n = 1	n = 0	n = 119	n = 0
		0.0%	0.8%	0.0%	99.2%	0.0%
	Internal medicine	n = 12	n = 5	n = 18	n = 40	n = 2
		15.6%	6.5%	23.4%	51.9%	2.6%
	Surgery	n = 2	n = 80	n = 0	n = 2	n = 0
		2.4%	95.2%	0.0%	2.4%	0.0%
	Urology	n = 0	n = 49	n = 0	n = 0	n = 0
		0.0%	100.0%	0.0%	0.0%	0.0%
	Other	0	0	4	5	0
Total		0.0%	0.0%	44.4%	55.6%	0.0%
		n = 14	n = 135	n = 22	n = 166	n = 2
		4.1%	39.8%	6.5%	49.0%	0.6%
Heparin name	Enoxaparin	n = 0	n = 12	n = 0	n = 0	n = 0
		0.0%	100.0%	0.0%	0.0%	0.0%
	Fraxiparin	n = 11	n = 61	n = 20	n = 144	n = 2
		4.6%	25.6%	8.4%	60.5%	0.8%
	Nadroparin	n = 2	n = 39	n = 2	n = 12	n = 0
		3.6%	70.9%	3.6%	21.8%	0.0%
	Heparin	n = 1	n = 0	n = 0	n = 9	n = 0
		10.0%	0.0%	0.0%	90.0%	0.0%
	Bemiparin	n = 0	n = 23	n = 0	n = 1	n = 0
Total		0.0%	95.8%	0.0%	4.2%	0.0%
		n = 14	n = 135	n = 22	n = 166	n = 2
		4.1%	39.8%	6.5%	49.0%	0.6%

DVT = deep venous thromboembolism; MI = myocardial infarction; UCAD = unstable coronary artery disease; VT = venous thrombosis.

3 groups of safety measures ($r_s=0.028$, $\chi^2=0.412$, $P<0.8$). The majority of patients was elderly, although no statistically significant differences between a subject's age and safety monitoring trends were identified ($r_s=-0.004$, $\chi^2=0.008$, $P<0.96$).

Dosage. We did not perform any additional assessment of correlation between heparin daily dose and development of adverse events. During the research it was identified that only heparin standard doses (recommended in corresponding summaries of product characteristics) were used by patients. These standard doses were not adjusted as per individual subject needs (i.e., weight, age, and renal function have not been taken into consideration selecting heparin dose).

Hospital Department. A statistically significant difference was observed when comparing the safety monitoring trends at various departments in the inpatient settings ($r_s=0.113$, $\chi^2=46.1$, $P<0.005$). The surgery and cardiology departments did not perform any safety monitoring in 36.2% and 55.3% of the cases, respectively. However, the department of internal medicine monitored safety for all patients; consequently, the highest numbers of discrepancies and ADRs were identified in this department. Even though safety was extensively monitored by the urology department, very few ADRs were reported in the medical records.

Duration of Exposure to Heparins. The mean duration of exposure to heparin therapy was 4.3 days ($SD\pm 4.4$). The shortest treatment period did not exceed 4 days and was applicable for 228 patients (67.3%). Seventy-three patients (21.5%) experienced a treatment period of 5 to 7 days, and only 38 patients (8.3%) were treated with heparin for a relatively long period (8 days or more). The last period also included 4 patients who were treated with heparins for 17, 25, 38, and 53 days, respectively.

The duration of exposure to heparin was also considered as an important factor due to its direct impact on the ADR rate ($r_s=0.270$, $\chi^2=33.2$, $P<0.005$). This important safety reference has to be considered before deciding to prolong the utilization of heparin in the inpatient setting. In prescribing heparin for long-term use, additional efforts have to be taken to ensure proper safety monitoring and adequate follow-up/review of relevant laboratory parameters. These actions have to be taken in order to maintain the appropriate level of patient safety.

Heparin Name Used for the Treatment. The following heparins were prescribed for treatment or prophylaxis: enoxaparin, nadroparin, dalteparin, bemiparin, and UFH. Doses of all heparins were within the guidelines recommended by the EMA's Summary of Product Characteristics. Dalteparin was the most frequently prescribed medicine and was used by 236 patients

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TABLE 3 Adverse Drug Reactions and Their Incidence Rates

Adverse Drug Reaction	Frequency	Percent
Coagulation abnormalities ^a (PT outside 70%-100% range and/or APTT outside 35-50s range and/or INR outside 0.8-1.2 range)	25	7.37
Renal dysfunction ^a (Creatinine outside 70-132 micromoles per liter range and/or urea outside 1.7-8.3 millimoles per liter range)	24	7.08
Thrombocytopenia ^a (PLT count < 100 × 10 ⁹ per liter)	10	2.95
Thrombocytosis ^a (PLT count > 450 × 10 ⁹ per liter)	8	2.10
Hyperkalemia ^a (Potassium level > 5.5 millimoles per liter)	4	1.18
Hematoma (bleeding)	2	0.60
Anaphylactic reaction	1	0.30
Headache/dizziness	1	0.30
Total	75	—

^aAll laboratory tests of interest were performed at the local lab in the corresponding clinical hospital. Automated methods were used to analyze lab samples.

APTT = activated partial thromboplastin time; INR = international normalized ratio; PLT = platelet; PT = prothrombin time.

(69.6%). The second- and third-most prescribed LMWHs were nadroparin (n = 55, 16.2%) and bemiparin (n = 24, 7.1%). Orders of other heparins did not exceed 4%. ADR development during the treatment was not associated with the type of the heparin used ($r_s = -0.044$, $\chi^2 = 13.6$, $P < 0.09$).

Relative Contraindications. Relative contraindications were reported for 256 patients (75.5%). The most frequently reported relative contraindication for the use of heparin was age (n = 234, 69%), followed by coagulation abnormalities (n = 92, 24.3%) and renal dysfunction (n = 41, 10.9%). One hundred and seventy-six patients (51.9%) had only 1 relative contraindication, while 50 patients (14.8%) had 2 relative contraindications, and 30 patients (8.9%) were identified with 3 or more relative contraindications. Corresponding dose adjustments were not reported for any of the patients having relative contraindications, and a standard dose of UFH or LMWH was used for these patients (Table 4).

Based on study results, patients with relative contraindications were associated with an increased risk for prolonged treatment with heparin ($r_s = 0.286$, $\chi^2 = 69.3$, $P < 0.0005$), an increased risk for the development of ADRs ($r_s = 0.277$, $\chi^2 = 17.5$, $P < 0.0005$), an increased risk for negative treatment outcomes ($r_s = 0.236$, $\chi^2 = 50.5$, $P < 0.0005$), and an increased risk for a prolonged hospitalization period ($r_s = 0.169$, $\chi^2 = 11.6$, $P < 0.003$).

Coadministration of Medicines That Have to be Prescribed with Caution. Based on products' summary characteristics data, due to increased risk of bleeding, LMWHs should be used with caution in patients receiving oral anticoagulants,

TABLE 4 Relative Contraindications and Their Incidence Rates

Relative Contraindication	Identified Before Treatment Phase Frequency (%)
Age (> 65 years)	234 (69.0)
Coagulation abnormalities ^a (PT outside 70%-100% range and/or APTT outside 35-50s range and/or INR outside 0.8-1.2 range)	92 (24.3)
Renal dysfunction ^a (Creatinine outside 70-132 micromoles per liter range and/or urea outside 1.7-8.3 millimoles per liter range)	41 (10.9)
Thrombocytopenia ^a (PLT count < 100 × 10 ⁹ per liter)	18 (4.7)
Hyperkalemia ^a (Potassium level > 5.5 millimoles per liter)	11 (2.9)
Thrombocytosis ^a (Platelet count > 450 × 10 ⁹ per liter)	10 (2.6)

^aAll laboratory tests of interest were performed at the local lab in the corresponding clinical hospital. Automated methods were used to analyze lab samples.

APTT = activated partial thromboplastin time; INR = international normalized ratio; PLT = platelet; PT = prothrombin time.

TABLE 5 Medicines to be Coprescribed with Caution with Low-Molecular-Weight Heparin

Drug Class	List of Agents
Anticoagulants	Warfarin, acenocoumarol
Platelet inhibitors	Acetylsalicylic acid, salicylates, ticlopidine, clopidogrel
NSAIDs	Ketorolac tromethamine, dipyridamole, sulfinpyrazone
Thrombolytics	Streptokinase, alteplase

NSAID = nonsteroidal anti-inflammatory drug.

platelet inhibitors, NSAIDs, and thrombolytics (Table 5). We identified only concomitant use of acetylsalicylic acid, clopidogrel, NSAIDs, and warfarin together with heparins in patient records. In cases where coadministration of LMWHs with these agents is necessary, it is advised to implement close clinical and laboratory monitoring of these patients (Table 6).

Subjects for whom warfarin, acetylsalicylic acid, clopidogrel, ketorolac, and NSAIDs were prescribed during the treatment phase were associated with an increased risk for the development of ADRs. The relationship was low but statistically significant. The strongest relationship was with the coadministration of acetylsalicylic acid ($r_s = 0.283$, $\chi^2 = 21.42$, $P < 0.0005$), while the coadministration of NSAIDs had only a very weak relationship to the development of ADRs ($r_s = 0.133$, $\chi^2 = 21.01$, $P < 0.0005$). Data are presented in Table 7.

Patients for whom warfarin, acetylsalicylic acid, clopidogrel, ketorolac, and NSAIDs were prescribed during the treatment phase showed an increased risk for the development of thrombocytopenia; the strongest risk was calculated for coad-

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TABLE 6 Frequency of Medicines to be Prescribed with Caution with Low-Molecular-Weight Heparin

Name of Agent Prescribed with Precaution	Frequency	Percent
Warfarin	5	1.47
Acetylsalicylic acid	115	33.92
Clopidogrel	13	3.83
Ketorolac	89	26.25
Other NSAIDs	40	11.80

NSAID = nonsteroidal anti-inflammatory drug.

ministration of warfarin ($r_s = 0.248$, $\chi^2 = 28.14$, $P < 0.0005$, Table 7), while coadministration of medicines from the list did not have a relationship to the risk of thrombocytosis (Table 7). We were unable to evaluate coadministration of medicines and the risk of bleeding due to a small number of patients suffering from bleeding as an ADR.

Discussion

Our analysis of heparin's utilization worldwide suggested that its use in clinical practice has increased significantly recently and Lithuanian utilization data shows the same utilization trends. The use of LMWH in Lithuania has increased from 40.12 DDDs per 1,000 inhabitants in 2003 to 272.75 DDDs per 1,000 inhabitants in 2010. Utilization studies of LMWH in other countries have reported a similar increase in use. For example, during the period 2001-2010, Croatia reported an increase in expenditure on heparin treatment from \$11.4 to \$38.5 million and an increase in utilization from 0.42 DDD per 1,000 inhabitants to 1.96 DDD per 1,000 inhabitants—4.66 times more.³ A study of medication utilization patterns in a tertiary care university hospital in Israel conducted in 2007-2008 showed that the various heparins were the most frequently prescribed drugs at their admission units; 2,102 DDDs were prescribed during the most recent 6 months of investigation. In general, this corresponded to an average of almost 10 DDDs of heparin being utilized by each individual patient during his or her hospital stay.²¹ Thus, the monitoring of rational and safe use of LMWH is essential in clinical practice.

Evaluation of Safety

Meta-analysis of comparative evaluations of UFH and LMWHs have revealed reductions in safety and efficacy of 30% to 40% in favor of LMWHs, with no conclusive evidence that LMWHs have intrinsically different safety and/or efficacy profiles.²²⁻²⁴ Furthermore, it is quite likely that these differences are related to, or are the direct result of, the markedly variable manufacturing strategies employed to produce each LMWH. There are no data, however, to suggest that these variable pharmacodynamic or pharmacologic properties translate into differences in clinical outcomes or safety. Consequently, the only conclusion

TABLE 7 Concomitant Use of Medicines with Caution and Increased Risk of Adverse Drug Reactions, Thrombocytopenia, and Thrombocytosis

	r_s	χ^2	P Value
Concomitant use of medicines with caution and increased risk for development of adverse drug reactions			
Acetylsalicylic acid	0.283	21.42	<0.0005
Ketorolac	0.272	27.16	<0.0005
Warfarin	0.249	27.16	<0.0005
Clopidogrel	0.203	19.29	<0.0005
NSAIDs	0.133	21.01	<0.0005
Concomitant use of medicines with caution and increased risk for development of thrombocytopenia			
Warfarin	0.248	28.18	<0.0005
Acetylsalicylic acid	0.238	20.24	<0.0005
Ketorolac	0.188	20.61	<0.0005
Clopidogrel	0.114	18.92	<0.0005
NSAIDs	0.101	11.10	<0.0005
Concomitant use of medicines with caution and increased risk for development of thrombocytosis			
Warfarin	-0.431	37.67	<0.0005
Ketorolac	-0.402	27.87	<0.0005
Clopidogrel	-0.399	39.39	<0.0005
Acetylsalicylic acid	-0.398	31.22	<0.0005
NSAIDs	-0.337	35.08	<0.0005

NSAID = nonsteroidal anti-inflammatory drug.

supported by these observations is that these LMWHs are essentially the same in treatment or prevention at the dosages used in clinical trials.^{25,26}

The ESCAPE-END study (Efficacy, Safety, Cost-effectiveness and Effect on PAI-1 of Enoxaparin, Nadroparin, and Dalteparin) was conducted to compare the 3 LMWHs in patients with unstable angina. Prospective, randomized, comparative, and open with blinded endpoints assessments with a 30-day follow-up (PROBE design) showed that all 3 LMWHs evaluated in this study were similar with respect to efficacy, safety, PAI-1 levels, and cost-effectiveness.²⁷

The results of our study also supported the hypothesis that LMWHs could be interchangeable in the treatment of DVT, pulmonary embolism, recurrent angina, and MI. In comparison to UFH, all LMWHs have independently demonstrated greater safety and effectiveness. None of the LMWHs demonstrated a significant superiority over another; therefore, the group of LMWHs could be interchangeable for the indications stated above in terms of safety and effectiveness.^{28,29}

Safety Monitoring Adherence to Heparin Use and Monitoring Guidelines

The results of our study confirmed low adherence to LMWH safety monitoring guidelines in local Lithuanian hospitals in comparison with international standards. The periodic

evaluation of real-life practices may improve adherence to guidelines and potentially improve clinical outcomes.³⁰ Underdosing can lead to lack of efficacy and new thromboembolic events during hospitalization, while overdosing often leads to an increase in ADRs. Thus, the rational dose of LMWH for a patient should be calculated based on a patient's age, weight, and renal function.

Despite the fact that monitoring is beneficial, many publications have cited very low monitoring of heparin effectiveness and safety in different countries. The United Kingdom's (UK) National Patient Safety Agency (NPSA) reported LMWH dosing errors and evidence of harm. Between January 2005 and September 2009, the NPSA received 2,716 patient safety incident reports related to LMWH use, including include 1 incident that led to death and 3 reports of severe harm to patients. Reports of the UK National Reporting and Learning System (NRLS) indicate that some patients are not weighed prior to administration, that the body weight is estimated or recorded inaccurately, or that doses based on a patient's weight are miscalculated. These documents reported numerous incidents in which the prescribed, dispensed, or administered dose and frequency of LMWH were outside the accepted guidelines and did not account for other predisposing conditions such as renal failure. Limited patient information (i.e., weight, dose, indication, and intended duration of treatment) communicated at transfers of care has also led to reports of harm.

In response to the NPSA alert, the Thrombosis Committee at the Barnet and Chase Farm Hospitals (BCFH) in the UK performed an audit of LMWH prescriptions at the hospitals. The audit covered 47 surgical and medical patients treated at BCFH during the period January 2-February 3, 2012. According to the audit findings, the body weight of 51.1% of patients was not documented in the bedside folders and on the inpatient charts; the renal function of 8.5% of patients was not considered after the second dose; and 26.9% of patients did not have an indication of their LMWH therapy documented on their discharge summaries, despite the fact that all 3 monitoring standards are mandatory in the hospital.²¹

An audit of a database of patients treated with LMWH at the University Medical Center Utrecht in the Netherlands revealed low compliance with platelet count monitoring, as well as initial management of suspected heparin-induced thrombocytopenia (HIT). Assessment of LMWH use in Dutch hospitals for the treatment of acute coronary syndrome in light of the current European Society of Cardiology guidelines showed that dose adjustment of LMWH therapy for patients with renal failure is not applied in 71% of hospitals. Likewise, LMWH dose adjustment is not applied for patients aged over 75 years in 92% of hospitals. The authors have concluded that an additional benefit may be achieved by the routine dose adjustment of LMWH for patients with renal insufficiency and aged over 75 years, since these patients are at high risk of bleeding complications secondary to antithrombotic treatment.²⁸ The

same risk of bleeding ADR was reported in elderly patients and patients with renal failure by a prospective LMWH utilization study at the University Hospital of Toulouse, France. The authors have also concluded that more pharmacoepidemiology studies in patients with several risk factors, particularly in elderly patients and in patients with renal failure, would be useful in order to determine the optimal method of use for each LMWH.^{6,12}

Clinicians should include evaluations of compliance with platelet count monitoring with UFH and LMWH, as well as the appropriateness of the initial management strategies for HIT and direct thrombin inhibitor protocols in their patient safety practice assessments.¹⁴ Practitioners in U.S. hospitals are implementing anticoagulation dosing and monitoring protocols to improve the safety of anticoagulation therapy.

The timely, adequate, and comprehensive reporting of ADRs is an essential part of patients' medical care, allowing the justification of future therapy alterations and helping to prevent medical inpatients from repeated ADRs during their hospital stays. A study on UFH and LMWH use in French hospitals showed that the implementation of guidelines in clinical practice has had a positive impact on medical practice, at least by improving the safety of the drugs used. A significant decrease in hemorrhagic ADRs was reported after the implementation of new guidelines on UFH and LMWH use in hospitals and changes in their use. The dosage of LMWH was adjusted more in accordance with renal function, and no ADRs were observed in patients with severe renal impairment.^{4,7}

As a response to the low monitoring of LMWH effectiveness and safety, health care providers have started to implement clinical guidelines regarding the use and monitoring of LMWH in community hospitals and community settings. The guidelines are designed to provide information to support the staff on the safe and appropriate use and monitoring of LMWH across secondary and primary care units and to reduce dosage errors when prescribing it.^{12,14,18}

Limitations

Our study has several limitations. This research was conducted at 1 of the secondary-level clinical hospitals in the country; thus, some variation might occur in similar investigations conducted at other health care facilities due to variation in local practices. Also, all data have been collected manually, since there are no unified orders or dispensing databases available in hospitals in Lithuania. Some of the study results were considered as not statistically significant mainly due to the variation of patients' distribution in the selected treatment groups.

Conclusions

It is essential to emphasize the importance of safety monitoring in patients when administering heparin. In particular, it is necessary to closely monitor patients with relative

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contraindications; patients to whom heparins are prescribed for a long-term treatment; and patients with concomitant use of antithrombotic medicines, NSAIDs, and warfarin due to increased risk of ADRs. Low-molecular-weight heparins did not differ in terms of their safety parameters; therefore, the requirement for additional follow-up was not affected by the heparin brand or name prescribed for each patient. The study results highlight some gaps in the documentation of information regarding the use of LMWH. A particular weakness was found in the recording and communication of information; thus, the implementation of national guidelines on the use of LMWH is preferable.

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DISCLOSURES

The authors report no financial conflicts of interest related to the subjects discussed in this article.

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